Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

GAMBRO.

Biological evaluation of SMA coated GamCath High Flow Dolphin Catheters: Review of all available biocompatibility data

Toxicological Expert Report (b)(4)

Written by:

(b)(6)

(b)(4)

Gambro R&D,
Sweden

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

GAMBRO.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(6)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

K100451

FDA CDRH DMC
FEB 17 2010
Received

3.0 510(k) COVER LETTER

Traditional 510(k) Premarket Notification Cover Letter

February 16, 2010

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 – G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

To Whom It May Concern:

Enclosed is a Traditional 510(k) Notification seeking marketing clearance for the GamCath® High Flow Dolphin® Catheter.

Administrative Information	
Type of 510(k) Submission	Traditional
Device Type	Short-Term Hemodialysis Catheter
510(k) Submitter	Gambro Renal Products, Inc. 14143 Denver West Parkway, Suite 400 Lakewood, CO 80401
Contact	Kae Miller, Regulatory Affairs Manager Phone: 303.222.6724 Fax: 222.6916
Confidentiality	Material marked "CONFIDENTIAL" is deemed by Gambro to be either trade secret or confidential commercial information. Therefore, we request that FDA apply all of the legislative safeguards pertaining to non-disclosure of such confidential material to the public. **Note: All information contained in the Attachments is CONFIDENTIAL**
Classification Name	Catheter Hemodialysis Non-Implanted
Device Trade Name	GamCath® High Flow Dolphin® Catheter
Device Variation	11,5 French 150 mm 11,5 French 200 mm 11,5 French 250 mm 13 French 150 mm 13 French 200 mm 13 French 250 mm Optional with straight or curved extension line.
Device Class	II
Product Code	78 MPB
Regulation Number	21 CFR 876.5540
Manufacturer	**Gambro Kathetertechnik Hechingen** Linsenaecker 1 Hechingen, Germany DE-72379

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Basis for Submission

The basis for this Traditional 510(k) Notification is the introduction of a new catheter for use in hemodialysis.

Design and Use of the Device

The table on the following page is provided as recommended in the FDA guidance document, *Format for Traditional and Abbreviated 510(k) s* issued on August 12, 2005.

Question	YES	NO
Is the device intended for prescription use (21 CFR 801 Subpart D)?	X	
Is the device intended for over-the-counter use (21 CFR 801 Subpart C)?		X
Does the device contain components derived from a tissue or other biologic source?		X
Is the device provided sterile?	X	
Is the device intended for single use?	X	
Is the device a reprocessed single use device?		X
If yes, does this device type require reprocessed validation data?		X
Does the device contain a drug?		X
Does the device contain a biologic?		X
Does the device use software?		X
Does the submission include clinical information?		X
Is the device implanted?		X

The premarket notification information required by 21 C.F.R. §807.87 is contained in the accompanying document in the format defined in the FDA guidance document, *Format for Traditional and Abbreviated 510(k)s* issued on August 12, 2005.

Additionally, this 510(k) includes the information recommended in the FDA *Guidance on Premarket Notification 510(k) Submission for Short-Term and Long-Term Intravascular Catheters, March 16, 1995* which is provided in Section 20.

Two copies of this traditional Premarket 510(k) notification are provided. One hardcopy and one identical duplicate on CD.

Please contact Kae Miller, Regulatory Affairs Manager at 303.222.6724 by phone or 303.222.6916 by fax for any questions regarding this submission.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

GAMBRO, Renal Products

Traditional 510(k) for GamCath® High Flow Dolphin® Catheter

Indications for Use Statement

510(k) Number (if known): K100451

Device Name: GamCath® High Flow Dolphin® Catheter

DEC 2 1 2010

Indications for Use Statement:

GamCath® High Flow Dolphin® catheters are indicated for use in attaining short term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. GamCath® High Flow Dolphin® Catheter is not intended for use in pediatric patients.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Reproductive, Gastro-Renal, and Urological Devices
510(k) Number K100451

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center ¿ WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

September 30, 2010

GAMBRO RENAL PRODUCTS, INC.
14143 DENVER WEST PARKWAY SUITE 400
LAKEWOOD, COLORADO 80401
UNITED STATES
ATTN: KAE MILLER

510k Number: K100451

Product: GAMCATH HIGH FLOW DOLPHIN

The additional information you have submitted has been received.

We will notify you when the processing of this submission has been completed or if any additional information is required. Pleaseremember that all correspondence concerning your submission MUST be sent to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. On August 12, 2005 CDRH issued the Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s. This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so in 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.

Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely,

510(k) Staff

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

K100451 1/5

GAMBRO Renal Products

14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 222 6500

September 28, 2010

FDA CDRH DMC

SEP 29 2010

Received

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 – G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: FDA Additional Information Request for 510(k) K100451 for the GamCath® High Flow Dolphin® Catheter

To Whom It May Concern:

Enclosed please find the response to the FDA request for additional information via email dated September 24, 2010, in reference to the Traditional 510(k) for GamCath® High Flow Dolphin® Catheter, submitted by Gambro Renal Products, Inc. on February 16, 2010.

The information requested from the FDA is restated followed by Gambro's response. Please contact me by telephone at 303.222.6724 or by fax at 303.222.6916 with any questions regarding this additional information. I can also be reached by email at kae.miller@us.gambro.com.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

K58

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

134

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

FDA Request for Additional Information via Email Dated September 24, 2010:

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

135

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Attachment 1 – New Indications for Use

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Indications for Use Statement

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Attachment 2 – Revised 510(k) Summary

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

5.0 510(k) SUMMARY

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Attachment 3 – Modified Instructions for Use

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2024-8952 Released by CDRH on 08-19-2024

Short-term vascular access for hemodialysis, hemoperfusion and apheresis therapy with GamCath HighFlow Dolphin Catheters

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

510(k) SUMMARY REQUIREMENTS CHECKLIST: K100451 21 CFR 807.92				
All 510(k) summaries shall contain the following information:		Y	N	N/A
1	The submitter's name, address, telephone number, a contact person, and the date the summary was prepared	√		
2	The name of the device, including the trade or proprietary name if applicable, the common or usual name, and the classification name	√		
3	An identification of the legally marketed device(s) to which the submitter claims equivalence.	√		
4	A description of the device that is the subject of the 510(k), including an explanation of how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device (e.g., device design, material used, and physical properties)	√		
5	A statement of the indications for use of the device that is the subject of the 510(k), including a general description of the diseases or conditions that the device will diagnose, treat, prevent, cure, or mitigate, including a description, where appropriate, of the patient population for which the device is indicated. Or, if the indication statements are different from those of the legally marketed device(s) identified in paragraph (3) of this section, an explanation as to why the differences are not critical to the intended therapeutic, diagnostic, prosthetic, surgical or other use of the device, and why the differences do not affect the safety and effectiveness of the device when used as indicated.	√		
6	If the device has the same technological characteristics (i.e., design, material, chemical composition, energy source, etc.) as the predicate device(s) identified in paragraph(3) of this section, a summary of the technological characteristics of the new device in comparison to those of the predicate device(s). Or, if the device has different technological characteristics from the predicate device(s), a summary of how the technological characteristics of the device compare to a legally marketed device(s) identified in paragraph (3) of this section.	√		
510(k) summaries for those 510(k)s in which a determination of substantial equivalence is also based on an assessment of performance data shall contain the following information				
7	A brief discussion of the nonclinical tests submitted, referenced, or relied on in the 510(k) for a determination of substantial equivalence	√		
8	A summary discussion of the clinical tests submitted, referenced, or relied on in the 510(k) for a determination of substantial equivalence. This discussion shall include, where applicable, a description of the subjects upon whom the device was tested, a discussion of the safety or effectiveness data obtained from the testing, with specific reference to adverse effects and complications, and any other information from the clinical testing relevant to a determination of substantial equivalence. (There can not be any patient identifier information in the summary.)			√
9	The conclusions drawn from the nonclinical and clinical tests that demonstrate that the device is as safe, as effective, and performs at least as safely and effectively as the legally marketed device identified in paragraph(3) of this section.	√		

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

Premarket Notification [510(k)] Review
Traditional/Abbreviated

K100451-S2

Date: December 20, 2010
To: The Record
From: Jeffrey Cooper, DVM

Office: ODE
Division: DRARD

510(k) Holder: Gambro Renal Products, Inc.
Device Name: GamCath® High Flow Dolphin® Catheter
Contact: Kae Miller, Regulatory Affairs Manager
Phone: 303 222-6724
Fax: 303 222-6916
Email:

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

8

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(5)

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(5)

Reviewer

12/20/10
Date

Branch Chief

12/21/10
Date

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Shackelford, Megan M

From: Cooper, Jeffrey (CDRH)
Sent: Tuesday, December 21, 2010 11:26 AM
To: Shackelford, Megan M
Subject: FW: K100451-S1
Importance: High

Please print this and add to the file if not too late.

Jeffrey Cooper, M.S., D.V.M.

From: Khanthaphixay, Maly [mailto:Maly.Khanthaphixay@us.gambro.com]
Sent: Tuesday, December 21, 2010 10:57 AM
To: Cooper, Jeffrey (CDRH)
Cc: Miller, Kae; Dielmann, Tom; Piazza, Fred; Schaefer, Michael; Jentsch, Wolfgang; Stemmer, Stefan; Ruhl, Uwe; Khanthaphixay, Maly
Subject: RE: K100451-S1
Importance: High

Dr. Cooper,

(b)(4)

Best regards,

Maly Khanthaphixay
Regulatory Affairs
Gambro Renal Products, Inc
14143 Denver West Parkway, Suite 400
Lakewood, CO 80401
Direct: 303.222.6698
Fax: 303.222.6879
maly.khanthaphixay@us.gambro.com

From: Cooper, Jeffrey (CDRH) [mailto:Jeffrey.Cooper@fda.hhs.gov]
Sent: Monday, December 20, 2010 1:06 PM
To: Khanthaphixay, Maly
Subject: FW: K100451-S1

Since Kae is out, can you answer the (b)(4) question below?

Jeffrey Cooper, M.S., D.V.M.

From: Cooper, Jeffrey (CDRH)
Sent: Monday, December 20, 2010 2:53 PM
To: 'Miller, Kae'
Subject: RE: K100451-S1

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Jeffrey Cooper, M.S., D.V.M.

From: Miller, Kae [mailto:Kae.Miller@us.gambro.com]
Sent: Wednesday, December 08, 2010 4:37 PM
To: Cooper, Jeffrey (CDRH)
Subject: RE: K100451-S1

Attached is the revised response. A new copy will arrive at the Document Mail Center tomorrow morning.

Thank you,
Kae

From: Miller, Kae
Sent: Wednesday, December 08, 2010 9:07 AM
To: 'Cooper, Jeffrey (CDRH)'
Subject: RE: K100451-S1

Dr. Cooper:

In this response, we inadvertently included the wrong documents in attachments 1 and 2. I will email you a new corrected response today.

I apologize for any inconvenience this may have caused.

Kae

From: Miller, Kae
Sent: Tuesday, December 07, 2010 9:57 AM
To: Cooper, Jeffrey (CDRH)
Subject: RE: K100451-S1

Dr. Cooper:

Attached is a copy of our response. It was delivered to the Document Mail Center this morning.

Thank you,
Kae

From: Cooper, Jeffrey (CDRH) [mailto:Jeffrey.Cooper@fda.hhs.gov]
Sent: Wednesday, October 13, 2010 4:44 PM
To: Miller, Kae
Subject: K100451-S1

Thank you for completely answering the previous questions. I am placing your submission on hold for these additional questions.

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Jeffrey Cooper, M.S., D.V.M.
Veterinary Medical Officer
Center for Devices & Radiological Health (CDRH)
Office of Device Evaluation (ODE)
Division of Reproductive, Gastro-Renal, and Urological Devices (DRGUD)
Gastroenterology and Renal Devices Branch (GRDB)
WO66 G228
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
(301) 796-6517
jeffrey.cooper@fda.hhs.gov

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GU | DRGUD

K100451

Fife, Elizabeth *

From: Fife, Elizabeth *
Sent: Wednesday, December 08, 2010 4:32 PM
To: 'Miller, Kae'
Subject: RE: K100451 Additional Information Received

Dear Kae Miller,

We appreciate your response. We will be watching for the replacement supplement to come in the mail.

Thank you,

Elizabeth Fife
File Technician
Emergint Contractor
FDA - Center for Devices and Radiological Health
301-796-0184 (w)
301-847-8113 (f)

From: Miller, Kae [mailto:Kae.Miller@us.gambro.com]
Sent: Wednesday, December 08, 2010 3:48 PM
To: Fife, Elizabeth *
Subject: RE: K100451 Additional Information Received

Dear Elizabeth:

We discovered an error in this response. It is possible to retrieve this submission? The corrected one will be delivered to the Document Mail Center tomorrow morning.

Thank you,
Kae

From: Fife, Elizabeth * [mailto:Elizabeth.Fife@fda.hhs.gov]
Sent: Wednesday, December 08, 2010 1:44 PM
To: Miller, Kae
Subject: K100451 Additional Information Received

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center, WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

December 08, 2010
MILLER
KAE
GAMBRO RENAL PRODUCTS, INC.
14143 DENVER WEST PARKWAY SUITE 400
LAKEWOOD, COLORADO 80401
UNITED STATES
ATTN: KAE MILLER
510k Number: K100451

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Product: GAMCATH HIGH FLOW DOLPHIN
MS-G

The additional information you have submitted has been received.
We will notify you when the processing of this submission has been completed or if any additional information is required. Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. On August 12, 2005 CDRH issued the Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s. This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510 (k).
The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so in 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.
Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.
If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely,

510(k) Staff

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Cooper, Jeffrey (CDRH)

From: Cooper, Jeffrey (CDRH)
Sent: Friday, September 24, 2010 4:12 PM
To: 'Miller, Kae'
Subject: RE: GamCath K100451Request for Additional Information Today

Kae-

We have been reviewing your submission, but realized that we cannot locate:

(b)(4)

I am placing your submission on "Inadequate incoming" hold until we receive these responses. Hopefully, this should be a quick response that you can email to me and send a paper copy to the Document Mail Center. As soon as we receive the paper copy, we will quickly finish our review and send you our concerns based on your complete responses.

Jeffrey Cooper, M.S., D.V.M.
Veterinary Medical Officer
Center for Devices & Radiological Health (CDRH)
Office of Device Evaluation (ODE)
Division of Reproductive, Gastro-Renal, and Urological Devices (DRGUD)
Gastroenterology and Renal Devices Branch (GRDB)
WO66 G228
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
(301) 796-6517
jeffrey.cooper@fda.hhs.gov

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

From: Miller, Kae [mailto:Kae.Miller@us.gambro.com]
Sent: Monday, August 30, 2010 5:58 PM
To: Cooper, Jeffrey (CDRH)
Subject: RE: GamCath K100451Request for Additional Information Today

Hi, I forgot to email you on Friday. This response was sent to the Document Mail Center on Friday for delivery today.

Thank you,
Kae

From: Cooper, Jeffrey (CDRH) [mailto:Jeffrey.Cooper@fda.hhs.gov]
Sent: Wednesday, July 28, 2010 10:42 AM
To: Miller, Kae
Subject: RE: GamCath K100451Request for Additional Information Today

That is acceptable.

Jeffrey Cooper, M.S., D.V.M.

From: Miller, Kae [mailto:Kae.Miller@us.gambro.com]
Sent: Wednesday, July 28, 2010 12:34 PM
To: Cooper, Jeffrey (CDRH)
Cc: Neuland, Carolyn Y.
Subject: RE: GamCath K100451Request for Additional Information Today

Dr. Cooper:

(b)(4)

(b)(4) Is it acceptable to provide this information to you the last week of August?

Thank you,
Kae

From: Cooper, Jeffrey (CDRH) [mailto:Jeffrey.Cooper@fda.hhs.gov]
Sent: Friday, July 16, 2010 11:49 AM
To: Miller, Kae
Cc: Neuland, Carolyn Y.
Subject: RE: GamCath K100451Request for Additional Information Today

Kae-

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Jeffrey Cooper, M.S., D.V.M.
Veterinary Medical Officer
Center for Devices & Radiological Health (CDRH)
Office of Device Evaluation (ODE)
Division of Reproductive, Abdominal and Radiological Devices (DRARD)
Gastroenterology and Renal Devices Branch (GRDB)
WO66 G228
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
(301) 796-6517
jeffrey.cooper@fda.hhs.gov

From: Miller, Kae [mailto:Kae.Miller@us.gambro.com]
Sent: Tuesday, July 13, 2010 12:22 PM
To: Cooper, Jeffrey (CDRH)
Subject: RE: GamCath K100451Request for Additional Information Today

Hi, No problem. (b)(4)

Thank you,
Kae

From: Cooper, Jeffrey (CDRH) [mailto:Jeffrey.Cooper@fda.hhs.gov]
Sent: Tuesday, July 13, 2010 8:58 AM
To: Miller, Kae
Subject: RE: GamCath K100451Request for Additional Information Today

Kae-

Sorry for the confusion. I hope the following helps.

(b)(4)

Jeffrey Cooper, M.S., D.V.M.
Veterinary Medical Officer
Center for Devices & Radiological Health (CDRH)
Office of Device Evaluation (ODE)
Division of Reproductive, Abdominal and Radiological Devices (DRARD)
Gastroenterology and Renal Devices Branch (GRDB)
WO66 G228
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
(301) 796-6517
jeffrey.cooper@fda.hhs.gov

From: Miller, Kae [mailto:Kae.Miller@us.gambro.com]
Sent: Monday, July 12, 2010 6:44 PM

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

To: Cooper, Jeffrey (CDRH)
Subject: GamCath K100451Request for Additional Information Today

Dr. Cooper:

I would like to clarify your last request from our telephone call today:

(b)(4)

Thank you,

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.
14143 Denver West Parkway, Suite 400
Lakewood, CO 80401
Direct: 303.222.6724
Main: 303.222.6500
Fax: 303.222.6916
Cell: 303.249.2211

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Annex 6-1

Below we provide the label

<u>No Alcohol Label</u>

of the predicate device in K040301:

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

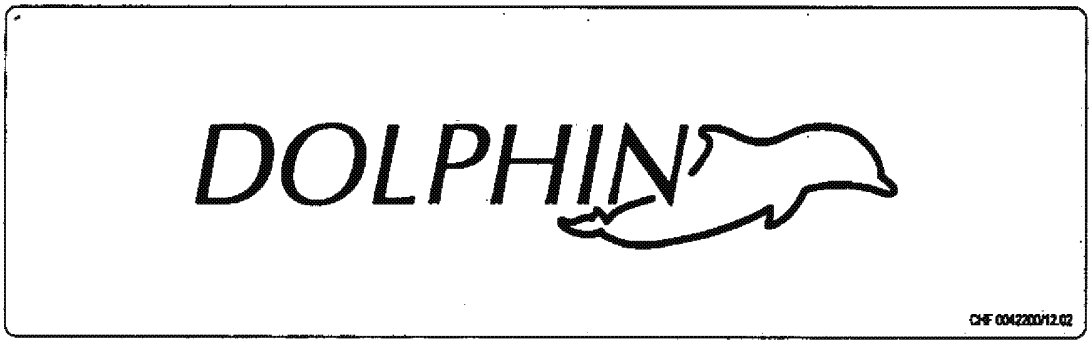
Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Annex 6-2

Below we provide the label

Dolphin Adhesive Label

of the proposed device:



(b)(4)

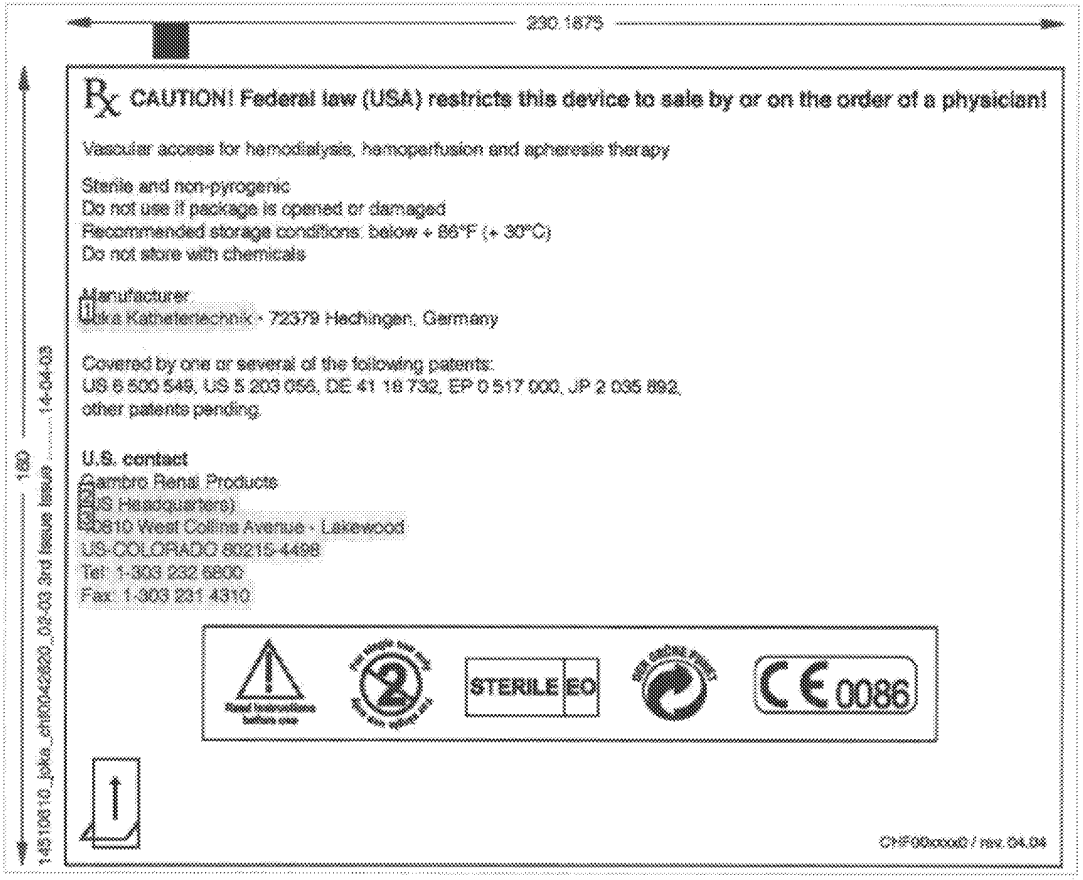
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Annex 6-3

Below we provide the label Breather Bag Pouch

for the predicate device in K040301:



(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Vascular access for hemodialysis, hemoperfusion and apheresis therapy

Sterile and non-pyrogenic
Do not use if package is opened or damaged
Recommended storage conditions: below +30°C (+86°F)
Do not store with chemicals

Covered by one or several of the following patents: US 6 641 255, US 6 500 549, US 5 203 056, DE 41 18 732, EP 0 517 000, JP 2 035 892, other patents pending.

Gambro Katheterfechnik Hechingen • 72379 Hechingen, Germany
Made in Germany

CE 0086

Rx

STERILE EO

+30°C

REF

LOT

U.S. contact
Gambro Renal Products, Inc.
14143 Denver West Parkway, Suite 400
Lakewood, CO 80401

CHF0042840 / rev. 2010-05

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Vascular access for hemodialysis, hemoperfusion and apheresis therapy

Sterile and non-pyrogenic
Do not use if package is opened or damaged
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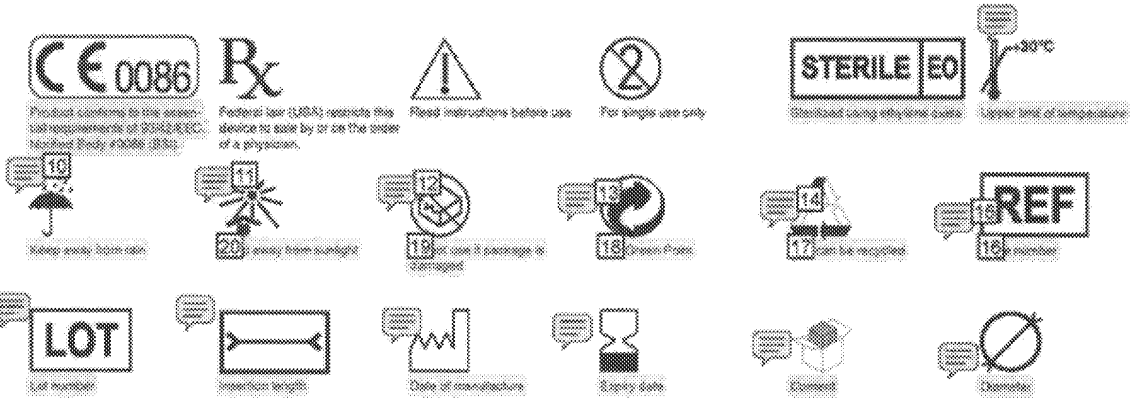
Covered by one or several of the following patents: US 5 941 255, US 6 500 549, US 5 203 056, DE 41 18 732, EP 0 517 000, JP 2 035 692, other patents pending.

Gambro Kathetertechnik Hechingen • 72379 Hechingen, Germany
Made in Germany

CE 0086

Rx

STERILE EO



U.S. contact
Gambro Renal Products, Inc.
14143 Denver West Parkway, Suite 400
Lakewood, CO 80401

CHP3042640 / rev. 2010-05

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Vascular access for hemodialysis, hemoperfusion and apheresis therapy

Sterile and non-pyrogenic
Do not use if package is opened or damaged
Recommended storage conditions: below +30°C (+86°F)
Do not store with chemicals

Covered by one or several of the following patents: US 6 841 255, US 6 500 549, US 5 203 056, DE 41 18 732, EP 0 517 000, JP 2 035 892, other patents pending.

Manufacturer

Gambro Katheterfachtrik Hechingen • 72379 Hechingen, Germany
Made in Germany

CE 0086

Rx

Federal law (USA) restricts this device to sale by or on the order of a physician.

Read instructions before use

For single use only

STERILE EO

Sterilized using ethylene oxide

<30°C

Upper limit of temperature

21 Keep dry

Keep away from sunlight

Do not use if package is damaged

Use no hooks

REF

Catalogue number

22 LOT

Lot number

23 Effective length

24 Date of manufacture

25 31 Volume

26 30 Blood flow

27 28 Venous pressure

D

Part name

U.S. contact
Gambro Renal Products, Inc.
14143 Denver West Parkway, Suite 400
Lakewood, CO 80401

CHF0042640 / rev. 2010-05

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Vascular access for hemodialysis, hemoperfusion and apheresis therapy

Sterile and non-pyrogenic
Do not use if package is opened or damaged
Recommended storage conditions: below +30°C (+86°F)
Do not store with chemicals

Covered by one or several of the following patents: US 6 641 255, US 6 500 549, US 5 203 056, DE 41 18 732, EP 0 517 000, JP 2 035 892, other patents pending.

Gambro Kathetertechnik Hechingen • 72379 Hechingen, Germany
Made in Germany

CE 0086

Rx

STERILE EO

+50°C

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

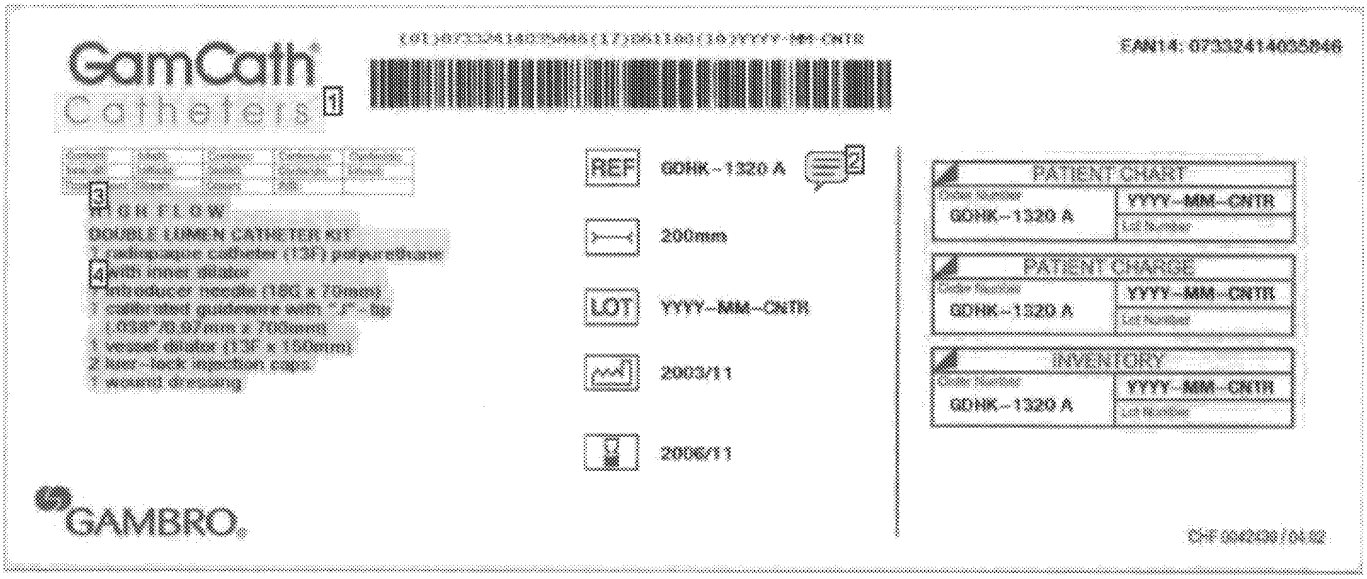
Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Annex 6-4

Below we provide the label

Individual adhesive label with variable data

for the predicate device in K040301:



(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

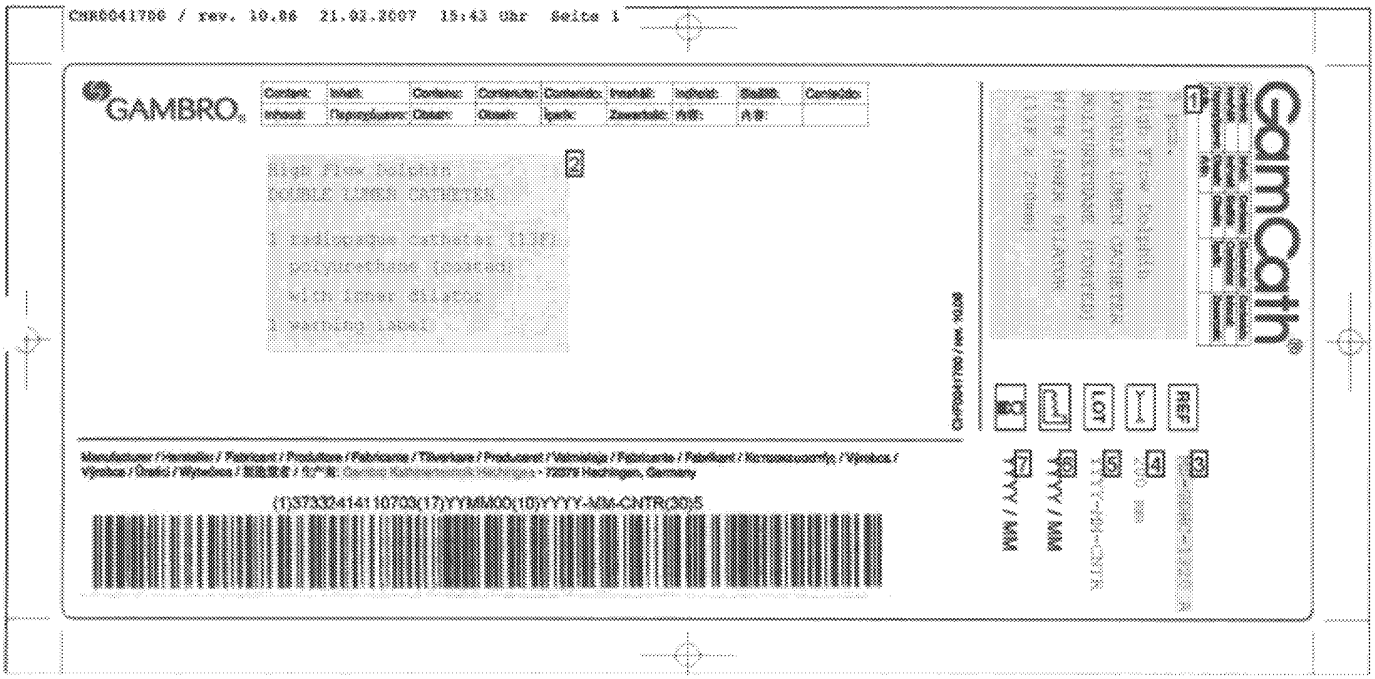
Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Annex 6-5

Below we provide the label

Box adhesive label with variable data

for the predicate device in K040301:



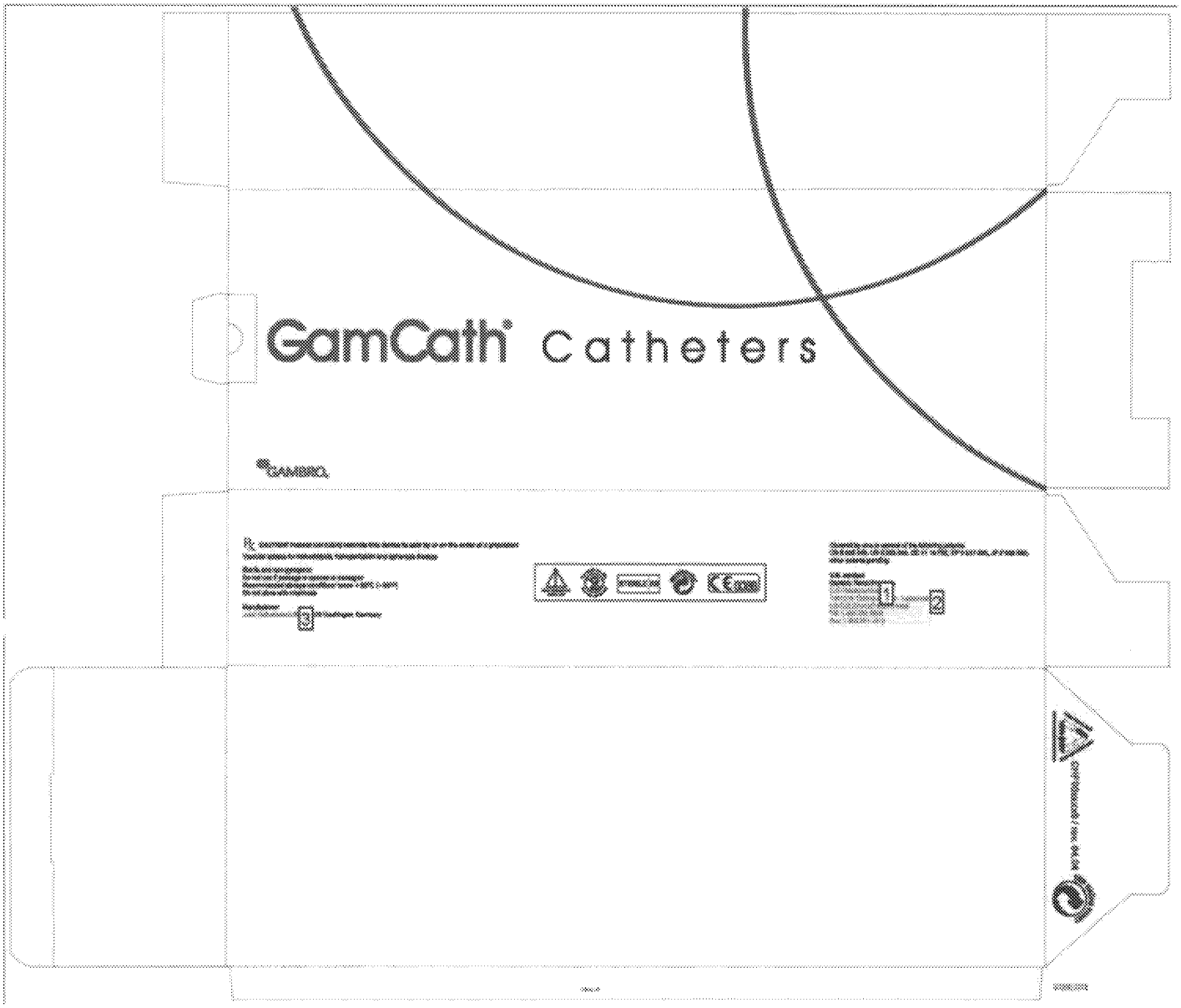
(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Annex 6-6

Below we provide the label Carton Box for the predicate device in K040301:



(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

2 90

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center ¿ WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

December 08, 2010

GAMBRO RENAL PRODUCTS, INC.
14143 DENVER WEST PARKWAY SUITE 400
LAKEWOOD, COLORADO 80401
UNITED STATES
ATTN: KAE MILLER

510k Number: K100451

Product: GAMCATH HIGH FLOW DOLPHIN

The additional information you have submitted has been received.

We will notify you when the processing of this submission has been completed or if any additional information is required. Pleaseremember that all correspondence concerning your submission MUST be sent to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. On August 12, 2005 CDRH issued the Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s. This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so in 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.

Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely,

510(k) Staff

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Document processed under FDA Request 2013-3902, Released by CDRH on 05-13-2014

RuD
10078236 RDe
ID 3778

Artificial Organs
16(2):146–150, Blackwell Scientific Publications, Inc., Boston
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Antithrombogenicity of Polyacrylonitrile–Polyethyleneoxide Hollow Fiber Membrane Developed for Designing an Antithrombogenic Continuous Ultrafiltration System

Masaaki Arakawa, Ikuo Aoike, Yasushi Sizuki, Fumitake Gejyo, *Ryozo Terada, *Hiroyuki Sugaya, *Takayuki Takeyama, and *Tetsunosuke Kunitomo

Department of Medicine (II), Niigata University School of Medicine, Niigata, Japan, and
**Basic Research Laboratories, Toray Industries, Inc., Kamakura, Japan*

Abstract: To develop a continuous arteriovenous hemofiltration (CAVH) system, which does not need systemic anticoagulation, for patients of acute renal failure having bleeding tendencies, a totally antithrombogenic continuous ultrafiltration system (ACUS) was designed, which consists of an antithrombogenic polyacrylonitrile–polyethyleneoxide (PAN–PEO) hollow fiber membrane and ionically heparin-bound catheter, tubing, and module header. Antithrombogenicity of PAN–PEO membrane, which occupies more than 90% of total inner surface area of ACUS, was considered to be due to highly concentrated PEO near the inner surface of the membrane and the finely dispersed (less than 500 Å) microstructure of the inner surface. ACUS was applied to 24 patients without systemic anticoagulation, and one filter worked for an average of 32 h without deteriorating their bleeding tendencies. Any significant changes in major parameters of biocompatibility during those treatments were not observed. More than 200 ml/h of ultrafiltrate was obtained even under very low mean blood pressure, less than 70 mm Hg. Based upon these results, ACUS was concluded to be suitable for mild and sustained treatment to control fluid and electrolyte balance in patients of acute renal failure with bleeding complications. **Key Words:** Antithrombogenicity—Biocompatibility—Hemofiltration—Heparinized surface–PAN–PEO membrane.

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Takekoshi Y. IgA nephritis in Behçet's disease: Case report and review of the literature. *Clin Nephrol* 1990; 34: 52–55
34. Tietjen DP, Moore WJ. Treatment of rapidly progressive glomerulonephritis due to Behçet's syndrome with intravenous cyclophosphamide. *Nephron* 1990; 55: 69–73
35. Hamuryudan V, Yurdakul S, Kural AR, İnce U, Yazici H. Diffuse proliferative glomerulonephritis in Behçet's syndrome. *Br J Rheumatol* 1991; 30: 63–64
36. Suemitsu T, Saga T, Inui A, Ariizumi M, Shogi E, Sato H. A ciclosporin A responsive case of Behçet's disease associated with IgA nephropathy. *Nippon Jinzo Gakkai Shi* 1993; 35: 189–194
37. Yang CW, Park IS, Kim SY *et al.* Antineutrophil cytoplasmic autoantibody associated vasculitis and renal failure in Behçet disease. *Nephrol Dial Transplant* 1993; 8: 871–873
38. Khan IH, Catto GRD, MacLeod AM. Antineutrophil cytoplasmic autoantibody associated vasculitis and renal failure in Behçet's disease. *Nephrol Dial Transplant* 1994; 9: 332
39. Akiyama Y, Suzuki T, Tanaka M *et al.* A case of Behçet's disease associated with aortic regurgitation and nephrotic syndrome. *Ryumachi* 1995; 35: 910–914
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Microdomain structure of polymeric surfaces—Potential for improving blood treatment procedures

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Continuing progress in improving the results of blood purification techniques requires, amongst others, an interdisciplinary approach applying innovative technologies to integrate the expertises of biotechnology and polymer science. In the following we wish to provide some novel insights into how the physicochemical structure of membranes impacts the interactions with blood components during membrane contact.

What triggers proinflammatory and procoagulatory signals during blood–material contact?

Briefly, the complement system, which is phylogenetically the oldest mechanism in the human body to discriminate between 'self' and 'non-self' structures, is activated by the molecular interaction of the C3 component with artificial surfaces containing hydroxyl (OH) or amino (NH_2) groups. A local imbalance—outside the body in the extracorporeal system—between activating and inhibiting proteins at the polymeric surface is the central step in the activation of the complement cascade. This has been clearly shown in detail e.g. for OH-containing cellulose and polyvinylalcohol (PVA) membranes, which are strong complement activating surfaces. In general, it is reasonable to conclude that the prevention of the interaction of C3 molecules with a polymeric surface by omission of nucleophilic groups at the surface is a powerful approach to limit complement turnover via the alternative pathway to a minimum. As a second requirement, polymeric surfaces should neither adsorb IgG, IgM, C1, C2, C4 complement components, nor derived complexes, to avoid activation of complement via the classical pathway [1,2].

Another relevant activation principle in extracorporeal blood circuits is the kallikrein–kinin system, i.e. the contact phase or intrinsic pathway of the coagulation system. It involves plasma proteins such as factor XII, prekallikrein (PK) and high molecular weight kininogen (HMWK) in the first activation step. It is documented that the presence of negatively charged groups on surfaces leads to an acceleration of contact phase activity [1,3]. Through this mechanism negatively charged dialysis membranes, glass surfaces and dextrane sulphate containing adsorber devices can generate severe clinical symptoms, i.e. vasodilation, hypotension, and bronchoconstriction. This foreign surface dependent activation principle is of special importance when the decay of the kininogen split product brady-

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kinin is blocked by angiotensin-converting enzyme (ACE) inhibitor medication. Briefly, the omission of negatively charged groups in polymers should have beneficial effects on the overall biocompatibility properties [1,3].

Since the first days of dialysis [4] it has not been possible to circulate blood outside the body without the use of anticoagulant drugs. Heparin is used to block in complex with the ATIII molecule at different levels of the intrinsic pathway of the coagulation system. The biochemical prerequisite to reduce coagulation via the intrinsic pathway is the lack of contact phase activity described above, since activated factor XII (XIIa) is the first intermediate product in the coagulation cascade which can be inhibited by ATIII. Further down the intrinsic pathway, i.e. at the stage of the factors XIa, IXa, Xa and IIa (thrombin), ATIII and ATIII-heparin complexes act as efficient inhibitors. Today, many observations suggest that the procoagulatory state after blood–membrane contact is the result of an initial event, e.g. contact phase activation, and a dysregulation of the inhibitory mechanisms in the coagulation system [1].

The coagulation cascade is further stimulated by tissue or platelet derived procoagulatory factors, which are not counterbalanced in the local environment of the extracorporeal circuit due to a lack of fibrinolytic activity, which is mainly dependent on endothelial cells. It is important to note that unopposed procoagulatory activity without any endothelial fibrinolysis activity is found during a period of 20–40 s, which is the period the blood requires to be perfused through the extracorporeal circuit during a routine dialysis procedure.

The wide reaction pattern of platelets is certainly an important determinant of thrombocyte activation by foreign surfaces. Following a general classification of polymeric surfaces according to their interaction with platelets proposed by Matsuda [3], positively charged and hydrophobic surfaces are the most active ones, but surfaces with electron acceptor and electron donor forces exhibit significant activation properties, too.

Which interactions during blood–material contact could be then acceptable, when polar hydroxyl-groups containing surfaces with known platelet compatibility should be excluded due to a strong complement activation potential?

Unspecific interaction of plasma proteins with artificial membranes and related deposition of cells through receptor binding or direct interference with the cellular membrane are able to initiate bioincompatibility reactions at a synthetic surface, and should be excluded to prevent activation of plasma and cellular components in blood.

Last, but not least, mononuclear cells and granulocytes have to be taken into consideration to fully assess the reaction patterns induceded by contact of blood with foreign surfaces. At first, monocyte and granulocyte activation is triggered by complement activation, since C3a, C5a, metastable C3/C3b, and terminal complement complexes are strong activation signals. These mediators are able to induce cytokine release and induce second messenger signals, thus initiating an autocrine activation loop. Ideally, a biocompatible surface should not cause cell adhesion, neither by direct physicochemical interaction, e.g. providing ligands for receptor interaction, such as L-fucose, which is present in cellulosic materials nor by proteins adsorbed to the artificial surface [2,5].

The different activation pathways involving plasmatic components and cells act synergistically to initiate bioincompatibility reactions. At this point, the following questions arise: (i) can artificial polymer surfaces be found that meet the requirements—as defined above—and prevent activation and (ii) can such materials be found by rational design from synthetic origin?

We reasoned that a broad limitation of protein and cell activation by tailor-made synthetic materials with a microdomain structure could be a reasonable approach. In principle, such heterogenous microdomain polymer structures should be less activating, if they are composed of non-charged polymers without nucleophilic groups [6,7].

Why are microdomain-structured synthetic polymer surfaces less activating?

The activation of plasmatic systems can be efficiently avoided by omission of chemical structures which are involved in the initial activation steps. However, can one avoid non-specific protein adsorption and cell adhesion, which cause activation?

First, proteins are macromolecules consisting of patches with opposing physicochemical properties, i.e. anionic or cationic areas, hydrophobic or hydrophilic moieties etc. They contain specific peptide motifs acting as specific ligands for cell receptors or binding proteins (Figure 1). Structural investigations indicate that the

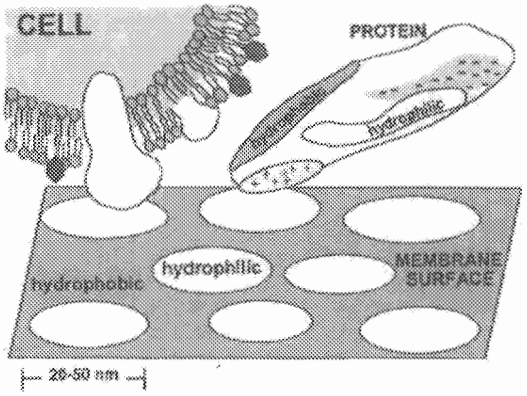

Fig. 1. Scheme of the local microenvironment of hydrophilic–hydrophobic surfaces in contact with blood components. The plasma membrane of the cell is illustrated according to the 'fluid mosaic' model [2].

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dimensions of such protein domains are in the nanometer range.

Second, cell membranes are not homogenous with a uniform specific pattern of interactions. Rather, according to Singer and Nicolson [8] the cell membrane architecture is well described by the 'fluid mosaic' model. The plasma membrane consists of heterogenous mosaic-like structures mainly composed of glycoproteins and phospholipids. These are not assembled in a rigid network, rather, most of the components display considerable lateral mobility. Consequently, membrane glycoproteins can form clusters which are involved in interactions with the environment. Ligand-induced cluster formation, so called 'patching' or 'capping' is thought to trigger transmembrane activation signals and intracellular reactions. Interactions of the microdomains in the cell membrane with the surface of a polymeric medical device, may affect cellular functions, such as (i) active transport and permeability, (ii) recognition and communication, (iii) cell movement and shape, and (iv) membrane synthesis and turnover [9]. All cell membranes share the following structural characteristics: (i) they are composed of a central hydrophobic core which functions as a barrier and (ii) they have hydrophilic external domains, i.e. integral membrane proteins mediating controlled permeability, transport and activation. According to the Singer's 'fluid mosaic' model (Figure 1) cell membranes consist of regions of phospholipid bilayers containing a varying composition of proteins. In addition, the outer surface is 'decorated' by the oligosaccharide moieties of glycoproteins and glycolipids, the so called 'glycocalyx', which may have specific binding properties involved in signal transmission. The lateral extension of the hydrophilic and hydrophobic domains of the cell membrane is in the nanometer range.

On the basis of the above background, several groups could detect reduced cell adhesion and activation after interaction of blood components with polymer systems in microdomain configuration, i.e. block-copolymers existing of hydrophilic and hydrophobic moieties. It is of historical interest that the beneficial effects of micro-separated polymer systems were first described by Lyman in 1974 [10], some years after Singer and Nicolson introduced the 'fluid mosaic' as model for cell membranes. The same line of research was later pursued by several Japanese authors [11–13].

Considering that cell membranes are dynamic and highly reactive, interactions between cells and material surfaces must take place at multiple distinct points. This leads to lateral movement of integral membrane proteins. The kind and extent of rearrangement of membrane components following contact with an artificial polymer system strongly affect cell functions, i.e. change of shape, permeability and transduction of activation signals. It is obvious that physicochemical microheterogeneity of polymeric substrates could play a crucial role in the activation of cells. A microdomain structure of artificial polymer surfaces yields an optimal 'trade-off' between undesirable effects of hydrophobic surfaces, i.e. strong adsorption of proteins and cells, and the undesirable effects of hydrophilic surfaces, i.e. polar or nucleophilic endgroups causing platelet adhesion, activation of complement and kallikrein-kinin system.

Is it possible to predict the dimension of the domains required to limit activation of proteins and cells?

To approach this issue, we will try to analyse what happens to macromolecular proteins or cell membranes (composed of phospholipids and glycoproteins) when they approach an artificial polymer system exhibiting a microdomain structure (Figure 1). If the size of a hydrophobic domain is below a critical threshold, the probability for stable hydrophobic interaction between the synthetic material and the macromolecules is sharply decreased, since the critical threshold value of free energy for a stable interaction is not reached. Basically the same thermodynamic considerations apply for hydrophilic or polar interactions. As a result, there will be no (or only limited) rearrangements in the cell membrane and consequently reduced cell activation. In other words, if the domains of the synthetic surface are in the range of nanometers, they fail to interact with the microdomains of the cell membranes.

How can such synthetic surfaces with microdomain structure be constructed?

The basic principles underlying the construction of such interfaces are based on colloid chemistry, a discipline at the interface between physics, chemistry, biology and technology [14]. It is interesting that Charles Sadron's pioneering work on the formation of 'organized structures' by block-copolymers was published in 1962 [15], 10 years before the 'fluid mosaic' model for cell membranes was proposed [8,9].

In a series of papers Okano *et al.* [11] described in detail hydrophilic–hydrophobic block-copolymer systems synthesized from hydroxylethylmethacrylate (HEMA) and dimethylsiloxane (DMS). They are characterized by variable effects on platelet activation and adhesion depending on microdomain size. The authors concluded that the inhibitory effect on platelet activation was most pronounced when the size of the domains in the polymer surface was in the order of 10 nm. Yui *et al.* [12] described reduced thrombogenicity of microdomain surfaces consisting of crystalline and amorphous regions of polypropyleneoxide (PPO)-polyamide block-copolymer. A closer look at the microstructure of this surface by X-ray-analysis reveals that the crystallites have a lateral extension of approx. 6 nm and 12 nm, respectively. Other examples for microdomain structured materials are different types of segmented polyurethanes which are used e.g. in vascular grafts or as components in the artificial heart or in left ventricular assist devices. The diversity of chemical structures which are able to form microdomains is illustrated by the use

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of polypeptide sequences in block-copolymer chains allowing biospecific molecular recognition [13].

What is the experience with blood purification using microdomain forming block-copolymers and polymer alloy systems?

Over the past years we accumulated experience with a polycarbonate-polyether block-copolymer used for the manufacturing of the low flux membrane Gambrane®, and with microdomain forming polymer alloy systems, i.e. polyamide–polyvinylpyrrolidone, polyamide–polyarylethersulfone–polyvinylpyrrolidone and polyarylethersulfone–polyvinylpyrrolidone in high and low flux membranes (Figure 2) [2,6,7]. Recently, we could improve the thrombogenic properties of bloodline systems by blending the base material polyvinylchloride with a polycaprolactone–polysiloxane block-copolymer during the injection moulding or extrusion process. Polycaprolactone–polysiloxane block-copolymer is known to form domain structures with a lateral extension in the range of 10 nm [16]. The domain morphology of block-copolymers or of polymer blends is the result of steric or chemical incompatibilities of chemically different polymer blocks or segments.

From the technological point of view polymer surfaces in the target range of microdomain size and distribution were found by systematic variation of thermodynamic key factors, i.e. temperature during processing, concentration of different polymer components, molecular weight of additives, and composition of solvents. For the manufacturing of microdomain structured dialysis membranes an optimal trade-off between desirable permeability features and hydrophilic–hydrophobic domain architecture had to be found. The hydrophobic polymer components (polyamide and/or polyarylethersulfone) contribute to the stability of the membrane morphology, whereas the hydrophilic component (polyvinylpyrrolidone) integrates diffusive permeability, the porous structure, and the hydrophilic microdomains in the blood-contacting surface.

The critical parameters for optimizing performance are size and distribution of the domains and their stability during different production steps, e.g. rinsing and high-energy sterilization. Arakawa *et al.* [17] also developed a membrane consisting of polyacrylonitrile–polyethyleneglycol block-copolymer exhibiting nanometer sized microdomain structure, which was associated with suppression of prothrombotic activity.

The technical development of the above polymer surfaces in our laboratories has primarily been guided by *in vitro* assay systems using human blood components to evaluate the effects on complement, contact phase, mononuclear cell activation and thrombogenicity. Such bioassays are particularly important, since analytical visualization of polymer structures in the nm-range is a complicated and costly exercise [7]. In systems with neutral polymers it was possible to significantly reduce thrombogenicity and cell activation by microdomain

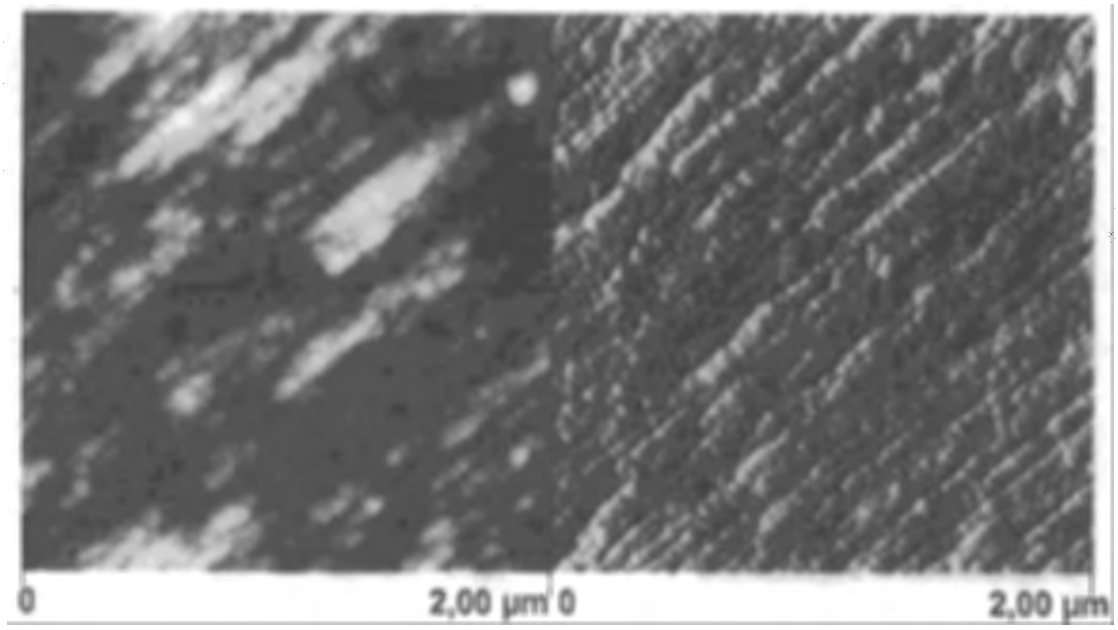

Fig. 2. Atomic force microscopy analysis of a polyamide–polyarylethersulfone–polyvinylpyrrolidone membrane (Polyflux™) using a technique in 'tapping' mode (courtesy of Dr Georg Bar, Material Research Center, University Freiburg, Germany).

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configuration, whereas the low complement and contact phase activation properties remained unchanged.

Figure 3 describes an illustrative experiment: freshly isolated human mononuclear cells were cultivated in protein-free media under identical conditions either on regenerated cellulose, i.e. a homogenous hydrophilic polymer surface, or on polycarbonate–polyether block-copolymer, i.e. a hydrophilic–hydrophobic polymer membrane. The purely hydrophilic surface clearly induced cell spreading and in addition, cell activation as indicated by increased intracellular free calcium or release of cytokines. In contrast, on the hydrophilic–hydrophobic microdomain surface no cell spreading and significantly lower cell activation signals were found. The density of cells accumulating on the polycarbonate–polyether membrane surface was less, although the sedimentation forces were identical in the two parallel incubations. This observation points to differences in the repulsive forces acting on cells when they move towards a conventional homogenous and a micro-domain structured surface, respectively. The existence of microdomains in the above materials has been directly visualized (i) by selective staining of polymer components followed by back-scatter scanning electronmicroscopy [7] or (ii) by the recently introduced technique of atomic force microscopy (Figure 2).

Are there alternative approaches to improve biocompatibility of surfaces?

Beside the microdomain approach two other major research lines have recently been pursued to improve

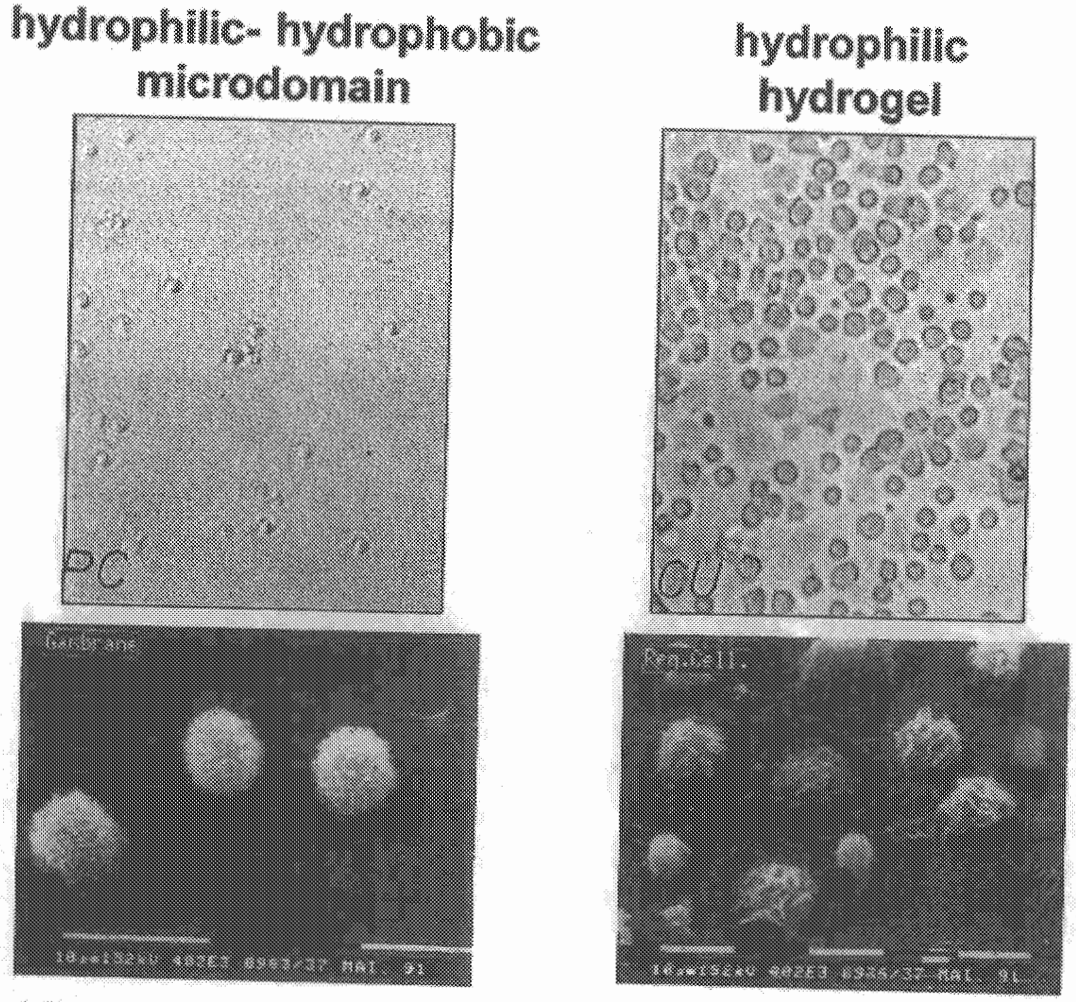

Fig. 3. Electron microscopic visualization of mononuclear cells on hydrogel-type regenerated cellulose (right panel) in contrast to microdomain structured polycarbonate–polyether (Gambrane®) low flux dialysis membranes (left panel).

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polymer surfaces for medical devices: (i) grafting or coating with phospholipid molecules to mimic the non-thrombogenic properties of the erythrocyte membrane [18] and (ii) derivatization of surfaces with biological molecules exhibiting specific inhibition of the coagulation cascade, i.e. heparin, hirudin, or endothelial cell-derived heparan sulfate molecules [19]. Attempts to heparinize surfaces have a long history, but a convincing breakthrough for medical application has not been achieved so far. This is due to the unsatisfactory antithrombogenic properties of the materials so treated and technological difficulties in producing such surfaces. There are a number of reports on *in vitro* and *in vivo* applications of different phospholipid-coated artificial surfaces. This approach is elegant and promising. It has not been shown, however, whether such purified or synthetic phospholipids also form a microdomain-like structure. In the long run, technological problems, i.e. issues whether such materials can be mass-produced under industrial conditions, will decide whether these approaches will be more widely used in (bio)materials for medical therapy.

Summary and perspectives

The experience accumulated from *in vitro* observations and from clinical application points to several benefits of microdomain polymer systems. First, as far as technology is concerned, microdomain-structured substrates can be manufactured using techniques without hazardous additives or solvents. In clinical application, the major advantage is the reduced thrombogenic potential and consequently the lower heparin requirement. This is of particular importance for extracorporeal devices in intensive care medicine. The potential clinical benefit of reduced complement and cell activating properties is currently less obvious, but common sense would indicate that such properties will certainly not hurt. So far, haemodialysis and related blood purification procedures are the main medical applications of artificial polymer materials exhibiting microdomain structured surfaces. However, there is certainly some room left for potential further improvements. On the horizon there are applications for 'upcoming' therapies, e.g. *ex vivo* stem cell culture or specific ligand based purification techniques.

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Conflict of interest acknowledgement. The authors were actively involved in microdomain polymeric material and membrane development in Gambro Group Research laboratories during the past decades.

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(12) **United States Patent**
Deppisch et al.

(10) **Patent No.: US 6,841,255 B2**
(45) **Date of Patent: Jan. 11, 2005**

(54) **BIOCOMPATIBLE POLYMER FILM**

(75) Inventors: **Reinhold Deppisch**, Hechingen (DE); **Ulrich Bauer**, Hechingen (DE); **Werner Beck**, Rottenburg (DE); **Ruth Dietrich**, Hechingen (DE); **Hermann Göhl**, Bisingen-Zimmern (DE); **Katja Krämer**, Reutlingen (DE)

(73) Assignee: **Gambro AB**, Stockholm (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/245,115**

(22) Filed: **Sep. 17, 2002**

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(51) **Int. Cl.**[7] **B32B 25/20**
(52) **U.S. Cl.** **428/425.5**; 525/447; 525/474; 525/464; 525/453; 428/411.1; 528/28; 528/59; 528/65
(58) **Field of Search** 428/425.5, 411.1; 525/447, 474, 464, 453; 528/28, 59, 65

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(57) **ABSTRACT**

The present invention includes a co-polymer film which can be applied over a surface of an article to form a continuous surface that is more biocompatible and has a smoother surface morphology than an untreated article. In general the co-polymer film of the invention can be formed by providing a hydrophobic polymer block, such as polydimethylsiloxane (PDMS) with functional —OH end groups and reacting the —OH ends with a conventional monomer or prepolymer of a film-forming polymer capable of reacting with —OH groups. Such reactions are exemplified, using as reactive PDMS a triblock copolymer of the polylactone-polysiloxane-polylactone (PL-PDMS-PL) type, or silicone polyesters. The —OH groups of the polylactone blocks can react with any of a variety of isocyanates in a suitable solvent to form a polymer having PDMS incorporated with its structure. The film can be applied to the surface of an article by any convenient means of coating the article with the reaction mixture in solvent, and allowing the solvent to evaporate.

16 Claims, 4 Drawing Sheets

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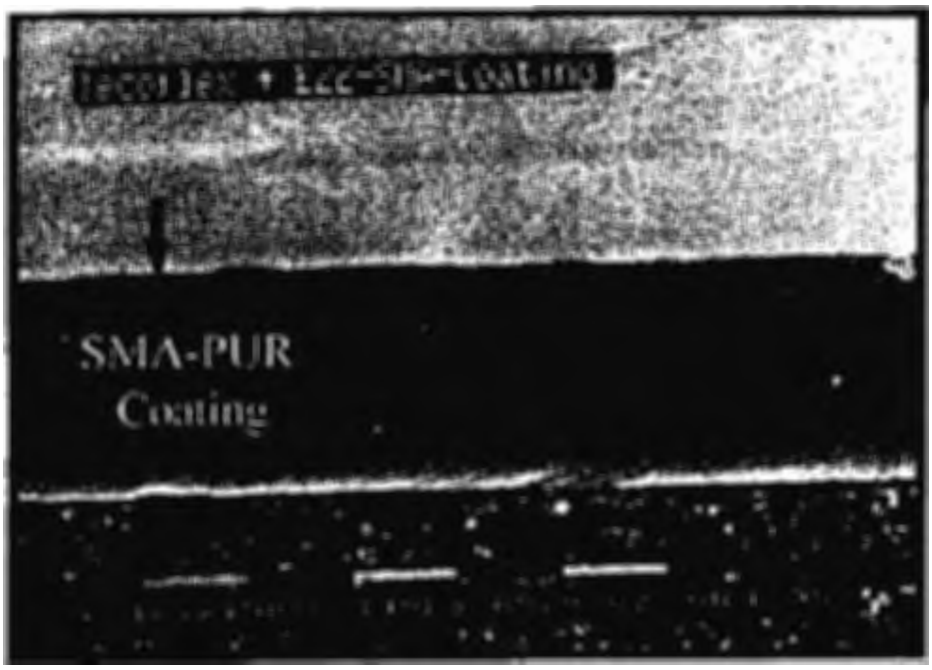

FIG. 1

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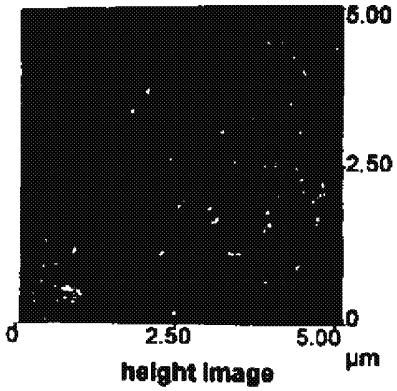
FIG. 2A

FIG. 2B

PUR (1 comp)



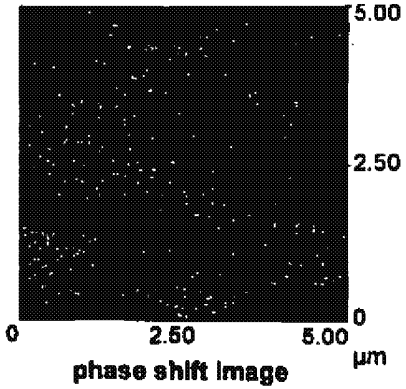
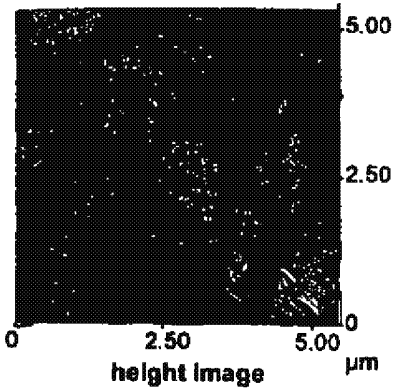


FIG. 2C

FIG. 2D

PUR (1 comp) with SMA



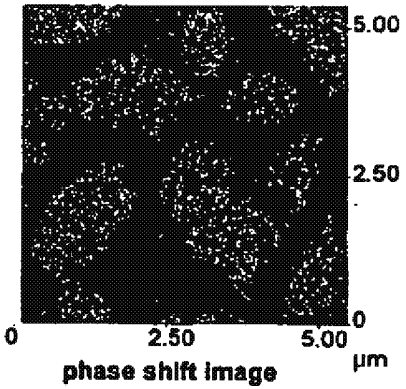


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FIG. 3A

FIG. 3B

PUR
(2 comp)

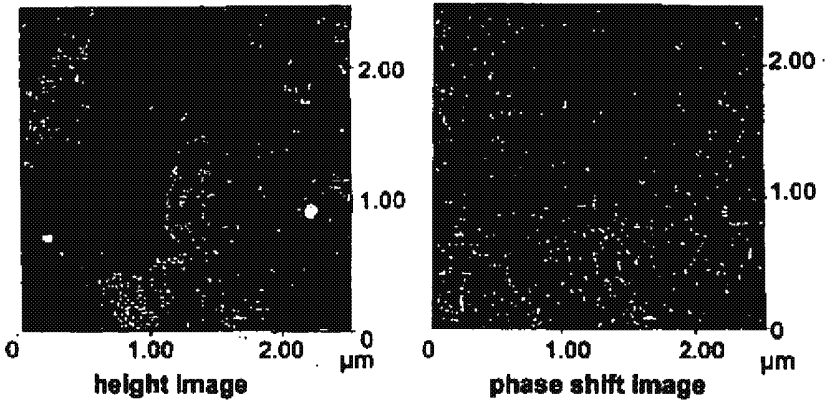
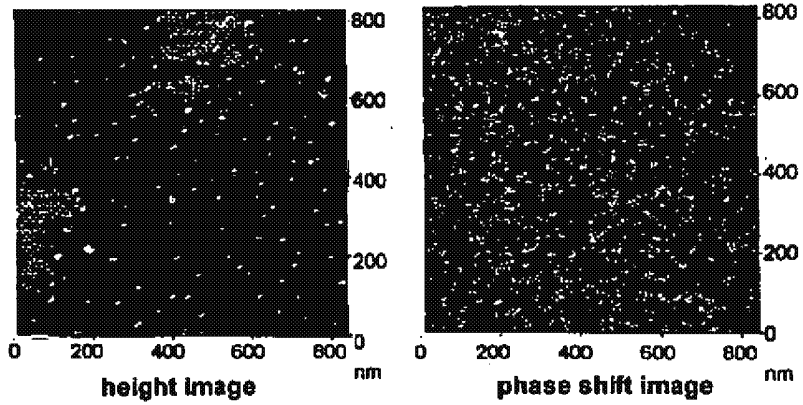


FIG. 3C

FIG. 3D

PUR (2 comp)
with SMA



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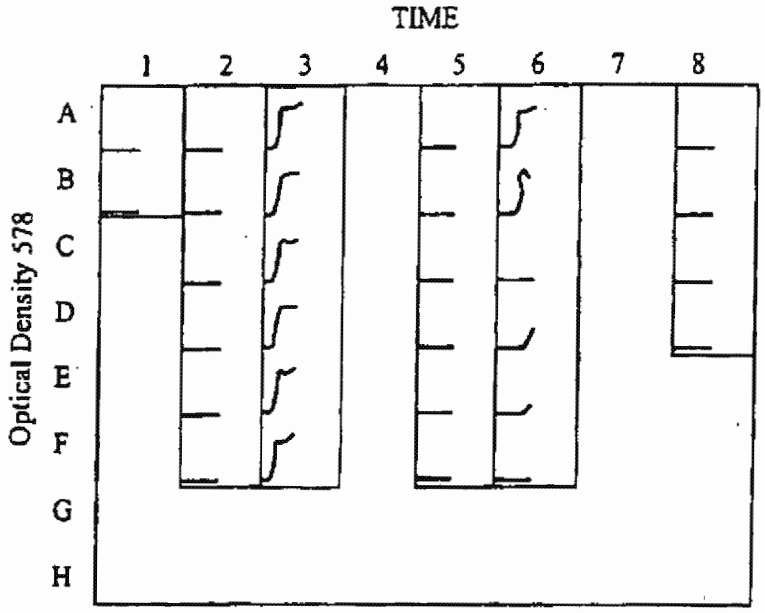

FIG. 4

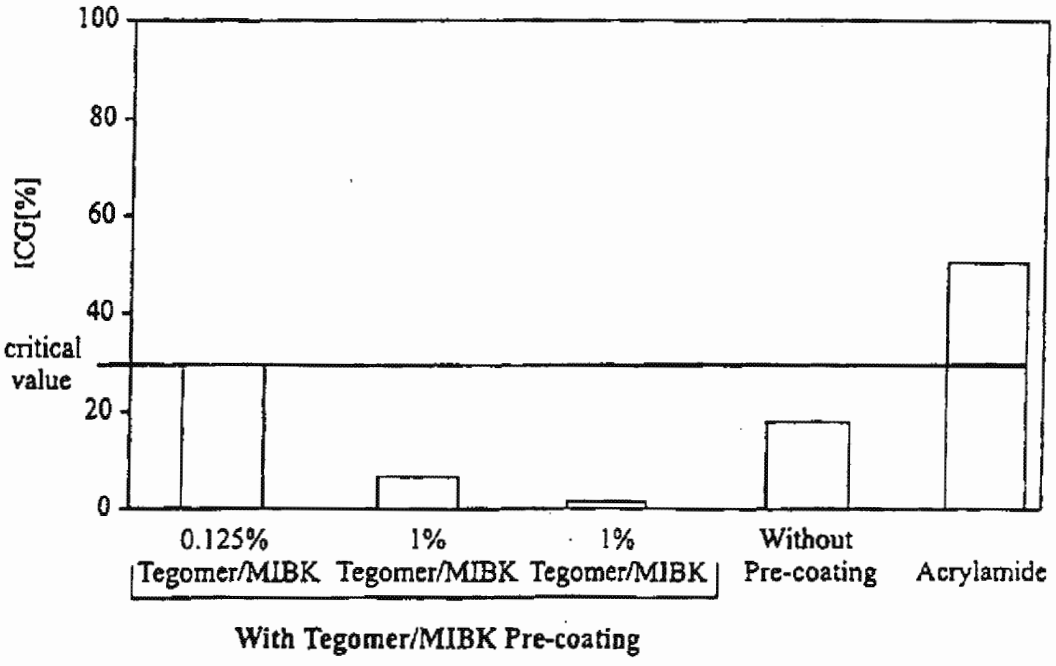

FIG. 5

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BIOCOMPATIBLE POLYMER FILM

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of U.S. patent application Ser. No. 09/415,943 filed Oct. 8, 1999, now U.S. Pat. No. 6,500,549, which claims priority from U.S. Provisional Application No. 60/104,001 filed Oct. 13, 1998.

BACKGROUND OF THE INVENTION

The present invention relates to the basic problem that many of the biomedical devices used in contact with live tissue or body fluids are made of materials of synthetic or natural origin which are not biocompatible. Lack of biocompatibility can lead to blood clotting as well as various other manifestations of inflammation and tissue activation.

In addition, microbial infection can establish themselves on device surfaces. Infectious agents such as bacteria that colonize and form biofilms on surfaces can prove exceedingly difficult to eradicate, [Costerton, J. W. et al. (1999) *Science* 284:1318–1322]. Devices intended for long-term contact such as implanted stents or indwelling catheters can also serve as a surface for host cell adhesion, permitting host cells to become activated, proliferate or to alter normal physiological function and to restrict function or intended use of a device, for example by restricting fluid flow through the device.

An approach used in the prior art to improve biocompatibility has been based on modifying the surface of a device to make it more hydrophobic. On the other hand increased biocompatibility at least in part can be achieved by making a surface more hydrophilic. Although certain types of polymers, such as silicones and siloxanes, are known to possess many attributes of biocompatibility, there are no reliable physical correlates which enable one to predict biocompatibility with any degree of certainty. Generally, hydrophobic surfaces are more biocompatible than hydrophilic surfaces. Zisman's critical surface tension [Zisman, W. A., (1964) *Adv. Chem: Ser.* 43] has been used as a parameter to help assess potential biocompatibility. Materials with an optimum critical surface tension are frequently biocompatible, yet there are notable exceptions. For example, polyethylene and polypropylene have critical surface tensions well within the optimum range, but they are not predictably biocompatible. Other factors are also important. Without a clear understanding of the nature of these factors, biocompatibility remains unpredictable.

Because of the attractive structural properties of polyolefins and polyurethanes, various blending and copolymerization techniques have been developed to impart greater biocompatibility. U.S. Pat. No. 4,872,867 discloses modifying a polyurethane with a water soluble polymer and crossing them in situ with a silane-type coupling agent to form a cross-linked and intertwined polysiloxane network. U.S. Pat. No. 4,636,552 discloses a polydimethyl siloxane with polylactone side chains which are said to be useful for imparting biocompatibility when combined with a base polymer, or used to replace plasticizer. U.S. Pat. No. 4,929,510 discloses a diblock copolymer having a more hydrophobic block and a less hydrophobic block. A solution of the diblock copolymer in a solvent which swells the matrix polymer is used to introduce the diblock into an article of matrix polymer. Thereafter, the article is transferred to water, to force orientation of the incorporated diblock copolymer such that the more hydrophobic block is embedded in the matrix and the less hydrophobic block is exposed

on the surface of the article. Examples of diblock copolymers included poly (ethyleneoxide-propylene oxide), N-vinyl-pyrrolidone-vinyl acetate and N-vinyl-pyrrolidone-styrene. U.S. Pat. Nos. 4,663,413 and 4,675,361 disclose segmented block copolymers, in particular polysiloxane-polycaprolactone linear block copolymers. The latter were incorporated into base polymer material to modify the surface properties thereof. Although initially blended in bulk into the base polymer, the copolymer migrates to the surface to form an exceptionally thin, possibly a monolayer film which imparts the desired surface characteristic, specifically, biocompatibility.

Triblock copolymers having a polydimethyl siloxane (PDMS) block flanked by polylactone (PL) blocks have been described; Lovinger, A. J. et al. (1993) *J. Polymer Sci.* Part B. (*Polymer Physics*) 31:115–123. Such triblock copolymers have been incorporated into bulk formulations, and also applied as surface coatings, to reduce thrombogenicity, as described in U.S. Pat. No. 5,702,823, incorporated herein by reference. PL-PDMS-PL triblock copolymers are commercially available, for example from Thoratec Laboratories, Berkeley, Calif., which provides a series of such polymers designated "SMA" in which the siloxane is dimethyl siloxane and the lactone is caprolactone, and also from Th. Goldschmidt A G, Essen Germany, under the name "Tegomer" (Trademark, Goldschmidt A G). The nominal molecular weights (number average) of the polysiloxane blocks suitable for use herein range from about 1000 to about 5000, while the nominal molecular weights of the caprolactone blocks range from about 1000 to about 10,000. Tsai, C-C. et al (1994) *ASAIO Journal* 40:M619-M824, reported comparative studies with PL-PDMS-PL blended into polyvinyl chloride and other base polymers or applied as a coating thereon.

Deppisch, R. et al. (1998) *Nephrol. Dial. Transplant.* 13:1354–1359 reported improved thrombogenic properties for films or membrane structures of polyamide-polyvinylpyrrolidone, polyamide-polyarylethersulfone-polyvinylpyrrolidone or polyarylether-polyvinylpyrrolidone. Improved thrombogenic properties were attributed to a microdomain surface structure of hydrophobic and hydrophilic surface patches.

U.S. Pat. No. 5,589,563 discloses polymers having surface-modifying end groups, for example, polyurethanes having hard segments and soft segments covalently bonded to end groups such as PDMS or aromatic polycarbonates. The surface-modifying end groups tend to concentrate on the polymer surface to increase the surface hydrophobicity.

More recently, it has been recognized that the interactions between biological substances and man-made materials leading to clotting, inflammatory responses and microbial and host cell reactions are more complex processes in which the surface hydrophobicity of the man-made material is but one factor. Interactions between biological materials and foreign substances have been shown to include, at a minimum, molecular interactions with components of the complement system, with the kallikrein-kinin system, with the intrinsic pathway of coagulation initiation, with platelet and with other cellular components of blood including peripheral blood cells, e.g. monocytes and granulocytes.

In addition, microbial growth and host cell activation and/or proliferation on the polymer surface are problems with potentially serious consequences, especially for implanted or indwelling articles such as catheters and stents. The design of materials having improved biocompatibility must take such factors into account.

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SUMMARY OF THE INVENTION

The invention includes a co-polymer film and method for improving the biocompatibility of any article of synthetic/polymeric, organic or metallic origin intended to contact blood, tissue or body fluids in the course of a medical treatment or procedure. Such articles include, without limitation, tubing, bags, catheters, stents, probes, feeding tubes, drainage lines, vascular grafts, artificial shunts and the like whether intended for long-term or short-term contact with blood, tissue or other body fluid or their plasma or corpuscular and cellular constituents. The co-polymer film of the invention provides reduced thrombogenicity, reduced bacterial growth and adhesion, reduced toxicity to host cells, and infiltration and seeding with inflammatory cells or host cells, when compared to articles or materials in conventional use or without the polymer film described.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1—Scanning electron microscopy of a catheter tube cross section having $BaSO_4$ incorporated into the catheter material for enhanced x-ray contrast. The interior, blood contacting surface is uppermost. The arrow designates a PUR-SMA film applied to the inner surface of the base material.

FIG. 2—Atomic force microscopy scans of single component PUR (top row) and PUR coated with a PUR-SMA film. Left row shows height variations, right row shows phase variations associated with drag on the probe tip. Light and dark areas have different physico-chemical characteristics, the light areas indicating a more soft and hydrophilic surface character, the dark areas indicating a surface that is relatively hard, hydrophobic and associated with a higher surface concentration of PDMS.

FIG. 3—Atomic force microscopy comparing surfaces of a two component PUR (top row) and a coating of 2 component PUR with SMA. Height and phase images, left and right respectively, are as described for FIG. 2.

FIG. 4—Bacterial colonization of polyurethane test plates uncoated (row 3) and coated with PUR-PL-PDMS-PL film (row 2) and films of PUR (row 5) and Pul-PL-PDMS-PL coplymer (row 6). Horizontal axis:time (24 hrs. maximum); vertical axis, optical density at 578 nm. Letters along vertical axis identify separate test plates.

FIG. 5—Bar graph showing cell toxicity (inhibition of cell growth) of extracts of coated catheters with and without pre-coating as described below and in Example 8.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes a co-polymer film which can be applied over a surface of an article to form a continuous surface that is more biocompatible and has a smoother surface morphology than an untreated article. In general the co-polymer film of the invention can be formed by providing a hydrophobic polymer block, such as polydimethylsiloxane (PDMS) with functional —OH end groups and reacting the —OH ends with a conventional monomer or prepolymer of a film-forming polymer capable of reacting with —OH groups. Such reactions are exemplified, using as reactive PDMS a triblock copolymer of the polylactone-polysiloxane-polylactone (PL-PDMS-PL) type, or silicone polyesters. The —OH groups of the polylactone blocks can react with any of a variety of isocyanates in a suitable solvent to form a polymer having PDMS incorporated with its structure. The film can be applied to the surface of an article by any convenient means of coating the article with the reaction mixture in solvent, and allowing the solvent to evaporate.

A polymeric film having PDMS blocks incorporated within the polymer forms over the coated surface. The resulting film is mechanically stronger than coatings of PL-PDMS-PL alone. The film integrity makes it possible to encase any structure made of any material compatible with solvents used to dissolve the starting materials. Materials can be chosen for their optimal mechanical properties, then an article made of the desired material can be encased in a polymeric film of the invention to render the article biocompatible. The polymeric films of the invention are further advantageous in that they can reduce surface roughness which may exist in the article. As an example, in polyurethane-based catheters, barium sulfate is added to provide x-ray contrast. The barium sulfate increases the surface roughness, which can degrade the biocompatibility, induce flow turbulence or enhance cellular or microbial deposits. The polymer film applied to the catheter surface not only increases the biocompatibility by changing the chemical composition of the surface, but also by reducing the roughness of the surface. Other types of surface roughness, such as are introduced during fabrication, e.g. by injection molding or by extrusion or by thermal processes during tip shaping or by mechanical manufacturing steps such as mechanical or LASER based hole drilling, can be reduced by applying a polymer film of the invention.

Without intending to be bound by a particular theory of operation, data is provided herewith demonstrating that the polymer film of the invention has surface characteristics that are consistent with current understanding regarding biocompatible surfaces. Such current understanding takes note of the fact that cells, proteins and other biological materials interact nonspecifically with surfaces in a variety of ways, including hydrophobic, hydrophilic, and ionic or electrostatic interactions, the binding often being of a cooperative nature. A review of such interactions is found in Deppisch, R. al. (1998) *Nephrol. Dial. Transplant* 13:1354–1359, which is incorporated herein by reference. The type of surface that provides the least opportunity for interaction is therefore considered to be one which presents a patchy surface with domains of varying character smaller than the corresponding interacting domains commonly found on proteins, cells and the like. The co-polymer films of the invention are characterized by a non-uniform surface having domains of varied properties. The characteristics associated with such domains include hydrophobic/hydrophilic, rough/smooth, hard/soft, and the like. Optimal sizes lie in the range from 0.1–100 nm of average diameter, although boundaries need not be regular or precisely delineated, domain size need not be uniform and domains outside the optimal range are functional. Surfaces having such optimal patchiness do not provide a sufficient contact area for any given surface trait to allow non-specific binding of biological materials. The surfaces of polymer-films of the present invention have been analyzed by atomic force microscopy (AFM). The results, presented herein, demonstrate that the exemplified such films possess a patchy surface with domains of varied hydrophobicity and hardness which have average diameters in the range 0.1–100 nm.

Also presented herewith are data demonstrating significantly increased biocompatibility of surfaces covered by a polymer film of the invention, compared to an uncoated surface.

The invention therefore includes a co-polymer film generated by reaction of a hydrophobic polymer block, for

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example a PDMS-containing block copolymer having reactive —OH groups, with a monomer or prepolymer of a film-forming polymer, for example, an isocyanate or isocyanate-polyol mixture. There are many ways of forming a co-polymer film according to the invention. Suitable hydrophobic polymer blocks include various siloxane polymers, fluoropolymers, polyethyleneglycol-polydimethylsiloxane copolymers, silicone polyesters, polyamides, polysulfones, polyarlyethersulfone, polycarbonates, polyolefins including cycloolefine-copolymers and the like. Basically all kinds of block-copolymers can be applied for coating films according to the described invention. Reactive end groups on the hydrophobic polymer block can be any sort of reactive group suitable for coupling the hydrophobic polymer block with monomer or prepolymer units of the film-forming polymer. Alternatively, coupling agents can be used to react with the hydrophobic block and then with monomer or prepolymer units of the film-forming polymer.

Examples of film-forming polymers include polyurethanes, polyolefins, polycarbonates, polyvinyl chlorides polyamides, polysulfones, polyarylethersulfones, cellulosic polymers, cycloolefin-copolymers and the like. Preferred are polyurethanes (PUR) which can be formed by reaction of isocyanate with a polyol. PL-PDMS-PL has —OH groups which allow it to be incorporated internally into a polyurethane by reaction with free isocyanate groups.

The invention also provides a method of coating an article with a polymer film, by applying the products of the described reaction in a solvent over the surface of the article and removing the solvent, whereby the film is formed as the solvent is removed.

The invention is exemplified by two types of polymer film; using a commercially available PL-PDMS-PL block copolymer such as SMA 422, SMA 423 or SMA 425 (Trademark, Thoratec Laboratories Corp., Berkeley, Calif.) or a silicone polyester such as Tegomer H-Si 6440 (Trademark, Th. Goldschmidt A. G., Essen, Germany) in either a one component reaction with a polyurethane prepolymer (Desmodur E22 or E23, Trademark, Bayer Corp.) or a two-component reaction with an isocyanate, PL-PDMS-PL block copolymer and a polyol. In both reactions, PL-PDMS-PL blocks react as bifunctional units that become incorporated internally in the PUR polymer chain.

The reaction conditions can be varied so as to control the proportion of hydrophobic blocks to polyurethane. A preferred molar ratio of OH/NCO endgroups is in the range of 0.1 to 10. Reaction conditions which tend to increase the proportion of the hydrophobic block also tend to increase the overall hydrophobicity of the resulting film, and to increase the average diameter of the hydrophobic patches.

As a further aspect of the invention, biocompatibility, particularly reduced cell toxicity, can be improved by providing an interlayer between the surface of the article and the coating film. The interlayer can be formed of a hydrophobic material having free —OH groups such as polyol or one that is also a component of the coating film, such as PL-PDMS-PL (also referred to by trade names herein as SMA or Tegomer). The interlayer, e.g. PL-PDMS-PL can be applied by painting or immersing the article to be coated in a solution of PL-PDMS-PL dissolved in a suitable solvent, for example methyl-isobutyl ketone, then allowing the solvent to evaporate. The process, termed pre-coating, yields a layer of PL-PDMS-PL which can subsequently be coated with a polymer film of the invention, such that the PL-PDMS-PL coating forms an interlayer between the surface of the article and the polymer coating. Formation of an interlayer can be advantageous for reducing cell toxicity of coated articles, such as catheters, especially where the catheter is made of a polyurethane base polymer having leachable isocyanates. Multilayered films can also be prepared to provide a composite of physical properties not available from a single-layer coating.

EXAMPLE 1

Step 1:

25 g Methylisobutylketone

1.5 g SMA 422 (Thoratec Corp.)

Warm up to 40° C. under light stirring, approximately 5 min.

SMA 422 is a triblock co-polymer of polycaprolactone-polydimethylsiloxane-polycaprolactone blocks having nominal molecular weights of 4000, 2000 and 4000 respectively.

Step 2:

Add 23.5 g Desmodur E22 (Bayer Co.)

Light stirring to avoid air bubble formation. Reaction can be carried out for up to two hours, in temperature range 0° C.–60° C.

Degassing

Desmodur E22 is a polyisocyanate prepolymer based on diphenyl methane diisocyanate. The —NCO content is 8.6% by weight. Equivalent weight is 488.

Step 3:

(a) Casting a film in various thickness on glass plate with a casting knife with or without support foil, e.g. PE (Polyethylene or injection molded plates made from polyurethane); or

(b) Film forming by transporting solution through catheter tubes (ID 1–3 mm or any other geometry). The polymerized film was then examined by scanning electron microscopy (see FIG. 1).

EXAMPLE 2

Step 1:

0.45 g SMA 422

23.7 g polyol (VP51 Bayer Co.)

15.9 g isocyanate (Desmodur PF Bayer Co.)

Isocyanate and SMA 422 were allowed to react together for up to 10 min. at 60° C. Polyol was then added and the reaction further carried out as in Example 1, Step 2.

Mixing and degassing at room temperature.

Step 2:

Casting as film (described above) or potting.

Other reactions of OH-groups on PL-PDMS-PL are well-known in the art and can be exploited for incorporating hydrophobic blocks into a film-forming polymer. The reaction for PL-PDMS-PL can be augmented by reaction with coupling reagents which can then react with functional groups present in other polymers or monomers. Coupling to monomers or prepolymers having —OH functional groups can be carried out using alkyl or aryl sulfonates, e.g. tosylchloride which can be reacted with the monomer or prepolymer, R—OH, then substituted by a OH-group of PL-PDMS-PL.

Monomers or prepolymers having an amine, thiol or alcohol functional group can be activated by cyanuric chloride, then coupled to PL-PDMS-PL. Monomers or prepolymers having an epoxy group can be reacted directly with the OH groups of PL-PDMS-PL. Other coupling agents include anhydrides such as maleic anhydride or maleic acid

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anhydride copolymer, active esters such as N-hydroxy succinimide and esters of carboxylic acids or carboxylic acids activated by various carbodiimides. In general, a wide variety of such coupling reactions is known in the art and can be exploited to incorporate hydrophobic blocks into film-forming polymers, using known reaction conditions.

EXAMPLE 3

Testing/Assessing Thrombogenicity

Films or coated catheter tubes were tested for thrombogenicity assessment using freshly donated human blood. During contact of blood components with the material the kinetic generation of thrombin-anti-thrombin III complex (TAT) was analyzed as an indicator of thrombin formation. Thrombin is the major component in the coagulation circuit, since thrombin is a potent activator for platelets and cleaves fibrinogen to fibrin, which finally leads to a polymerized network, i.e. a clot. TAT was measured by a commercially available ELISA test according to the instruction of the manufacturer (Behring Co., Germany). The comparison of materials/surfaces is done in direct comparison of the modified versus the non-modified polymer system. Accelerated reaction kinetics for TAT indicates less biocompatible, more thrombogenic material.

For details on methodology for thrombogenicity assessment: Deppisch R. et al. (1993) *Nephrol. Dial Transplant* Supp. 3 (1994)17–23 and Tsai et al. (1994) *ASAIO J.* 40:M619-M624

In vitro analysis was performed with freshly donated human whole blood. Similar results, i.e. reduction of TAT, was measured for Example 2—SMA in 2 component PUR.

TABLE I

TAT data for SMA-PUR coated tubes according to Example 1.

Types Blood contact time	TAT (ug/ml) t = 21 min	TAT (ug/ml) t = 42 min	TAT (ug/ml) t = 81 min	TAT (ug/ml) t = 81 min
Non-treated	2	251	1570	clot already formed
Treated (60% solvent/ 5% SMA, 35% E22	1	73	605	1313
Treated (50% solvent/ 5% SMA, 45% E22	1	1	54	65

EXAMPLE 4

Si/PDMS Surface Concentration (XPS)

In order to assess the presence of Si, the central component in PDMS molecule x-ray fluorescence spectroscopy was applied. The technique used was described before, e.g. for PVC-SMA mixtures by Tsai et al. (1994) *ASAIO J.*, 40:M619-M624.

Results for films containing no or 3% SMA (related to isocyanate compound) were obtained for different take-off angles (TOA), i.e. 10, 45 and 90°. It is important to note the greater the take-off angle the higher is the penetration depth for the analysis.

TABLE II

Types	Atom (%) TOA 10°	Atom (%) TOA 45°	Atom (%) TOA 90°
Ex. 1 product non-treated	0	0	0
Ex. 1 product treated 3% SMA	17.9	12.4	9.62

These data show that Si, due to the presence of PDMS-content in the SMA-PUR, increased with decreasing TOA which indicates enrichment of SMA-PUR when cast as described above. In the given example an approximate 20-fold enrichment was realized. This experiment demonstrates that enrichment of the PDMS occurs in the surface.

TABLE III

Types	Atom (%) TOA 10	Atom (%) TOA 45	Atom (%) TOA 90
PUR 2 component non-treated	0	0	0
PUR 2 component treated (3% SMA)	15.7	8.2	6.0

These data confirm the enrichment of SMA-PUR polymer chains to the uppermost surface.

EXAMPLE 5

Scanning Electron Microscopy (SEM)

Non-modified and SMA-modified films on catheter tubes prepared as cross-cuts were sputter coated with a thin Pt/Au layer and analyzed in a Philips electron microscope. As shown in FIG. **1**, a coating film of approximately 20 μm forms labeled "SMA-PUR coating." The coating process allows variation of the film thickness optimally from about 0.1 μm to several 100 μm. Furthermore, SEM also identifies small white spots which are due to the addition of $BaSO_4$ into the catheter material. $BaSO_4$ gives a change in emission of electrons in SEM. FIG. 1 shows a clear separation of the $BaSO_4$ from the blood contacting surface. As a conclusion: coated, blood-contacting surface lacks roughness due to $BaSO_4$ crystals, there is no release of $BaSO_4$ into blood, instead $BaSO_4$ remains in the catheter material.

EXAMPLE 6

AFM Pictures in Tapping Mode

The next issue in analysis was the confirmation of hypothesized nano-domains. Atomic force microscopy (AFM) is the most powerful technique to analyze nano-structures consisting of patches with different chemical or physico-chemical properties.

The AFM analysis was performed applying tapping mode technique with low forces on the tip of the cantilever (reference for methods: Magonov et al. (1996) in *Surface Analysis with STM and AFM*, VCH, Weinheim), see FIG. **2** and FIG. **3**.

The pictures of the surfaces taken or generated by AFM in tapping show different spots in the size of nanometers (10–100 nm in diameter). The picture defined as height image shows a kind of depth profile, whereas the picture defined as phase shift image shows the phase shift when the cantilever or tip is 'scratching' or moving on the surfaces (e.g. due to chemical forces or different softness). Light areas are more soft and hydrophilic. Darker areas have higher PDMS and are harder. By varying the molecular weight or chain length of the coating polymers, the person of ordinary skill in the art can readily modify the lateral structure of the nanodomain morphology.

EXAMPLE 7

Bacterial Adhesion

Evaluation of bacterial adhesion to co-polymer films and coated test plates was conducted by the method of Bechert, T. et al. (1998), XIth Aachen Colloquium on Biomaterials, Poster 26., German Offenlegung DE 19751581 A1. Adhesion of *Staphylococcus epidermis* on the material surface was quantified by means of photometry using an ELISA reaction to fix a dye to cells adhering on the surface of the material. Optical density measurements provide a relative

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quantitative measurement of adherent bacteria, under standardized conditions.

Various combinations of polyurethane (PUR) films, co-polymer films of PUR and PL-PDMS-PL, polyurethane test plates uncoated and coated with co-polymer films were tested.

Test plates were made of Tecoflex EG60DB20 (Thermedics, Inc., Woburn, Mass.) a thermoplastic, aliphatic polyurethane synthesized of methylene bis (cyclohexyl) diisocyanate (40%), polytetramethylene ether glycol (9.6%) and 1,4 diol chain extender (30.4%) with barium sulfate (20.0%) to impart x-ray opacity. Coating material was a one-component polyurethane essentially as in Example 1 formed from 35% Demodur E22, 5% PL-PDMS-PL (Tegomer) and 60% methyl isobutyl ketone (MIBK), cast as a film or coated on the Tecoflex test plates.

Test plates or films were exposed to a viable culture of *S. epidermis* for a period of 48 hours, with absorbance readings every twenty minutes.

Results are shown in FIG. 4. Optical density is plotted on the vertical axis against time on the horizontal axis, for a series of test replicates A–F. Uncoated plates (row 3) rapidly and reproducibly supported increasing density of adherent bacteria. Coated plates over the same time interval did not support measurable bacterial adherence. Films formed of polyurethane alone did not support measurable adherence. Co-polymer films of PUR and PL-PDMS-PL significantly retarded the adherence of bacteria compared to uncoated test plates, by an average of about 30 hours for the same optical density. Surprisingly the presence of PDMS at the surface reduces in a dose-dependent manner the bacterial adhesion and proliferation.

EXAMPLE 8

Cell Toxicity Studies

The toxicity of various combinations of test plate materials, film coatings and film-coated test plates was evaluated by measuring inhibition of cell growth (ICG). ICG was measured by making aqueous eluates of the various test materials, then incubating growing mammalian cells in culture medium containing the eluate, then evaluating cell viability by neutral red uptake.

The ICG test was begun by seeding a 96-well tissue culture plate with 1500–2000 mouse fibroblast cells (strain L-929) previously grown to subconfluence for 48–72 h in complete Eagles MEM. The plates were incubated for 24 h at 37° C. The medium was then removed and test eluates were added. The test eluates were made by incubating test plates or films in distilled water (1 ml for each 10 cm^2 test material) at 70° C. for 24 h.

For each plate, 250 μl 0.4% Neutral red solution was mixed with 20 ml of complete Eagle's MEM. The eluate incubation medium was removed and 200 μl/well of neutral red containing medium was added. The plates were then incubated for 3 h at 37° C. The solution was then discarded, the plates rinsed with 200 μl PBS/well. After that, 200 μl/well of 50% (v/v) ethanol and 1% (v/v) acetic acid in distilled water was added. After a 10 min wait the absorbance at 540 nm of each well was measured. ICG % was calculated as

$$\frac{A_k - A_T}{A_k} \times 100$$

where A_T=mean absorbance in test solution minus mean absorbance in blank, A_k=mean absorbance in control (no cells) minus mean absorbance in blank. The materials are deemed non-toxic if ICG is <30% as described by Wieslander et al. (1991) *Kidney International* 49:77–79.

The following materials were employed:

Completed Eagles MEM:

500 ml Eagles MEM

50 ml Fetal calf serum

5 ml 200 m ML-Glutamine

5 ml Non-Essential Amino Acid solution.

0.5 ml Gentamycin 50 mg/ml

PBS (10× stock solution):

NaCl	80 g
KCl	2 g
KH_2PO_4	2 g
Na_2HPO_4	11 g

dissolve in H_2O to 1000 ml final volume.

The stock solution is diluted 10-fold and pH adjusted to 7.2.

50% ethanol, 1% acetic acid solution:

500 ml ethanol (96%)

490 ml water

10 ml Glacial acetic acid

4% Neutral red stock solution:

4 g Neutral red (Merck No.1376)

100 ml distilled water

Diluted 10-fold with water prior to use.

In parallel experiments uncoated Tecoflex catheters and co-polymer films were non-toxic, i.e. ICG<30% compared to water or saline solution as reference. However, catheters and test plates coated with co-polymer films were toxic. Substituting Desmodur E23 for Desmodur E22 resulted in co-polymer films which were non-toxic as films and non-toxic when applied to a catheter or test plate. Desmodur E23 has 15%-NCO groups.

Toxicity was also reduced or eliminated by interposing an interlayer of polyol or PL-SMA-PL over the test material, prior to applying the co-polymer film. Test catheters were pre-coated with either 0.125% or 1.0% PL-PDMS-PL by applying the pre-coating in a solution of methyl-isobutyl ketone and curing at 40° C. to remove the solvent. Test catheters were then coated with co-polymer essentially as described in Example 1 except the co-polymer starting solution was 45% Desmodur E23, 5% PL-PDMS-PL and 50% MBK. The data are shown in FIG. 5. Catheters pre-coated with a PL-PDMS-PL interlayer had significantly reduced toxicity although catheters coated without an interlayer were also below the 30% ICG threshold for toxicity. Therefore, toxicity can be reduced either by interposing an interlayer having free-OH groups, or by employing rapidly reacting components to form the co-polymer film. Either strategy avoids or minimizes the possibility of reaction between the reaction components of the co-polymer film and the base polymer of which the article to be coated is formed. This multilayer concept as described above allows a great flexibility in composing the polymers.

EXAMPLE 9

Non-Attachment of Mammalian Cells

The failure of mammalian cells, such as fibroblasts, to attach and overgrow articles coated with a co-polymer film of the present invention was demonstrated in the following way: Fibroblast cells were inoculated on a tissue culture plate pre-coated on the bottom with a co-polymer film of the

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invention, a portion of which was overlaid by a glass plate with the entire apparatus bathed in growth medium. Growth on the co-polymer surface was compared to growth on the glass surface. Cells grew on the glass surface but failed to attach or proliferate on the co-polymer surface. The failure of cells to attach or proliferate on co-polymer film surfaces of the invention indicates that such surfaces are unlikely to be damaged when implanted, by ingrowth or overgrowth of host cell tissue.

The invention having been described by examples of specific embodiments of the operating principals of the invention, other embodiments will be recognized by those skilled in the art following the general teachings and principles taught or suggested herein. Those variations that fall within the scope of the invention include the use of alternative materials for forming the co-polymer films of the invention, alternative reaction conditions for film formation and/or coating, alternatives for interlayer formation or combinations thereof.

Summary of the Results:

The described SMA-PUR films show a series of improvements in terms of properties:

1. Mechanical stability of the film compared to a simple coating of PL-PDMS-PL;
2. Reduced roughness below 0.1 nm compared to technology used up to now;
3. Micro/Nano-domains in the range of 5–100 nm as proven by AFM:
4. Reduced thrombogenicity: lower TAT generation kinetics; and
5. Enrichment of PDMS to the surface as documented by ESCA and XPS analysis.

We claim:

1. A co-polymer film comprising a film-forming polymer component and a hydrophobic polymer block having reactive end groups, said film having a non-uniform surface characterized by domains of varied properties of hydrophobicity, roughness, hardness or other physico-chemically distinct patches, said domains having average diameters in the range 0.1 nm–100 nm, wherein the film-forming polymer is selected from the group consisting of polyurethanes, polyolefins, cellulosic polymers, polycarbonates, polyarylethersulfones, polysulfones, polyvinylchlorides, and polyamides, and the hydrophobic polymer block is selected from the group consisting of siloxane polymers, fluoropolymers, polyethyleneglycol-polydimethyl siloxane co-polymers, silicone polyesters and polylactone-polysiloxane-polylactone triblock co-polymers.

2. The co-polymer film of claim **1** wherein the film-forming polymer is a polyurethane and the hydrophobic polymer block is a polylactone-polysiloxane-polylactone triblock co-polymer.

3. The co-polymer film of claim **1** wherein the film-forming polymer is a polydiphenyl methane diisocyanate prepolymer and the hydrophobic block is a polycaprolacton-polydimethylsiloxane-polycaprolactone triblock co-polymer.

4. The film of claim **3** wherein prior to condensation, the proportion of —OH groups on the hydrophobic block to —NCO groups on the film-forming polymer is in the range of 0.1 to 10.0.

5. A method of making a co-polymer film comprising the steps of:

a) combining a film-forming polymer component and a hydrophobic polymer block having end groups reactive with the film-forming polymer component in the presence of a solvent such that all components are dissolved in the solvent, wherein the film-forming polymer is selected from the group consisting of polyurethanes, polyolefins, cellulosic polymers, polycarbonates, polyarylethersulfones, polysulfones, polyvinylchlorides, and polyamides, and the hydrophobic polymer block is selected from the group consisting of siloxane polymers, fluoropolymers, polyethylenealycol-polydimethyl siloxane co-polymers, silicone polyesters and polylactone-polysiloxane-polylactone triblock co-polymers;

(b) applying the components dissolved in the solvent to a surface to be coated; and

(c) forming a film over the surface to be coated under conditions that allow the solvent to evaporate and the components to react with one another,

whereby a co-polymer film having a non-uniform surface characterized by domains of varied properties of hydrophobicity, roughness, hardness or other physico-chemically distinct patches, and said domains having average diameters in the range 0.1 nm–100 nm, is obtained.

6. The method of claim **5** wherein the film-forming polymer component is a polyurethane-forming component and the hydrophobic block is a polylactone-polysiloxane-polylactone triblock co-polymer.

7. The method of claim **6** wherein, prior to reaction, the proportion of —OH groups on the hydrophobic block to —NCO groups on the film-forming polymer is in the range from 0.1 to 10.0.

8. A The method of claim **6** where in the film-forming polymer component consists essentially of a mixture of an isocyanate and a polyol.

9. The method of claim **5** wherein the step of applying the components dissolved in the solvent to a surface to be coated is carried out by immersing an article to be coated by the film in the solution, then removing the article to permit the solvent to evaporate.

10. The method of claim **5** wherein the surface to be coated has been pre-coated with a layer comprising a polyol, or a polylactone-polysiloxane-polylactdone triblock co-polymer.

11. A method of coating a surface with a biocompatible co-polymer film comprising the steps of:

(a) covering the surface with a solution comprising a film-forming polymer component and a hydrophobic polymer block component having end groups reactive with the film-forming polymer component, the components being dissolved in a solvent, wherein the film-forming polymer is selected from the group consisting of polyurethanes, polyolefins, cellulosic polymers, polycarbonates, polyarylethersulfones, polysulfones, polyvinylchlorides, and polyamides, and the hydrophobic polymer block is selected from the group consisting of siloxane polymers, fluoropolymers, polyethyleneglycol-polydimethyl siloxane co-polymers, silicone polyesters and polylactone-polysiloxane-polylactone triblock co-polymers; and

(b) removing the solvent from the solution covering the surface to allow the components react with one another, whereby a co-polymer film having a non-uniform surface characterized by domains of varied properties of hydrophobicity, roughness, hardness or other physico-chemically distinct patches, and said domains having average diameters in the range 0.1 nm–100 nm, is formed on the surface.

12. The method of claim **11** wherein the film-forming polymer component is a polyurethane-forming component and the hydrophobic block is a polylactone-polysiloxane-polylactone triblock co-polymer.

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13. The method of claim 12 wherein prior to reaction, the proportion of —OH groups on the hydrophobic block to —NCO groups on the film-forming polymer is in the range from 0.1 to 10.0.

14. The method of claim 12 wherein the film-forming polymer component consists essentially of a mixture of an isocyanate and a polyol.

15. The method of claim 11 wherein the surface has been pre-coated with a layer comprising a polyol, or a polylactone-polysiloxane-polylactone triblock co-polymer.

16. The method of claim 15 comprising the added step of forming a film over the pre-coating, prior to forming the bio-compatible co-polymer film.

* * * * *

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,841,255 B2
DATED : January 11, 2005
INVENTOR(S) : Deppisch et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

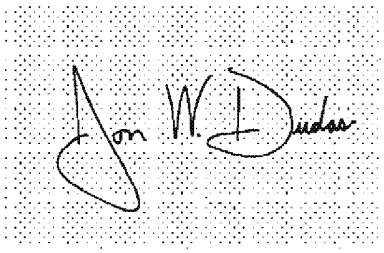
Column 5,
Line 9, delete "polyarlyethersulfone" and replace with -- polyarylethersulfone --.

Column 11,
Line 49, delete "polyethylenealycol-polydimethyl siloxane" and replace with -- polyethyleneglycol-polydimethyl siloxane --.

Column 12,
Line 39, delete "polylactone-polysiloxane-polylactdone triblock" with -- polylactone-polysiloxane-polylactone triblock --.

Signed and Sealed this

Twenty-sixth Day of April, 2005



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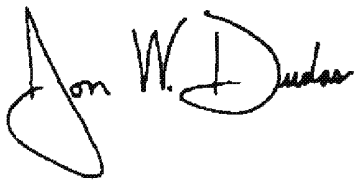
Line 9, delete "polyarlyethersulfone" and replace with -- polyarylethersulfone --.

Column 12,
Line 9, delete "polyethylenealycol-polydimethyl siloxane" and replace with
-- polyethyleneglycol-polydimethyl siloxane --.
Line 41, delete "polyalctone-polysiloxane-polylactdone triblock" with
-- polyalctone-polysiloxane-polylactone triblock

This certificate supersedes Certificate of Correction issued April 26, 2005.

Signed and Sealed this

Thirtieth Day of August, 2005



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Abstracts: XXIX ESAO Congress "Bridging to Regeneration", Vienna - Austria, 28-31 August 2002

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IMPROVEMENT OF THE PURIFICATION WITH MUSCULAR MOBILIZATION DURING DIALYSIS

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Aim: In previous studies it was observed that in the haemodialyzed patients, a moderated physical activity, carried out either during the dialytic treatment or in the interdialytic days, determines considerable physical and psychological benefits. The aim of the study was verifying the hypothesis that a muscular mobilization, voluntary or electrostimulated, during the haemodialytic session could determine an improvement of the dialytic efficiency.
Methods: The research was led on 20 volunteer patients in conventional haemodialytic treatment (11 M, 9 F; mean age 48.5±11.1). The study planning was concerned with three observation phases of two weeks each. The first phase basal line (BL), during which the patients had muscular rest sittings, the second phase (E1) during which the patients practised a muscular mobilization by voluntarily physical isotonic exercises, and the third phase (E2), during which the patients had passively muscular mobilization by electrostimulation. For every dialytic session were recorded the urea curve (time 0, 120, 240 and 270 minutes), the pressure profile, the Kt/V, the Protein Catabolic Rate (PCR) and the bioelectrical impedance measurements.
Statistical analysis was performed using ANOVA and Student t test.
Results: Kt/V: BL=1.29±0.13, E1=1.40±0.15, E2=1.37±0.16; PCR: BL=1.13±0.19, E1=1.18±0.18, E2=1.18±0.16; Post dialytic rebound (%): BL=6.17±2.44, E1=1.18±0.18, E2=1.18±0.16.
Conclusions: The intradialytic muscular activity improves the dialytic efficiency, causing an improvement of the urea clearance, an improvement of the Kt/V and a decrease of the post-dialytic rebound.

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LEAKAGE CURRENT MAY BE A RISK FOR PATIENTS IN HEMODIALYSIS (HD) IF THE DEVICES ARE DEFECT

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Background: If a difference in (electrical) potential between patient and HD-machine occurs during HD the result will be a leakage current (LC). If LC is high enough this could be a risk for the patient. Notable is that the HD-machines are classified: class I type B (def. for non-patient connected device). This *in vitro* study investigated if LC in priming fluid or blood at entry into the patient constitutes a risk for the patient (>80 µA) during dialysis to examine the safety situation for the patient.
Method: LC was measured in single fault condition (SFC). Priming fluid (NaCl) was circulated through a conventional tubing set and HD-device connected to a HD-machine (Fresenius 2008C). 8 different dialyzers of the same brand were tested (120 GFS plus, Gambro). In addition analyses were performed with whole blood from 8 different donors using the same dialyser. The dialysate was connected with the dialyzer (by an electrode) not allowing change of the priming fluid or blood during the HD. Electrodes were placed at different positions including at the tip of a central venous catheter (CDC, Optiflow, 34 cm, Medcomp) and from the needle-position at the venous side. Dialysate flow was either off (Doff) or on (Don) and blood flow put on 80 ml/min (Bon). A safety measure using a Metron QA-90 electrical safety analyzer was performed. Testmode was set to class I, CF according to IEC 60 601-1 (equipment allowed to be connect close to the heart).
Results: The LC test-step 'mains on applied part' (SFC), at the end of the CDC, was lower for NaCl than for blood when the blood pump was stopped (34.5 versus 476 µA, p<0.001) but higher for NaCl with the blood pump on (Bon: 1009 versus 610 µA, p<0.001). The LC was higher at the needle site compared to the end of the CDC (p=0.006).
Conclusion: If a defect in another device connected to the same patient develops, current flow may be high enough to be a risk for arrhythmia for the patient especially when using a CDC. Observe that the limit is 50 µA for CF but class I type B (dialysis machines) has no limit. This indicates that HD-machines should be classified: class I type CF.

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MINIMIZED WEIGHT GAIN BETWEEN HEMODIALYSIS MAY CONTRIBUTE TO A REDUCED RISK FOR DEATH

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The risk for death is increased for dialysis patients compared to age-matched subjects. The main reason is cardiovascular. This prospective study investigated if the extent of ultrafiltration (UF) need was of importance for the outcome.
Material and Methods: 88 hemodialysis patients were included and followed prospectively. The outcome was registered in regard to death, acute myocardial infarction or coronary vascular intervention. The extent of UF needed at dialysis was calculated as a mean during the observation period as were other variables. The mean extent of UF was compared for patients who had survived without end-points (group 1, n=53) versus those who reached any end-point during the period (group 2, n=35).
Results: In total, 40% of the patients reached end-point during the observation period. There was no difference at baseline between the groups in regard to age, prevalence of diabetes mellitus or history of previous cardiovascular disease, Kt/V, residual renal function, UF-need, C-reactive protein, s-albumin, cholesterol, LDL-cholesterol, HDL-cholesterol, appetite or wellbeing, while triglyceride was lower in group 2 (p=0.035). The observation period for group 1 was at a mean 24.7 months (SD 13.1) and for those in group 2 at a mean 13.8 (±11.7 months, p<0.0001). Patients representing group 1 at 24 and 30 months had less need of ultrafiltration than those did in group 2. Thus, the need of ultrafiltration was about 27% lower at 24 months (for 29 persons in group 1: 3.63±1.93 versus 4.97±1.70 weight% for 9 patients from group 2, p=0.046) and 46% at 30 months (for 18 from group 1: 3.48±1.95 versus 6.45±1.55 for 3 from group 2, p 0.030). C-reactive protein did not differ between the groups during the period.
Conclusion: After a prolonged period of 24 months the extent of UF-need seems to be important for the outcome of the patients. Thereby those with higher UF-need had worse prognosis. It seems important to motivate patients to reduce the extent of volume gain between dialysis to prolong survival.

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EVIDENCE FOR RELEASE OF BARIUM SULPHATE RADIOGRAPHIC CONTRAST MATERIAL FROM STANDARD TEMPORARY HEMODIALYSIS CATHETERS

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Background: Recently it was shown that barium sulphate (BS) in conc. < 0.5 g/L is able to significantly inactivate stimulated phagocytic cells. BS is added as contrast agent to hemodialysis catheters. We hypothesized that BS released from the catheter surface could lead to local depression of phagocytic activity when challenged, and evaluated BS release during use.
Methods: Clinical study with conventional (CC) and surface-coated (SC) polyurethane catheters. The coating consisted of a microdomain-forming, surface-smoothing, low-thrombogenicity polymer supposed to prevent BS release. CC and SC were randomly applied in 8 intensive-care patients acc. to clinical routine. Catheters were removed after <= 1 week as clinically indicated. Tips with side holes were cut off, rinsed, and fixed in 2% glutardialdehyde. For scanning electron microscopy, the tips were freeze-dried to preserve morphology, and coated with carbon-gold for surface conductivity.
Results: CC features: (1) Unhomogeneities (range 1-10 µm) due to mechanical processing during manufacture (2) BS moieties at the surface covering approx. 10-20% (3) Approx. 20-30 pores/500 µm² surface with diameters of 0.1-1 µm after use (4) Pores are likely to be generated by BS removal, as deduced from combined surface and cross-section analysis. SC features: (1) Smooth surface due to the 10-30 µm coating. (2) Complete masking of BS moieties. (3) Reduced deposition of blood components and clots compared to CC.
Conclusions: (1) BS can be released from CC during use. (2) Coating prevents BS release during contact with blood. (3) Further investigations need to show whether presence of BS in catheters results in suppressed local phagocyte activity upon challenge at the site of vascular access *in vivo*.

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ANNEX 1 - 4

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REVIEW

Bacterial Biofilms: A Common Cause of Persistent Infections

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Bacteria that attach to surfaces aggregate in a hydrated polymeric matrix of their own synthesis to form biofilms. Formation of these sessile communities and their inherent resistance to antimicrobial agents are at the root of many persistent and chronic bacterial infections. Studies of biofilms have revealed differentiated, structured groups of cells with community properties. Recent advances in our understanding of the genetic and molecular basis of bacterial community behavior point to therapeutic targets that may provide a means for the control of biofilm infections.

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NDT
Nephrology Dialysis Transplantation

Original Article

The role of polymer surface degradation and barium sulphate release in the pathogenesis of catheter-related infection

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Abstract

Background. Susceptibility to infection and thrombosis of intravascular catheters is increased by surface irregularities, which might be prevented by coating.

Methods. BaSO4 release from conventional haemodialysis catheters (CC) and modified catheters (MC) which had been coated with a surface-modifying additive (SMA) was assessed *in vivo* and *in vitro*. For the *in vivo* part, patients were randomized to receive a temporary CC or MC, with crossover after 1 week. After retrieval, catheters were examined using scanning electron microscopy to assess surface integrity, and an *in vitro* model of catheter exposure to the bloodstream was used to evaluate surface morphology and susceptibility to bacterial adhesion and proliferation.

Results. $BaSO_4$ moieties covered 14.7 ± 3.7% of the surface of unused CC. After *in vivo* use in 16 patients, 62.7 ± 32.9 × 10^3 holes/mm^2 were detected, indicating $BaSO_4$ detachment from 3.3 ± 1.7% of the catheter surface. No defects were observed in unused CC and in MC, whether used or unused. After incubation of four catheters (two of each type) with *Staphylococcus epidermidis*, the two degraded CC showed an immediate and strong bacterial growth as indicated by an increase in medium impedance of 0.512%/10 min compared to −0.021%/10 min in MC ($P < 0.001$).

Conclusions. Short-term exposure of CC to the bloodstream causes $BaSO_4$ particle release, resulting in surface irregularities predisposing to bacterial proliferation. $BaSO_4$ release can be prevented by SMA coating.

Keywords: catheter infection; haemodialysis; polydimethylsiloxane; surface modification; surface roughness

Introduction

Central venous catheters are widely used in clinical practice for therapeutic purposes such as extracorporeal blood purification, drug administration, fluid replacement and parenteral nutrition. Haemodialysis catheters provide a fast access for renal replacement therapy in both acute and chronic kidney failure [1]. Blood stream infection remains the most important complication accounting for morbidity, mortality and cost [2,3]. A major culprit for this complication is roughness of the catheter surface due to microscopic irregularities which promotes thrombogenicity [3] as well as biofilm formation [4]. One of the factors potentially contributing to roughness is the addition to the polymer formulation of radio-opaque materials, such as barium sulphate ($BaSO_4$), allowing the verification of position [5,6]. In addition, implanted polymers may undergo biodegradation and breakdown caused by local hydrolytic or proteolytic conditions at sites of leukocyte activation and adhesion or ingrowth of germs colonizing the biofilm on the polymer surface [7,8].

We hypothesized that in haemodialysis catheters areas of $BaSO_4$ aggregation make catheters prone to surface degradation after prolonged exposure to the bloodstream. Release of $BaSO_4$ particles due to biodegradation at the surface in turn increases surface irregularity which as such might act as a promoting factor for aggregation of bacteria [4,8–10].

Improvements in design of biomaterials over the past decade include the development of surface-modifying additives (SMA). SMA are a family of polysiloxane-containing copolymers that exhibit a microdomain structure containing areas with opposing physicochemical properties in the nanoscale range [11,12]. Surface-coating films composed by these copolymers have a lower potential for coagulation activation and platelet adhesion and activation [13].

In the present study, we compared a commercially available SMA-coated polyurethane catheter with a conventional polyurethane catheter in a prospective randomized crossover clinical trial to test our hypothesis that $BaSO_4$ moieties are released from the catheter surface *in vivo* and that the resulting roughness of the catheter surfaces contributes to susceptibility to bacterial adhesion and proliferation. Scanning electron microscopy was used

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to assess catheter surface integrity, and an *in vitro* model of catheter exposure to the bloodstream was used to evaluate surface morphology and susceptibility to bacterial adhesion and proliferation. Because of the randomized crossover design, the study was limited to clinical conditions requiring a temporary catheter and the evaluation of changes after short-term exposure to the bloodstream.

Materials and methods

Catheters

Conventional polyurethane catheters (CC) and surface-modified catheters with a polyurethane-based block copolymer coating (MC) but otherwise identical (GamCath® and GamCath® Dolphin, Gambro Kathetertechnik, Hechingen, Germany) were compared in both the *in vivo* and *in vitro* study. MC were produced using a reactive polymeric film-coating process as final manufacturing step. Single- and double-lumen catheters were available. Although the initial choice for each patient was left to the attendant nephrologist, the same number of lumina was to be used throughout the entire study period. All catheters were CE-marked.

Patients

Patients aged 18–80 years and undergoing intermittent haemodialysis for acute kidney injury or stage 5 (end-stage) kidney disease with a need for a central venous catheter as vascular access were eligible for the study. Pregnancy, treatment with vitamin K antagonists or the need for continuous renal replacement therapy were exclusion criteria. After inclusion, patients were randomly assigned to be dialysed initially with the MC or CC, with a crossover after 7 ± 1 days. The investigator in charge of patient inclusion, catheter insertion and clinical data collection was blinded to the type of catheter. Intermittent haemodialysis was performed at a constant blood flow rate (range 100–300 ml/min) for at least three haemodialysis sessions per catheter, without changing the type of dialysis machine, dialyser, tubings or anticoagulation lock. The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

Catheter application

Catheters were inserted into the internal jugular or femoral vein. After 7 ± 1 days, the catheter was exchanged using a guidewire. Seven days later, the second catheter was withdrawn as well and replaced by a conventional catheter when still required as vascular access. Immediately after removal, the catheters were rinsed with a 50-mL flush of a 0.9% sterile saline solution through the inlet and outlet tubings, applying a low infusion rate. The external catheter surface was rinsed in a bath of 0.9% sterile saline using an appropriate container. After rinsing, the catheter was fixed by flushing 50 mL of 2% glutaraldehyde in 0.9% saline through the inlet and outlet tubings. Subsequently, the catheter tip with side holes was stored at 4°C in a 50-mL container filled with 2% glutaraldehyde until analysis.

In vitro model investigations for $BaSO_4$ release

Catheter surfaces were exposed to hydrogen peroxide to simulate the clinical situation of biodegradation by an oxidative, hydrolyzing agent. Surface contact with oxidants was pursued by incubation of the catheters in rotating tubes, filled with 3% hydrogen peroxide at 37°C for a period of 8 days. To simulate *in vivo* conditions with respect to proteolytic surface degradation, catheters were incubated in freshly donated human serum under the same conditions. After incubation, the catheters were fixed with 2% glutaraldehyde (GDA) and processed for scanning electron microscopic analysis.

The fixation procedure per se did not induce any increase in surface roughness nor hole formation in unused CC and MC.

Morphological studies

Surface and cross-section characterization with scanning electron microscopy. New unused catheters and fixed samples after *in vivo* use or *in vitro* degradation were rinsed with distilled, sterile-filtered water, dried and sputter-coated with gold using an SCD 040 equipment (Bal-Tec, Witten, Germany).

Cross-sections and surfaces of new catheters, and surfaces of used or *in vitro*-degraded catheters were analysed in a scanning electron microscope (SEM, Philips SEM 515, Eindhoven, The Netherlands). Thin layer sputter coating (carbon-Pt target) was applied to investigate the polymeric specimen. Secondary electron emission was used to identify material contrasts, i. e. bright electron-dense areas embedded in the grey matrix area were identified as barium collections whereas dark spots were considered as holes devoid of barium sulphate. Validation was performed by energy-dispersive X-ray spectroscopy (EDX) as described below.

Identification of $BaSO_4$. $BaSO_4$ was identified with EDX. Spots with bright appearance and grey matrix as displayed in the SEM image were analysed for elemental composition.

Surface characterization with atomic force microscopy. In analogy to the catheter-coating process, plain polyurethane films with and without block copolymer were produced. These films were analysed by atomic force microscopy (AFM, NanoScope, Veeco Inc., USA) without preceding sample conditioning, in tapping mode with phase detection to obtain material contrast. Standard silicium tips with a nominal radius of 10–50 nm were used. Measurement was performed at the natural resonance of the cantilever.

Quantification of $BaSO_4$ release. SEM images were used to assess the number of holes at the surface after *in vivo* use of the catheters. The evaluated display window area was 334 μm^2.

Greyscale analysis of the SEM images with the Zeiss KS400 software (version 3.0) was used to distinguish between bright areas of high electron density and dark areas of low electron density appearing as holes embedded in the matrix. The respective areas were quantified by grey value segmentation to generate binary regions (bright/dark). From this analysis, the percentages of surface areas covered by bright electron-dense $BaSO_4$ moieties and by holes at the surface which had released $BaSO_4$ were calculated.

Assessment of susceptibility of degraded catheter surfaces to bacterial proliferation. As reported previously in other centres [14,15], also in our hospital, *Staphylococci* species are responsible for most catheter-related infections. Therefore, we chose an experimental setup where *in vitro* serum-exposed catheter surfaces were brought into contact with *Staphylococcus epidermidis* (ATCC 12228; concentration of McF = 0.01 corresponding to ~3 × 10^5/mL) under controlled closed-system conditions, avoiding any contamination, for a period of 4 h. Bacterial metabolic activity on the catheter surfaces was investigated by measurement of medium impedance during an additional catheter incubation with trypticase soy bouillon (Bio Mérieux, Nürtingen, Germany) in a BacTrac 4110 device (Sy-Lab, Neupurkersdorf, Austria). The impedance of such a suspension changes when ions are formed through metabolic cleavage of molecules with low or no electric charge by live/proliferating bacteria

Table 1. Characteristics of patients and dialysis modalities

Male (%)	44	
Age (year)	69 ± 10	
Indication (no. of patients)		
ESRD	12	
ARF	4	
Position (no. of patients)		
Jugular	12	
Femoral	4	
	CC	MC
Sessions/patient (no.)	57	35
Duration (hours)	3.6 ± 0.9	3.9 ± 0.8
Blood flow rate (mL/min)	202 ± 35	199 ± 20
Units of LMWH per session	5346 ± 3890	6214 ± 3465

Data are mean ± SD or numbers. ESRD, end-stage renal disease (CKD stage 5); AKI, acute kidney injury; LMWH, low-molecular weight heparin. To facilitate comparison, units of different LMWHs are summed; within each patient, the same type of LMWH was used.

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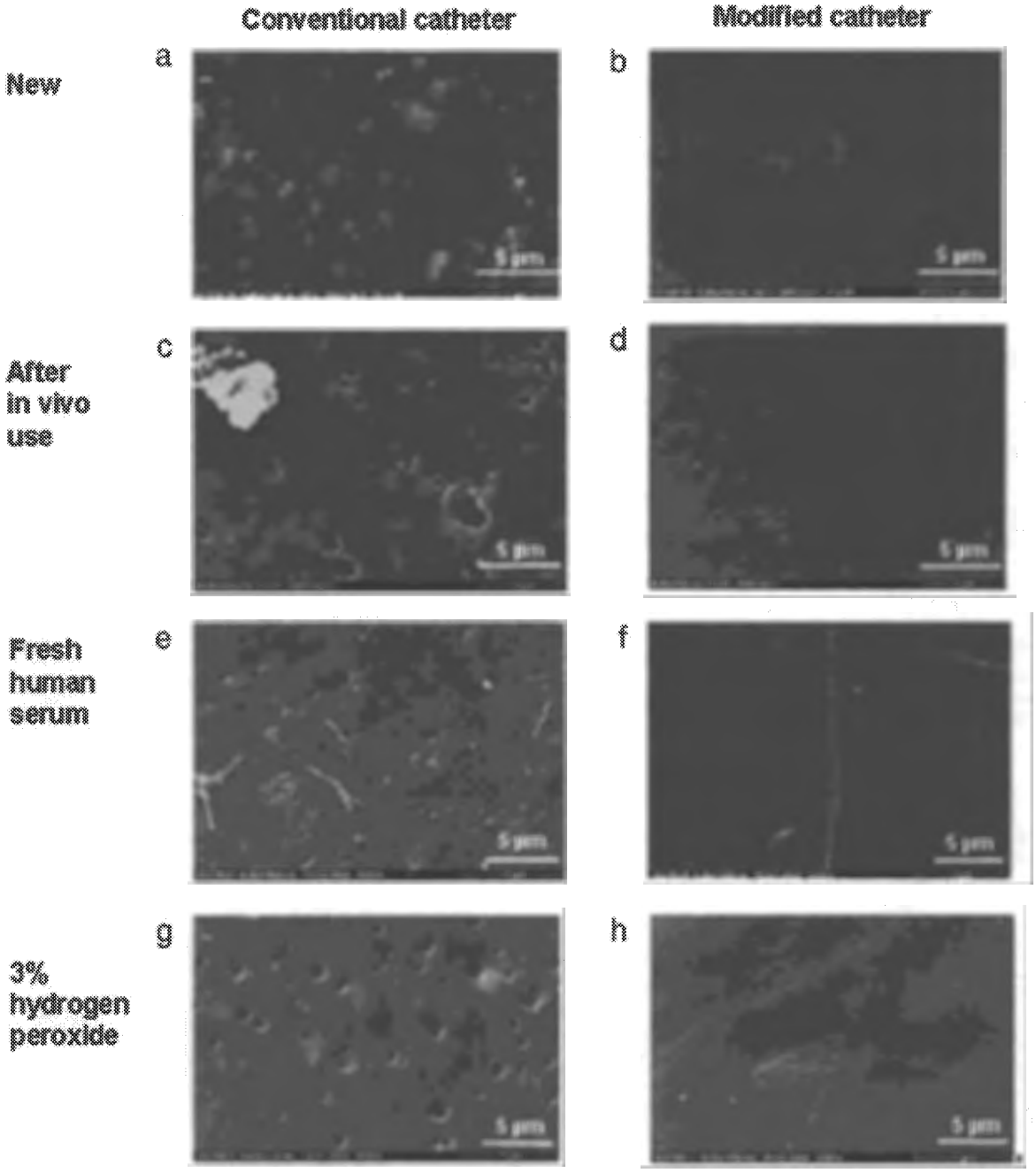

Fig. 1. Inner surface morphology of a CC (left) and an MC (right) assessed with SEM, before (a, b) and after (c, d) contact with blood *in vivo*; after *in vitro* incubation with fresh human serum (e, f) and hydrogen peroxide (g, h). Before use, electron-dense areas are seen in the CC (a) but not in the MC (b). After *in vivo* use or *in vitro* degradation, holes of different sizes are observed in the CC (c, e, g) but not in the MC (d, f, h).

[16]. The rate of change in impedance depends on the number and type of bacteria adhered to the surface during the preceding incubation step. Duplicate experiments were performed in parallel, i.e. with serum-exposed CC and MC, respectively.

Statistics

Data were tested for normal distribution with the Shapiro–Wilk test. Normally distributed data are presented as mean ± SD, and non-normally distributed data are given as median and range if not otherwise stated. The change in impedance over time after bacterial exposure was assessed using linear regression analysis with a dummy variable used for the type of catheter (MC = 0; CC = 1). An interaction term of time by catheter type was used to test for a difference in slopes between the two catheters.

Results

In vivo study

Sixteen patients were included in whom 92 haemodialysis sessions were performed during the study period. The ma-

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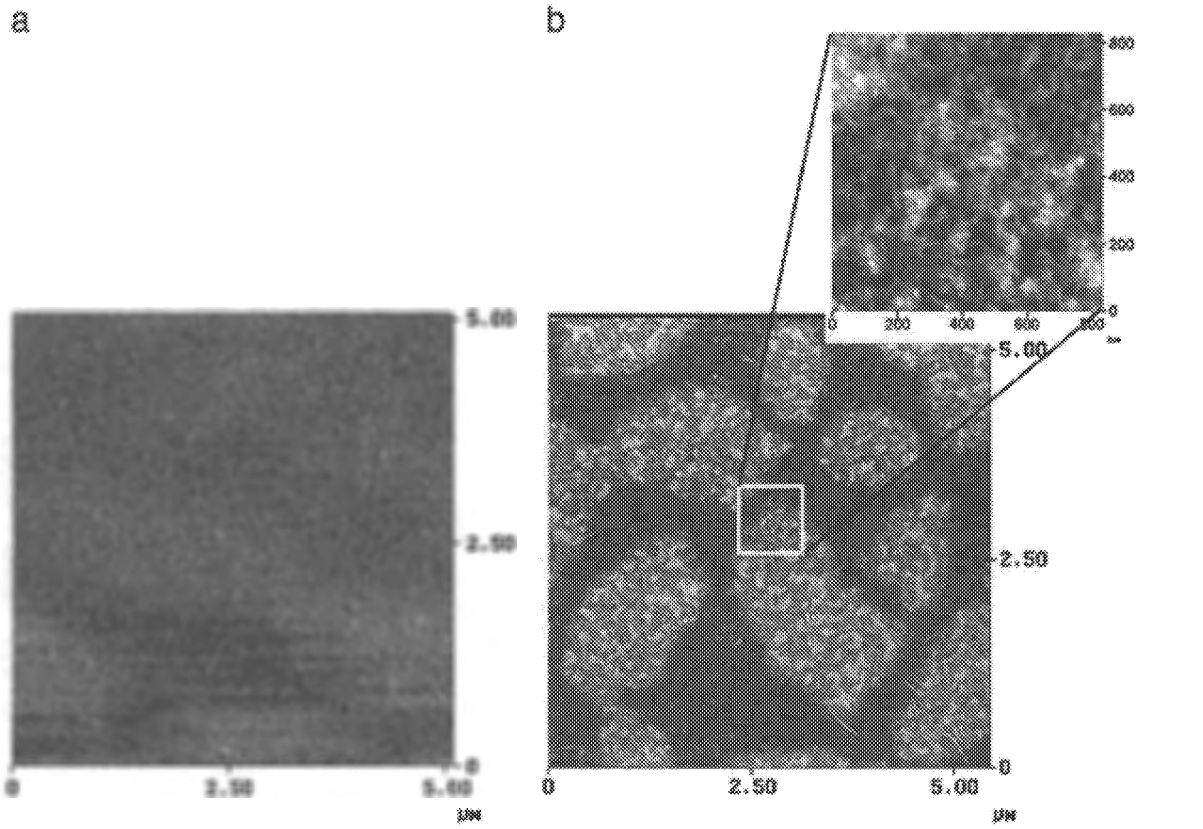

Fig. 2. AFM of the surface of a CC (**a**) and an MC (**b**) depicting hydrophilic–hydrophobic microdomain structure on the CC but not on the MC surface.

jority were chronic haemodialysis patients who needed a temporary catheter because of vascular access problems. Characteristics of patients and dialysis modalities are shown in Table 1. Two patients received daily dialysis during the week while they were on the CC whereas they were treated by alternate day dialysis while on MC, and three other patients dropped out of the study while on CC before the MC study period was started, resulting in a larger number of dialysis sessions with the CC. Otherwise both catheters were comparable regarding ease of insertion, duration of dialysis sessions, blood flow rates and anticoagulation use.

Analysis of the catheter surfaces by SEM revealed no holes at the surface of the unused CC (Figure 1a) whereas, after 1 week of haemodialysis, multiple holes were obvious at the CC surface (Figure 1c). Neither before use (Figure 1b) nor after *in vivo* use (Figure 1d), were any holes detected on the MC surface. Multiple bright areas corresponding to barium sulphate in new CC (Figure 1a) were replaced by dark areas corresponding to hole formation, suggesting that a substantial amount of barium sulphate had been lost in used CC (Figure 1c).

Quantification of $BaSO_4$ release. Through quantification by greyscale analysis of the SEM images, it was estimated that bright electron-dense areas, corresponding to $BaSO_4$ moieties, covered 14.7 ± 3.7% of the surface of the new CC (n = 8). After exposure to blood *in vivo*, many of these electron-dense areas disappeared in CC, and multiple defects in the catheter surface appeared as holes of variable size, as depicted in Figure 1c. In used CC, 62.7 ± 32.9 × 10^3 holes/mm^2 surface area were detected, with diameters ranging from 0.1 to 1.0 µm (n = 13 used catheters). The percentage area of holes as assessed with greyscale analysis was 3.3 ± 1.7%, ranging from 0 to 4.6% (median 4.0%).

In a representative imaging experiment, the SEM image of the CC surface after *in vivo* use displayed a dark area fraction of 4.4%, corresponding to the zone of barium sulphate particle release, and a bright area fraction of 9.0%, totaling 13.4% which is in the range of the average 14.7% of area corresponding to $BaSO_4$-containing surface in CC mentioned above.

Neither bright electron-dense areas nor holes were visible at the surface of the new MC (Figure 1b) or *in vivo* used MC (Figure 1d). Thus, no greyscale analysis or evaluation of number of holes was performed with MC.

In vitro studies

Identification of $BaSO_4$. Characterization of the CC surface by EDX for elemental composition revealed that the spots with bright appearance on the SEM image consist of Ba, C, O and S whereas C, O and N were identified in the dark matrix which thus represents the polyurethane base material.

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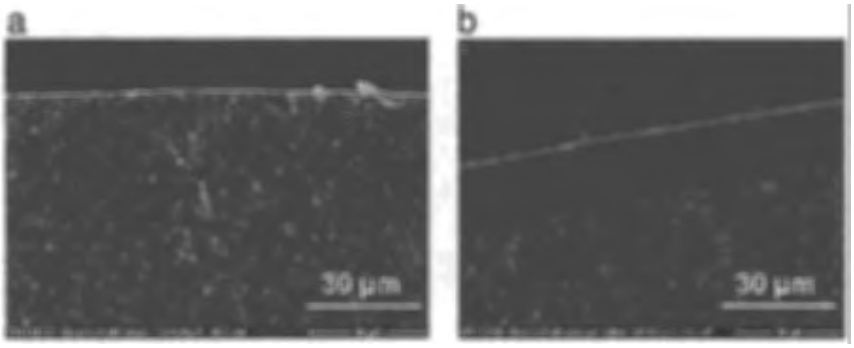

Fig. 3. Cross-section of CC (a) and MC (b) assessed with SEM, showing a smoother surface for MC.

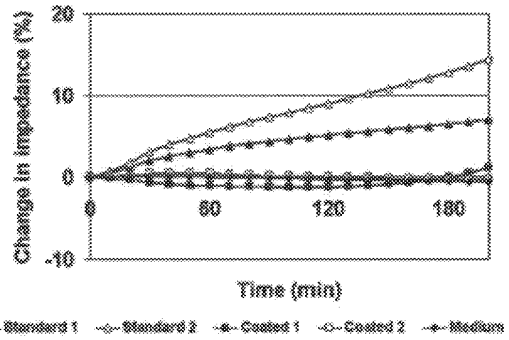

Fig. 4. Bacterial proliferation on two CC catheters (open triangles and filled triangles), and two MC catheters (open squares and filled squares), after *in vitro* treatment with serum and subsequent incubation with *S.epidermidis* for 4 h. A serum-treated catheter maintained in medium (diamonds) alone was used as a control experiment.

Analysis by SEM of surface degradation. A series of *in vitro* studies was performed to further elucidate underlying mechanisms: incubation in fresh human serum to simulate proteolytic degradation; incubation with 3% hydrogen peroxide to simulate oxidative polymer surface degradation. As depicted in Figure 1e and 1g, holes of similar diameter range as seen *in vivo* after 1 week of dialysis with CC (Figure 1c) were found on the CC but not on the MC surface (Figure 1f and 1h).

Microscopic characterization of surface structure and catheter cross-section. AFM applied to plain polyurethane films confirmed the presence of microdomains in the surface structure of the block copolymer containing polyurethane (MC) (Figure 2b) which were absent in the pure polyurethane (CC) (Figure 2a).

Cross-sectional analysis with SEM revealed the characteristic surface with improved smoothness of the MC (Figure 3b) compared to the CC (Figure 3a).

Quantification of $BaSO_4$ release. Greyscale analysis of SEM images of *in vitro*-degraded CC surfaces revealed hole formation due to release of $BaSO_4$ moieties of 5.65% (range 4.7 to 6, $n = 4$) of surface area after contact with hydrogen peroxide and 7.65% (range 4.4 to 8.2, $n = 4$) after incubation with human serum which is in the same range as found for CC after *in vivo* use. Bright electron-dense $BaSO_4$ moieties covered 5.2% (range 1.2 to 33.6%) of the surface after incubation with hydrogen peroxide and 6.15% (range 1.9 to 19.5) after incubation with serum.

Bacterial adhesion and growth on degraded catheter surfaces. Two catheters of each type that had been in contact with serum were challenged with *S. epidermidis* for 4 h and subsequently analysed by the BacTrac method to assess the influence of surface degradation on bacterial adherence and activity.

As depicted in Figure 4, a continuous linear increase in impedance is observed for CC but not MC, indicating ion formation from cleavage of molecules with low or no electric charge by the metabolic activity of proliferating bacteria. MC revealed a markedly delayed bacterial activity, whereas on the surface of the degraded CC, an immediate and strong bacterial growth was observed. In two parallel experiments, impedance with CC increased by 6.47 and 12.81% after 180 min. In contrast, on MC, the change in impedance after 180 min of 0.03 and −0.20% was indistinguishable from that of medium alone (−0.45%).

Multiple linear regression analysis indicated a significant time by catheter interaction, with an increase in impedance of 0.512%/10 min in CC compared to −0.021%/10 min in MC catheters ($P < 0.001$ for interaction; model $R^2 = 0.87$, $P < 0.001$).

Discussion

The present study identifies the release of $BaSO_4$ as an important factor contributing to irregularities of the catheter surface after contact with blood. Summing up the areas covered with holes and with bright electron-dense $BaSO_4$ moieties, as identified with EDX, results in a percentage area that closely corresponds to the area covered by $BaSO_4$ moieties at the new CC surface, as assessed with greyscale analysis. Based on these findings, we conclude that release of $BaSO_4$ might be the predominant mechanism leading to surface defects.

Moreover, we were able to demonstrate that these defects are related to an increased susceptibility to bacterial growth. Coating of the catheter with a thin polyurethane/SMA layer prevented the release of $BaSO_4$ and conferred protection against bacterial proliferation. From these results, we hypothesize that catheter-related infections, one

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of the two major complications of haemodialysis catheters and a major cause of morbidity and mortality among dialysis patients, can be preceded by surface irregularities as a common pathway and that the release of $BaSO_4$ plays an important role in this process. Likewise, and although not addressed in the present study, also thrombogenicity might be enhanced by this roughness due to surface irregularities. Bacterial adhesion and biofilm formation, however, may start very rapidly after catheter insertion, so that roughness should be considered as one of the many factors that may play a role in this complex process.

The finding of this study that catheter surface irregularities result from the release of $BaSO_4$ from the catheter surface provides new insights in the mechanisms involved in the thrombogenicity and susceptibility to infection of artificial surfaces. Many other medical devices such as pacemaker leads, vascular ports and arterial catheters contain $BaSO_4$ moieties. Therefore, these results may be relevant for a wide range of medical disciplines and may have large implications on future evolutions in design and development of biomaterials in medicine, especially since this effect can be prevented by adequate coating of the catheter surface.

Previous studies have shown that catheters with rougher surfaces are more thrombogenic than those with smooth surfaces because surface irregularities play a major role in the initiation of thrombosis in and on intravascular catheters [5]. The reason why some catheters have smoother surfaces than others has not been well evaluated. Manufacturing processes such as drilling of side holes [10] as well as the physicochemical properties of the material may play a role. Polyethylene catheters tend to be less thrombogenic than polyurethane catheters that have a rough and irregular surface [17,18]. Our study revealed for the first time the release of $BaSO_4$ moieties during contact with blood as an important mechanism contributing to surface irregularities. This explains the previously observed association of roughness with the presence of radio-opaque particles. In one study, irregularities were concentrated into radio-opaque tracer strips [5]. A recent case report of a broken haemodialysis catheter implicated irregular $BaSO_4$ powder lumps that formed elongated cavities on extrusion [19]. These aggregates of $BaSO_4$ were very similar to those observed in our study. Another study described a very irregularly arranged structure at distance marks containing radio-opaque admixtures, which were placed on the surface and parts of the catheter wall [6]. Moreover, it was demonstrated in these studies that these parts of the catheter wall were much more prone to adhesion of formed elements of the blood and bacteria or spores than other areas of the wall. An SEM study of Franson *et al.* revealed lodgment of bacteria into surface irregularities in both infected catheters *in vivo* and unused catheters *in vitro* [20]. Irregularities of artificial surfaces thus also favour the adhesion of microorganisms, either directly or indirectly by adhesion to conditioning films formed by the precipitation of proteins such as fibrinogen, fibronectin and laminin. Bacterial adhesion subsequently triggers the expression of genes responsible for biofilm formation [9].

Besides damage to the catheter surface, the release of $BaSO_4$ may also exert deleterious effects related to the toxicity of the compound itself. At clinically relevant concentrations, $BaSO_4$ causes a deactivation of the phagocytic response upon stimulation [21]. Due to the sustained release of $BaSO_4$ from the catheter surface, local $BaSO_4$ concentrations could be reached that are sufficient to produce a similar effect thus lowering the immunologic defence against bacterial colonization and biofilm formation.

The recognition of the adverse effects of surface irregularities stimulated the development of devices with microdomain-structured synthetic polymer surfaces. These block copolymers, also called SMAs, are blended in a reactive mixture with polyurethane polymer resins and coated on device surfaces, as was the case for the SMA dialysis catheter (MC) we used (US patent 6841255). SMAs improve biocompatibility by delaying contact activation and reducing thrombin–antithrombin complex generation [12], and diminish the thrombogenicity by hampering adhesion of platelets [22,23]. The SMA-coated catheters we used had a very smooth surface compared to the conventional catheters, and more importantly, this coating prevented the release of $BaSO_4$ by sealing the surface with a continuous and closed polymer film. Hence, SMA coating confers an additional benefit of preventing damage to the catheter surface induced by $BaSO_4$ release. The *in vitro* model we used allowed us to confirm that coating with SMA also protects against bacterial proliferation, even after an important bacterial load. Obtaining a smoother surface by SMA coating thus reduces susceptibility to bacterial adhesion. Surface irregularities resulting from the release of $BaSO_4$ may represent a common causative pathway for these complications.

A drawback of the present study is that, although it is partly based on catheter samples collected *in vivo*, it does not evaluate hard clinical endpoints. Before starting a clinical study of sufficient power, we needed, however, to evaluate whether our hypothesis of barium moiety loss and creation of surface irregularity indeed could be corroborated morphologically. By adding bacteriological studies on catheters which had been treated by serum, and which showed the same characteristics as catheters extricated *in vivo*, we could in addition show that these irregularities indeed were linked to increased susceptibility to bacterial growth. For ethical reasons, we could only perform this randomized crossover study in clinical conditions where a temporary catheter was needed. Although long-term indwelling catheters are protected by the barrier of the subcutaneous trajectory, they also contain barium and are exposed to the bloodstream for much longer periods than in the present study. Therefore, we expect that the changes observed in temporary catheters after only 1 week, also occur in indwelling catheters. The clinical impact of $BaSO_4$ release, both in tunnelled-cuffed catheters and in temporary catheters, remains to be determined.

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Conflict of interest statement. This study was sponsored by Gambro.

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MP356 LESS THROMBOGENIC MICROPATTERNED POLYMER MODIFIED SURFACE IMPROVES TEMPORARY HEMODIALYSIS CATHETER SURVIVAL IN PATIENTS WITH END-STAGE RENAL DISEASE

Pascal Meier, Rachel Meier, Edouard Blanc. *Service of Nephrology, CHCVs Hopital de Sion, Sion, Switzerland*

(b)(4)

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Test Protocol

Mechanical testing of dialysis catheters non coated and coated with SMA according ISO 10555-1

(b)(4)

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PROTOCOL FOR ACCELERATED AGING (b)(4)
(b)(4) (GAMBRO DIALYSATOREN) HEMODIALYSIS CATHETER (b)(4)
(b)(4)

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GAMBRO. Gambro Kathetertechnik Hechingen

Test Report		Ident.-No: (b)(4)	
Subject:	Shelf life of thrombogenicity for GamCath High Flow Dolphin (SMA) catheters	Date: 05.05.2010	
		Sign:	(b)(4)
Receiver:	(b)(4)		

(b)(4)

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GAMBRO Renal Products Gambro Kathetertechnik Hechingen

Test Report	Ident.-No: (b)(4)
Subject: Delamination test of SMA coated PUR Catheters after 5 years ageing (Shelf life)	Date: 22.01.2007 (b)(4)
Receiver:	

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GAMBRO Renal Products Gambro Kathetertechnik Hechingen

Test Report	Ident.-No: (b)(4)
Subject: Clamp test of SMA coated PUR Catheters after 5 years ageing (Shelf life)	Date: 11.07.2007
Receiver:	(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center ¿ WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

November 12, 2010

GAMBRO RENAL PRODUCTS, INC.
14143 DENVER WEST PARKWAY SUITE 400
LAKEWOOD, COLORADO 80401
UNITED STATES
ATTN: KAE MILLER

510k Number: K100451
Product: GAMCATH HIGH FLOW DOLPHIN MS-G

Extended Until: 12/13/2010

Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information (AI) is not received by the "Extended Until" date shown above, your premarket notification will be considered withdrawn (21 CFR 807.87(l)). If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

Marjorie Shulman

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

GAMBRO Renal Products

Gambro Renal Products, Inc.
14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 222 6500

November 8, 2010

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

FDA CDRH DMC
NOV 09 2010
Received

RE : 510(k) K100451 – GamCath HighFlow Dolphin Catheter

Dear Dr. Cooper:

Gambro would like request an extension of time to prepare our response to your email questions dated October 13, 2010 requesting additional information for K100451.

We would like to request an additional 30 days to prepare our response.

I can be reached at 303.222.6724 or by email at kae.miller@us.gambro.com.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

K24

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Annex 7

IFU

The Instructions for Use for the predicate device in K040301

are provided in Annex 7-2

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Short-term vascular access for hemodialysis, hemoperfusion and apheresis therapy with GamCath HighFlow Dolphin Catheters

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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OPERATOR'S MANUAL

SHORT-TERM VASCULAR ACCESS FOR HEMODIALYSIS, HEMOPERFUSION AND APHERESIS THERAPY WITH GAMCATH CATHETERS

CAUTIONS

- The guidewire should thread easily into the vein without resistance.
- If during insertion of the guidewire a resistance is noticed or further movement is not possible, the guidewire must be removed together with the combined product.
- Cardiac arrhythmia may result if the guidewire is allowed to pass into the right atrium. It is therefore recommended to monitor the procedure either by ECG or sonography.
- Before every use the correct position of the catheter has to be checked.

WARNING! DO NOT pull back the guidewire through the insertion needle as this may sever the tip of the wire. If the guidewire must be removed, withdraw needle and guidewire together.

7. While holding the guidewire in place, remove the insertion needle and discard.
8. Secure the guidewire in place.
9. Create a small incision at the insertion site.
10. Use the dilator to widen the tissue. Pass it over the guidewire into the tissue. Make sure not to damage the vessel.
11. Withdraw the dilator.
12. Insert the catheter over the guidewire by gentle rotation through the tissue into the vessel. For this, in double-lumen catheters the venous lumen should be used. Insert the catheter to the appropriate depth. At the same time ensure that the guidewire is free by withdrawing it in small steps. For best safety and patient comfort the catheter should be inserted all the way down to the guide mark.
13. Withdraw the guidewire and close the clamp. For catheters with inner dilator / stylette, the inner dilator / stylette should be removed together with the guidewire.
14. Test the flow: Attach a 20 ml syringe, unclamp the catheter extension line and aspirate blood and any air present. The syringe should fill up to 20 ml within 6 seconds, which corresponds to a blood flow of 200 ml/min. This test should be performed on all lumens.
15. When a satisfactory flow is achieved, flush each lumen with at least 20 ml of sterile saline.
16. Instil heparin as per the priming volume stated on the catheter clamp and close the clamp.

CAUTION! Clamp each lumen under positive pressure. Failure to clamp lumens can lead to air embolism or extensive blood loss.

17. Put caps provided by the manufacturer on the connectors of the extension lines.
18. To avoid migration the catheter should be secured by sutures and a proper wound dressing should be applied.

CAUTION! Correct catheter placement should be verified through the use of fluoroscopy or X-ray.

GUIDELINES FOR CATHETER AND EXIT-SITE CARE

WARNING! DO NOT use alcohol or acetone based products or ointments. Failure of catheter will result. Iodine based solutions without alcohol are recommended as the antiseptic solution that can be used with this catheter.

- Keep the catheter and the exit-site dry.
- Never leave the catheter open. Always seal with syringes or caps.
- Ensure that the suture is correctly placed. The catheter should not be able to move in and out of the exit-site.
- Exchange the caps after each treatment.
- Cover the extension lines between treatments.

GUIDELINES FOR APPLICATION OF HEPARIN LOCK

1. After extracorporeal treatment, flush with 20 ml sterile saline and instil fresh heparin.
2. To maintain patency between treatments, keep the lumens of the catheter filled with a sufficient concentration and volume of heparin. In most cases, a concentration of 5,000 units/ml is most successful. Refer to the priming volume imprinted on the clamp of the catheter.
3. Instil fresh heparin, flushing quickly to ensure that heparin reaches the distal end of the lumens. Instilling too slowly may cause heparin to exit the catheter from the proximal inlet holes, leaving the distal hole unprotected against thrombus formation.
4. Clamp the extension lines under positive pressure.

WARNING! To further prevent thrombus formation at the tip of the catheter, the clamp on the extension tube should not be opened once the lumen has been primed with heparinized saline. If the clamp has to be opened, the priming volume of that lumen would increase slightly as a result of the extension tube returning to its "normal", unclamped state. This would create a vacuum at the tip, causing blood to be sucked up into the distal portion of the catheter, ultimately resulting in thrombus formation.

GUIDELINES FOR CATHETER REMOVAL

CAUTION! Only a qualified, licensed physician should remove the catheter.

1. Place the patient in the Trendelenburg position. (Not applicable with femoral catheters.)
2. Remove suture of the catheter.
3. Compress the venous entry site and pull the catheter gently out of the vessel.
4. Apply appropriate wound dressing.

NOTE! Because of the risk of bleeding, the patient should, if possible, sit up rather than lie down after the catheter removal. (Not applicable with femoral catheters.)

TROUBLESHOOTING

One-way obstruction

Suspect one-way obstruction when a lumen can be flushed but cannot be aspirated. This is usually caused by tip malposition with the catheter suctioned against the vessel wall.

One of the following adjustments may eliminate the obstruction (sutures may have to be removed):

- Reposition the patient.
- Have the patient hold his arm above his head and cough. (Not applicable with femoral catheters.)
- Flush with sterile saline to push the catheter away from the wall.
- Rotate the catheter. (Not applicable if the catheter is sutured to skin.)
- Withdraw the catheter slightly to reposition the tip. (Not applicable if the catheter is sutured to skin.)

WARNING! DO NOT insert the catheter further into the vein as vessel damage, cardiac arrhythmia and increased infection rate could result.

Kinking

- Check catheter position.
- Check sutures at the exit-site.
- Does the catheter move in and out of the exit-site?
- Does it bend when the patient moves or lies on the same side as the catheter site?

Symptoms of kinking at the tip include decreased blood flow and increased venous resistance. An X-ray can confirm internal kinking.

Vessel collapse or spasm

Start and adjust pump speed slowly.

Thrombus formation

1. If catheter is blocked, first check to ensure it is not kinked.
2. If a thrombus is present, attempt to aspirate the clot gently with a syringe. If blood flow is still low, or blood cannot be withdrawn at all, the physician may choose to dissolve the clot with a chemical intervention utilizing an approved anti-thrombolitic agent.

WARNING! DO NOT use excessive force when flushing an obstructed lumen. Overpressurizing the catheter will damage it and can cause trauma to the patient.

NOTE!

- A catheter could be blocked by a substance other than a blood clot.
- The cleared catheter may be used immediately.

Infection

Any signs of catheter-related infection have to be considered as an indication for catheter removal.

CAUTION! Due to the risk of exposure to blood borne pathogens, health care professionals should always use Universal Blood and Body Fluid Precautions in the care of all patients.

WARRANTY AND LIMITATION OF LIABILITY

a) The manufacturer warrants that GamCath catheters have been manufactured in accordance with their specifications and in compliance with Medical Device Directive 93/42/EEC, other applicable industry standards and regulatory requirements. If provided with the lot number of the defective product, the manufacturer will, by replacement or credit, remedy manufacturing defects in GamCath catheters becoming apparent before the expiration date.

b) The warranty under paragraph a) above is in lieu of, and to the exclusion of, any other warranty, whether written or oral, expressed or implied, statutory or otherwise, and there are no warranties of merchantability or other warranties which extend beyond those described in paragraph a) above. The remedy set out above for manufacturing defects is the sole remedy available to any person as a result of to defects in the GamCath catheters and the manufacturer shall not be liable for any consequential or incidental loss, damage, injury or expense arising directly or indirectly from the use of the GamCath catheters, whether as a result of any defect therein or otherwise.

c) The manufacturer shall not be liable for any misuse, improper handling, non-compliance with warnings and instructions, damage arising from events after the manufacturer's release of the GamCath catheters, failure or omission to inspect the product before use in order to insure that the GamCath catheter is in proper condition, or any warranty given by independent distributors or dealers.

d) The manufacturer is Joka Kathetertechnik, Linsenaecker 1, 72379 Hechingen, Germany.

Covered by one or several of the following patents: US 6 500 549, US 5 203 056, DE 41 18 732, EP 0 517 000, JP 2 035 892, other patents pending.

CHF0043220 / rev. 04.04

CE 0086

U.S. contact
Gambro Renal Products
(US Headquarters)
10810 West Collins Avenue - Lakewood
US-COLORADO 80215-4498
Tel: 1-303 232 6800
Fax: 1-303 231 4310

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

SHORT-TERM VASCULAR ACCESS FOR HEMODIALYSIS, HEMOPERFUSION AND APHERESIS THERAPY WITH GAMCATH CATHETERS

EXPLANATION OF SYMBOLS

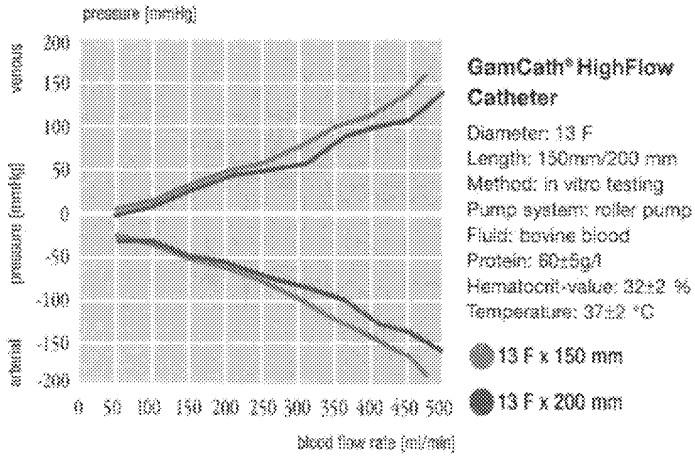
- = Read instructions before use
- = For single use only
- = Sterilized using ethylene oxide
- REF = Code number
- LOT = Lot number
- = Insertion length
- = Sterilization date
- = Expiry date
- = Diameter
- Rx = Federal law (USA) restricts this device to sale by or on the order of a physician

MATERIAL LIST

Product	Description	Material	Abbreviation
Catheter, Polyurethane (PUR), 1 lumen or multilumen	Catheter tube	Polyurethane	PUR
	Extension line	Polyurethane	PUR
	Connector	Polyvinylchloride	PVC
	Protection cap	Polyethylene	PE
Dilator	Dilator	Tetrafluorethylene	FEP
Inner Dilator	Inner Dilator	Tetrafluorethylene	FEP
Inner Dilator	Inner Dilator	Polypropylene	PP
Stylette	Stylette	Polypropylene	PP
Guidewire	Guidewire	Stainless steel	-
	Dispenser	Polypropylene	PP
Injection cap	Cap	Polypropylene	PP
	Membrane	Synthetic Isoprene	IR
Puncture Needle	Needle tube	Stainless steel	-
	Needle hub	Polycarbonate	PC
Wound dressing	Film	Polyurethane	PUR

FLOW RATE OF GAMCATH HIGH-FLOW CATHETER

(as suggested by in vitro data)



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GAMBRO Renal Products

Gambro Renal Products, Inc.
14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 222 6500

June 4, 2010

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

FDA CDRH DMC

JUN 08 2010

Received

RE : 510(k) K100364

Dear Mr. Pudwill:

Gambro would like request an extension of time to prepare our response to your letter requesting additional information for K100451.

We would like to request an additional 120 days to prepare our response.

I can be reached at 303.222.6724 or by email at kae.miller@us.gambro.com.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

1C23

(b)(4)

396

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

February 18, 2010

GAMBRO RENAL PRODUCTS, INC.
14143 DENVER WEST PARKWAY SUITE 400
LAKEWOOD, COLORADO 80401
UNITED STATES
ATTN: KAE MILLER

510k Number: K100451
Received: 2/17/2010
Product: GAMCATH HIGH FLOW DOLPHIN MS-G

The Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH), has received the Premarket Notification, (510(k)), you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act(Act) for the above referenced product and for the above referenced 510(k) submitter. Please note, if the 510(k) submitter is incorrect, please notify the 510(k) Staff immediately. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in all future correspondence that relates to this submission. We will notify you when the processing of your 510(k) has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (DMC) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official 510(k) submission.

On September 27, 2007, the President signed an act reauthorizing medical device user fees for fiscal years 2008 - 2012. The legislation - the Medical Device User Fee Amendments of 2007 is part of a larger bill, the Food and Drug Amendments Act of 2007. Please visit our website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm
for more information regarding fees and FDA review goals. In addition, effective January 2, 2008, any firm that chooses to use a standard in the review of ANY new 510(k) needs to fill out the new standards form (Form 3654) and submit it with their 510(k). The form may be found at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.

We remind you that Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the PHS Act by adding new section 402(j) (42 U.S.C. § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Section 402(j) requires that a certification form http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm accompany 510(k)/HDE/PMA submissions. The agency has issued a draft guidance titled: "Certifications To Accompany Drug, Biological

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007" http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134034.htm. According to the draft guidance, 510(k) submissions that do not contain clinical data do not need the certification form.

Please note the following documents as they relate to 510(k) review: 1) Guidance for Industry and FDA Staff entitled, "Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs and BLA Supplements". This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. Please refer to this guidance for information on a formalized interactive review process. 2) Guidance for Industry and FDA Staff entitled, "Format for Traditional and Abbreviated 510(k)s". This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

In all future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's e-Copy Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please visit our web site at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.html. In addition, the 510(k) Program Video is now available for viewing on line at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm070201.htm .

Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

Lastly, you should be familiar with the regulatory requirements for medical devices available at Device Advice http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm. If you have questions on the status of your submission, please contact DSMICA at (301)796-7100 or the toll-free number (800)638-2041 , or at their internet address http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm. If you have procedural questions, please contact the 510(k) Staff at (301)796-5640.

Sincerely,

510(k) Staff

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852, Released by CDRH on 09-13-2024

K100451 SE A001

GAMBRO Renal Products

14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 222 6500

June 18, 2010

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 – G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: FDA Additional Information Request for 510(k) K100451 for the GamCath® High Flow Dolphin® Catheter

To Whom It May Concern:

Enclosed please find the response to the FDA request for additional information dated April 19, 2010, in reference to the Traditional 510(k) for GamCath® High Flow Dolphin® Catheter, submitted by Gambro Renal Products, Inc. on February 16, 2010.

The information requested from the FDA is restated followed by Gambro's response. Please contact me by telephone at 303.222.6724 or by fax at 303.222.6916 with any questions regarding this additional information. I can also be reached by email at kae.miller@us.gambro.com.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

FDA CDRH DMC
JUN 21 2010
Received

K 54

(b)(4)

Gambro CONFIDENTIAL

158

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

FDA Request for Additional Information Dated April 19, 2010:

(b)(4)

159

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GAMBRO Renal Products

14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 222 6500

December 8, 2010

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 – G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: FDA Additional Information Request for 510(k) K100451 for the GamCath® High Flow Dolphin® Catheter

To Whom It May Concern:

Enclosed please find the response to the FDA request for additional information via email dated October 13, 2010, in reference to the Traditional 510(k) for GamCath® High Flow Dolphin® Catheter, submitted by Gambro Renal Products, Inc. on February 16, 2010.

The information requested from the FDA is restated followed by Gambro's response. Please contact me by telephone at 303.222.6724 or by fax at 303.222.6916 with any questions regarding this additional information. I can also be reached by email at kae.miller@us.gambro.com.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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FDA Request for Additional Information via Email Dated October 13, 2010:

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Indications for Use Statement

510(k) Number (if known):_____

Device Name: GamCath® High Flow Dolphin® Catheter

Indications for Use Statement:

GamCath® High Flow Dolphin® catheters are indicated for use in attaining short term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. GamCath® High Flow Dolphin® Catheter is not intended for use in pediatric patients.

Prescription Use ___X_____ (Part 21 CFR 801 Subpart D)	AND/OR	Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

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510(k) SUMMARY

Submitter's Name	Gambro Renal Products, Inc.
Address	14143 Denver West Parkway, Suite 400 Lakewood, Colorado 80401
Establishment Registration Number	2087532
Contact Person	Kae Miller, Regulatory Affairs Manager
Telephone Number	303.222.6724
Fax Number	303.222.6916
Date Summary Was Prepared	December 02, 2010

Device Information	
Name of the Device	GamCath® High Flow Dolphin® Catheter
Common or Usual Name	Short-Term Hemodialysis Catheter
Classification Name	Catheter Hemodialysis Non-Implanted
Device Class	II
Product Code	MPB
Regulation Number	21 CFR 876.5540

Predicate Device Information (1)	
Name of the Device	GamCath® High Flow Catheter
510(k) Number	K040301
Classification Name	Catheter Hemodialysis Non-Implanted
Device Class	II
Product Code	MPB
Regulation Number	21 CFR 876.5540

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Predicate Device Information (2)	
Name of the Device	Medcomp Duo-Flow II Catheter with Lubricious Heparin
510(k) Number	K991320
Classification Name	Catheter Hemodialysis Non-Implanted
Device Class	II
Product Code	MPB
Regulation Number	21 CFR 876.5540

DEVICE DESCRIPTION

The GamCath® High Flow Dolphin® Catheters are single use medical devices for short term use to obtain vascular access in patients with acute or chronic renal failure. The GamCath® High Flow Dolphin® Catheter combines the GamCath® High Flow Catheter with an additional coating based on a block copolymer. The polymer layer results in a surface structure that locks in barium sulfate particles. The coated catheter is free of heparin, therefore the use of the catheter is not contraindicated in patients with HIT syndrome.

Catheters made of Polyurethane are equipped with small rotatable Polypropylene suture rings, still allowing rotation of catheter when sutured to skin. Polyurethane Extension lines, present on each lumen, are equipped with PVC luer-lock connectors according to ISO 594-1 with Polyethylene protection caps and are provided with clamps which may be color coded to indicate the venous (blue), arterial (red). Clamp inserts bear easily legible and permanently fixed imprints indicating usable catheter length and outer diameter of catheter shaft (in French calibration) as well as priming volumes. The Catheter is available in 13 French and 11,5 French straight and curved extension line configuration. An inner dilator made of FEP is provided in the venous lumen for insertion. The insertion length is available in range from 150 mm (5.906“) up to 250 mm (9.843”). The Dolphin coating is a co-polymer film which is applied over the catheter surface to form a continuous surface that has a smoother surface morphology than an untreated catheter. The copolymer film is formed by providing a hydrophobic polymer block, such as polydimethylsiloxan (PDMS) with functional –OH end groups.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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INDICATIONS FOR USE

GamCath® High Flow Dolphin® catheters are indicated for use in attaining short term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. GamCath® High Flow Dolphin® Catheter is not intended for use in pediatric patients.

TECHNOLOGICAL CHARACTERISTICS COMPARED TO PREDICATE DEVICE

The GamCath® High Flow Dolphin® Catheter is substantially equivalent to the GamCath® High Flow Catheter, K040301 and the MedComp Duo-Flow II Catheter with Lubricious Heparin manufactured by Medical Components, Inc. K991320.

Substantial equivalency was shown by detailed comparisons of Intended Use, Patient Population, Mode of Operation, Labeling and Catheter Type. Technological characteristics showed substantial equivalency with respect to material of the catheter (Connector, Catheters Tube, Extension Line), position of insertion of the catheter, sizes of the catheter, design/physical characteristics (number of lumens, sterility, distal end configuration, intended anatomical location of distal end, proximal end configuration).

Both GamCath® High Flow Dolphin® Catheter and MedComp Duo-Flow II Catheter are having a coating. The materials used differ. MedComp Duo-Flow II Catheter uses a lubricious heparin coating whereas GamCath® High Flow Dolphin® Catheter uses the Dolphin® coating. The Dolphin coating is a co-polymer film which is applied over the catheter surface to form a continuous surface. In general the copolymer film is formed by providing a hydrophobic polymer block, such as polydimethylsiloxan (PDMS) with functional –OH end groups. The reliance of Dolphin coating was placed on testing against recognized standards to evaluate safety and performance (see section non-clinical performance data below). GamCath® High Flow Dolphin® catheter coating is free of heparin; therefore the use of the catheter is not contraindicated in patients with HIT syndrome.

NON-CLINICAL PERFORMANCE DATA

The non-clinical tests submitted included biocompatibility data as per ISO 10993-1 (including Cytotoxicity, Sensitization, Intracutaneous reactivity, Acute Systemic toxicity, Genotoxicity, and Hemolysis). Ethylene Oxide sterilization was validated as per ISO 11135-1 and 10993-7. Package integrity testing was done successfully.

Substantial equivalence versus the predicate device was shown by the following tests: Integrity of the catheter was shown by testing for air leakage and liquid leakage as per ISO 10555-1. Clamping tests up to 300 cycles were done to prove absence of visible delamination or visible detachable particles. Pressure in the catheter was measured over the range of flow rates. Performance data was collected to verify tensile strength according ISO 10555-1 of Connector to extension line, Extension line to hub (bifurcation), Hub to catheter shaft, and Catheter shaft to tip.

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CONCLUSION OF SAFETY AND EFFECTIVENESS

The comparison of technological characteristics demonstrated that GamCath® High Flow Dolphin® Catheters are substantially equivalent to the predicate devices. The GamCath® High Flow Dolphin® Catheters met all performance criteria of the test performed and is safe and effective when used as intended.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Operator's Manual

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Short-term vascular access for hemodialysis, hemoperfusion and apheresis therapy with GamCath HighFlow Dolphin Catheters

Contents

- Definition of expressions used in this manual
- General warnings and cautions
- Specifications
- Indications
- Contraindications
- Adverse reactions
- Directions for use
  - Guidelines for insertion of catheters
  - Insertion site
  - Preparation
  - Guidelines for catheter and exit-site care
  - Guidelines for application of heparin lock
  - Guidelines for catheter removal
  - Troubleshooting
- Warranty and limitation of liability

Definition of expressions used in this manual

WARNING! is used to alert the operator **NOT** to take a specific action that may cause a hazard which, if ignored, could result in an adverse reaction, injury or death.

CAUTION! is used to alert the operator to **TAKE** a specific action to protect against a possible hazard which, if ignored, could have an adverse reaction on the patient or equipment.

NOTE! is used to remind the operator of normal treatment functions and what is the suitable action in a particular situation.

General warnings and cautions

The medical techniques and procedures described in these instructions do not represent all medically acceptable protocols, nor are they intended as a substitute for the physician's experience and judgement in treating any specific patient. The following procedures are offered to clinicians only as a guide.
Read all instructions about the GamCath HighFlow Dolphin Catheters carefully before using them.
To ensure safe and effective treatment, the following information must be observed.
Please ensure that you are completely familiar with the complications listed below prior to inserting a GamCath HighFlow Dolphin Catheter:
air embolism, atrial or ventricular perforation, bacteremia, brachial plexus injury, cardiac arrhythmia, cardiac tamponade secondary to vessel wall, catheter embolism, central venous thrombosis, dysrhythmias, endocarditis, exit-site infection, exsanguination, femoral artery puncture, femoral nerve injury, hematoma formation, hemorrhage, hemothorax, laceration of the vessel, luminal thrombosis, nerve damage, perforation of the vessel, pleural or mediastinal injury, pneumothorax, retroperitoneal bleed, right atrial puncture, septicemia, subclavian/inadvertent artery/arterial puncture, subcutaneous hematoma, subcutaneous tunnel infection, superior vena cava puncture, thoracic duct laceration, thrombosis, trauma to major vessel or right atrium, vascular thrombosis.

Cautions

- For single use only. **DO NOT** reuse, reprocess or resterilise. Reuse, reprocessing or resterilisation may create a risk of contamination of the device and cause patient infection or cross infection, including, but not limited to the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.
- Contents sterile and non-pyrogenic in unopened, undamaged package.
- Sterilized by ethylene oxide.
- **DO NOT** use if unit package is damaged.
- **DO NOT** store with chemicals. Failure of catheter can result.
- Recommended storage conditions: below +30°C (+86°F).
- **DO NOT** use catheter or accessories if any sign of product damage is visible.
- **DO NOT** use catheter or accessories when expiry date indicated on labeling is lapsed. The manufacturer will not be liable for any damage caused by use of expired products.
- The devices should only be used by licensed physicians who are totally familiar with the procedure.
- Use maximal sterile barrier precautions during catheter insertion and removal.
- Strict aseptic technique including the use of a cap, mask, sterile gown, sterile gloves, and a large sterile sheet must be used during the insertion procedure. Have patient wear mask.
- Strict aseptic technique including the use of a cap, mask, sterile gown, sterile gloves for staff and patient, and a large sterile sheet must be used during the removal procedure.
- Strict aseptic technique including the use of a surgical mask for staff and patient and clean gloves must be used during maintenance procedures.
- Before every use the correct position of the catheter has to be checked.
- After use, this product may be a potential hazard. Handle and dispose of in accordance with accepted medical practice and applicable local, state and federal laws and regulations.
- Percutaneous procedures require confirmation of correct placement by fluoroscopy or chest X-ray.
- Place the patient in the Trendelenburg position on a firm surface during catheter placement, flushing/heparinization, or other procedure. (Not applicable with femoral catheters.)
- Avoid air embolism by keeping the catheter clamped at all times when not connected to syringes or blood lines.
- Use only protection caps and other accessories provided by the manufacturer.
- Luer connectors of GamCath HighFlow Dolphin Catheters comply with international standard ISO 594. Safe and tight connection, however, can only be assured when the matching bloodline connector is also in compliance with this standard. Use of bloodline connectors deviating from the above standard may cause problems during connection such as stress cracks and leaks which are associated with risks of air embolism and blood loss.
- Protection caps and tubings should be connected without applying excessive force.
- Overtighting catheter connection can crack luer connectors.
- Place clamps only in the centre of the extension lines. Repeated clamping particularly near or on the hard plastic portion by the connectors may cause tubing fatigue and possible disconnection.
- With each change in tubing connections, purge air from the catheter and all connecting tubing.
- Before initiating treatment, aspirate indwelling heparin and discard.
- The catheter must be re-filled with heparin after each use in order to maintain patency.
- **DO NOT** infuse against a closed clamp or forcibly infuse a blocked catheter: back pressure will cause catheter failure.
- Tape all non-locking connections to prevent accidental separation.
- The catheter must always be secured against dislocation by additional plaster adhesions.
- Tape the caps between treatments to safeguard them against accidental removal.
- A clotted catheter should be replaced if the clot cannot be aspirated or dissolved (see also Troubleshooting: Thrombus formation).
- Patients requiring ventilator support are at increased risk of pneumothorax during subclavian vein cannulation.
- Remove the catheter as soon as it is no longer necessary.
- Federal law (USA) restricts this device to sale by or on the order of a physician.

Warnings

- **DO NOT** expose extension tubes to sharp edges or objects such as metal clamps and **DO NOT** use scissors to remove dressing as extension tubes can be damaged and fatal blood loss or air embolism can occur.
- **DO NOT** use alcohol, drugs containing alcohol, acetone based products or ointments. Failure of catheter will result. Iodine based solutions without alcohol are recommended as the antiseptic solution that can be used for care of this catheter.
- **DO NOT** resterilize the catheter by any method. The manufacturer will not be liable for any damage caused by reuse of this product.
- **DO NOT** damage the catheter when suturing.
- **DO NOT** use a heparin lock for patient with heparin induced thrombocytopenia (HIT) syndrome.

Specifications

Product description and materials:

The GamCath HighFlow Dolphin Catheter combines the GamCath HighFlow Catheter with an additional coating based on a block copolymer. The polymer layer results in a surface structure that locks in barium sulfate particles. The coated catheter is free of heparin, therefore the use of the catheter is not contraindicated in patients with HIT syndrome.

Priming volumes:

See preprint at the guiding insert of the clamps on every catheter.

Flow path:

In multilumen catheters the arterial side is indicated by the red clamp and the venous side is indicated by the blue clamp.

Indications

GamCath HighFlow Dolphin Catheters are indicated for use in attaining short-term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. GamCath HighFlow Dolphin Catheter is **NOT** intended for use in pediatric patients.

Contraindications

These catheters are not intended for any use other than which is indicated. **DO NOT** insert the catheter in thrombosed vessels.

Adverse reactions

Special attention must be paid to patients with known hypersensitivity reactions to products sterilized with ethylene oxide, to components itemized in the material list or other allergic reactions with other substances. The consultation of a physician is indispensable to judge the risk and take appropriate action if there is a suspicion of a hypersensitivity reaction.

Directions for use

Guidelines for insertion of catheters

CAUTION! Strict aseptic technique including the use of a cap, mask, sterile gown, sterile gloves, and a large sterile sheet must be used during the insertion procedure.

NOTE! The physician must utilize his or her own judgement, experience and discretion in determining which insertion technique should be used for each individual patient.

The selection of the appropriate catheter length is at the sole discretion of the physician. To achieve proper tip placement, proper catheter length selection is important.

CAUTION! The location of the vessels should be detected by appropriate technique each time before insertion.

Routine X-ray should always follow the initial insertion of this catheter to confirm proper placement prior to use.

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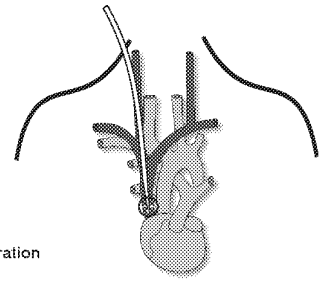
Short-term vascular access for hemodialysis, hemoperfusion and apheresis therapy with GamCath HighFlow Dolphin Catheters

Insertion site

WARNING! DO NOT place the catheter into or allow it to remain in the right atrium or right ventricle.

Tip Placement
(internal jugular/subclavian position)



Preparation

1. Use maximal sterile barrier precautions during catheter insertion.
2. The catheter must be inserted only under strict aseptic conditions in which the operator must wear a cap, mask, sterile gown, sterile gloves. A large sterile sheet must also be used during the insertion procedure. Have patient wear mask.
3. Flush all lumens of the catheter with heparinized saline and clamp all extension lines.

WARNING! To prevent air embolism, keep the catheter clamped at all times when not attached to a syringe, or blood lines.

4. **For subclavian and jugular insertion:** Place the patient in the Trendelenburg position, turning the head to the side opposite the insertion site.

   For femoral insertion: Place the patient flat on the back. Flex the patient's knee on the same side as the insertion site, while abducting and rotating the leg outwards.
5. A local anaesthetic is administered to the insertion site.
6. Following vessel puncture with the introducer needle, aspirate a small amount of blood to ensure the needle is correctly positioned in the vein.

CAUTION! If arterial blood is aspirated, remove the needle and apply immediate pressure to the site. Ensure that the bleeding has stopped and that no hematomas have developed before attempting to cannulate the vein again.

7. Insert the guidewire through the needle and into the vessel.
8. Advance the guidewire to the appropriate location in the vessel.

Cautions

- The guidewire should thread easily into the vein without resistance.
- If during insertion of the guidewire a resistance is noticed or further movement is not possible, the guidewire must be removed together with the combined product. If withdrawal cannot be easily accomplished, a chest X-ray should be obtained and further consultation requested.
- To avoid injury, **DO NOT** insert the guidewire or dilators forcibly.
- Also, cardiac arrhythmia may result if the guidewire is allowed to pass into the right atrium. It is therefore recommended to monitor the procedure either by ECG or sonography.
- Before every use the correct position of the catheter has to be checked.

WARNING! DO NOT pull back the guidewire through the introducer needle as this may sever the tip of the wire. If the guidewire must be removed, withdraw needle and guidewire together.

9. While holding the guidewire in place, remove the introducer needle and discard.
10. Secure the guidewire in place.
11. Create a small incision at the insertion site.
12. Use the dilator to widen the tissue. Pass it over the guidewire into the tissue. Make sure not to damage the vessel.
13. Withdraw the dilator.
14. Insert the catheter over the guidewire by gentle rotation through the tissue into the vessel. For this, in double-lumen catheters the venous lumen should be used. Insert the catheter to the appropriate depth. At the same time ensure that the guidewire is free by withdrawing it in small steps. For best safety and patient comfort the catheter should be inserted all the way down to the guide mark.
15. Withdraw the guidewire and close the clamp. For catheters with inner dilator/stylette, the inner dilator/stylette should be removed together with the guidewire.

WARNING! To prevent air embolism, expel all air from syringes before injecting solutions.

16. Test the flow: Attach a 20 ml syringe, unclamp the catheter extension line and aspirate blood and any air present. The syringe should fill up to 20 ml within 6 seconds, which corresponds to a blood flow of 200 ml/min. This test should be performed on all lumens.
17. When satisfactory flow is achieved, flush each lumen with at least 20 ml of saline.
18. Instil heparin as per the priming volume stated on the catheter clamp and close the clamp.

CAUTION! Clamp each lumen under positive pressure. Failure to clamp lumens can lead to air embolism or extensive blood loss.

19. Put caps provided by the manufacturer on the connectors of the extension lines.
20. To avoid migration the catheter should be secured by sutures and a proper wound dressing should be applied.

CAUTION! Correct catheter placement should be verified through the use of fluoroscopy or X-ray.

Guidelines for catheter and exit-site care

WARNING! DO NOT use alcohol, drugs containing alcohol, acetone based products or ointments. Failure of catheter will result. Iodine based solutions without alcohol are recommended as the antiseptic solution that can be used for care of this catheter.

CAUTION! Strict aseptic technique including the use of a surgical mask for staff and patient and clean gloves must be used during maintenance procedures.

- Keep the catheter and the exit-site dry.
- Replace the catheter-site dressing when it becomes damp, loosened, or soiled or when inspection of the site is necessary.
- Replace dressings used on short-term CVC sites every 2 days for gauze dressings and at least every 7 days for transparent dressings.
- Never leave the catheter open. Always seal with syringes or caps.
- Ensure that the suture is correctly placed. The catheter should not be able to move in and out of the exit-site.
- Exchange the caps after each treatment.
- Cover the extension lines between treatments.

Guidelines for application of heparin lock

1. After extracorporeal treatment, flush with 20 ml sterile saline and instil fresh heparin.
2. To maintain patency between treatments, keep the lumens of the catheter filled with a sufficient concentration and volume of heparin. In most cases, a concentration of 5,000 units/ml is most successful. Refer to the priming volume imprinted on the clamp of the catheter.
3. Instil fresh heparin, flushing quickly to ensure that heparin reaches the distal end of the lumens. In case of catheters with side holes, instilling too slowly may cause heparin to exit the catheter through its side holes, leaving the distal hole unprotected against thrombus formation.
4. Clamp the extension lines under positive pressure.

WARNING! To further prevent thrombus formation at the tip of the catheter, the clamp on the extension tube should not be opened once the lumen has been primed with heparinized saline. If the clamp would be opened, the priming volume of that lumen would increase slightly as a result of the extension tube returning to its "normal", unclamped state. This would create a vacuum at the tip, causing blood to be sucked up into the distal portion of the catheter, ultimately resulting in thrombus formation.

Guidelines for catheter removal

CAUTION! Only a qualified, licensed physician should remove the catheter.

CAUTION! Strict aseptic technique including the use of a cap, mask, sterile gown, sterile gloves, and a large sterile sheet must be used during the removal procedure. Have patient wear mask.

1. **For subclavian and jugular position:** Place the patient in the Trendelenburg position, turning the head to the side opposite the insertion site.

   For femoral position: Place the patient flat on the back. Flex the patient's knee on the same side as the insertion site, while abducting and rotating the leg outwards.
2. Remove dressing and suture of the catheter.
3. Compress the venous insertion site and pull the catheter gently out of the vessel.
4. Apply appropriate wound dressing.

NOTE! Because of the risk of bleeding, the patient should, if possible, sit up rather than lie down after the catheter removal (not applicable with femoral catheters).

Troubleshooting

One-way obstruction

Suspect one-way obstruction when a lumen can be flushed but cannot be aspirated. This is usually caused by tip malposition with the catheter suctioned against the vessel wall.

One of the following adjustments may eliminate the obstruction (sutures may have to be removed):

- Reposition the patient.
- Have the patient hold his arm above his head and cough. Not applicable with femoral catheters.
- Flush with saline to push the catheter away from the wall.
- Rotate the catheter. Not applicable if the catheter is sutured to skin.
- Withdraw the catheter slightly to reposition the tip. Not applicable if the catheter is sutured to skin.

WARNING! DO NOT insert the catheter further into the vein as vessel damage, cardiac arrhythmia and increased infection rate could result.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

EN

Short-term vascular access for hemodialysis, hemoperfusion and apheresis therapy with GamCath HighFlow Dolphin Catheters

Kinking

- Check catheter position.
- Check sutures at the exit-site.
- Does the catheter move in and out of the exit-site?
- Does it bend when the patient moves or lies on the same side as the catheter site?

Symptoms of kinking at the tip include decreased blood flow and increased venous resistance. An X-ray can confirm internal kinking.

Vessel collapse or spasm

Start and adjust pump speed slowly.

Thrombus formation

1. If catheter is blocked, first check to ensure it is not kinked.
2. If a thrombus is present, attempt to aspirate the clot gently with a syringe. If blood flow is still low, or blood cannot be withdrawn at all, the physician may choose to dissolve the clot with a chemical intervention utilizing an approved thrombolytic agent.

WARNING! DO NOT use excessive force when flushing an obstructed lumen. Overpressurizing the catheter will damage it and can cause trauma to the patient.

NOTE!

- A catheter could be blocked by a substance other than a blood clot.
- The cleared catheter may be used immediately.

Infection

Any signs of infection have to be considered as an indication for catheter removal.

CAUTION! Due to the risk of exposure to blood borne pathogens, health care professionals should always use Universal Blood and Body Fluid Precautions in the care of all patients.

Warranty and limitation of liability

a) The manufacturer warrants that GamCath HighFlow Dolphin Catheters have been manufactured in accordance with their specifications and in compliance with Medical Device Directive 93/42/EEC, other applicable industry standards and regulatory requirements. If provided with the lot number of the defective product, the manufacturer will, by replacement or credit, remedy manufacturing defects in GamCath HighFlow Dolphin Catheters becoming apparent before the expiration date.
b) The warranty under paragraph a) above is in lieu of, and to the exclusion of, any other warranty, whether written or oral, expressed or implied, statutory or otherwise, and there are no warranties of merchantability or other warranties which extend beyond those described in paragraph a) above. The remedy set out above for manufacturing defects is the sole remedy available to any person as a result of to defects in the GamCath HighFlow Dolphin Catheters and the manufacturer shall not be liable for any consequential or incidental loss, damage, injury or expense arising directly or indirectly from the use of the GamCath HighFlow Dolphin Catheters, whether as a result of any defect therein or otherwise.
c) The manufacturer shall not be liable for any misuse, improper handling, non-compliance with warnings and instructions, damage arising from events after the manufacturer's release of the GamCath HighFlow Dolphin Catheters, failure or omission to inspect the product before use in order to insure that the GamCath HighFlow Dolphin Catheter is in proper condition, or any warranty given by independent distributors or dealers.
d) The manufacturer is Gambro Kathetertechnik Hechingen, 72379 Hechingen, Germany.
Made in Germany
Covered by one or several of the following patents: US 6 841 255, US 6 500 549, US 5 203 056, DE 41 18 732, EP 0 517 000, JP 2 035 892, other patents pending.
Subject to change material regarding product improvements.

U.S. contact: Gambro Renal Products, Inc., 14143 Denver West Parkway, Suite 400, Lakewood, CO 80401

CHF0043220 / rev. 2010-12

CE 0086

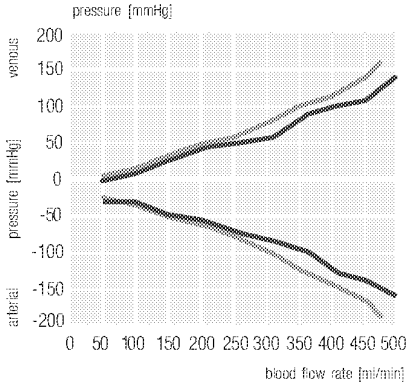
Explanation of symbols

- = Read instructions before use
- = For single use only
- STERILE EO = Sterilized using ethylene oxide
- REF = Code number
- LOT = Lot number
- = Insertion length
- = Date of manufacture
- = Expiry date
- = Manufacturer
- = Upper limit of temperature
- = Keep away from rain
- = Keep away from sunlight
- = Do not use if package is damaged
- = Content
- = Diameter
- = The Green Point
- = Box can be recycled
- = Peel here
- Rx = Federal law (USA) restricts this device to sale by or on the order of a physician.
- CE 0086 = Product confirms to the essential requirements of 93/42/EEC. Notified Body #0086 (BSI).

Material list

Product	Description	Material	Abbreviation
Catheter, Polyurethane (PUR), 1 lumen or multilumen	Catheter tube	Polyurethane	PUR
	Extension line	Polyurethane	PUR
	Coating	Polyurethane/Polysiloxane-Polycaprolactone Copolymer	PUR/PDMS-PCL
	Connector	Polyvinyl chloride	PVC
	Protection cap	Polyethylene	PE
Inner dilator	Inner dilator	Tetrafluoroethylene/Hexafluoropropylene-Copolymer	FEP

Flow rate of GamCath HighFlow Dolphin Catheter (as suggested by in vitro data)



GamCath HighFlow Dolphin Catheter

Diameter: 13F
Length: 150mm/200mm
Method: in vitro testing
Pump system: roller pump
Fluid: bovine blood
Protein: 60±5g/l
Hematocrit-value: 32±2%
Temperature: 37±2°C

- 13F x 150mm
- 13F x 200mm

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

11.6.4 The complete listing of all materials, which are used for the catheter.

(b)(4)

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Attachment #5: revised Instructions for use (detailed changes)

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-EOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Short-term vascular access for hemodialysis, hemoperfusion and apheresis therapy with GamCath HighFlow Dolphin Catheters

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-EOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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(b)(4)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

GAMBRO Renal Products

Gambro Renal Products, Inc.
14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 222 6500

May 15, 2010

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

FDA CDRH DMC
MAY 18 2010
Received

RE : 510(k) K100451

Dear Dr. Cooper:

Gambro would like request an extension of time to prepare our response to the April 19, 2010 letter requesting additional information for K100451.

We would like to request an additional 30 days to prepare our response.

I can be reached at 303.222.6724 or by email at kae.miller@us.gambro.com.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

K145

(b)(4)

398

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

GAMBRO.Renal Products

Material qualification of EtO sterilized Dilator tube for catheters.

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

K100451/S2

GAMBRO Renal Products

14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 222 6500

December 6, 2010

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 – G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

FDA CDRH DMC
DEC 07 2010
Received

Re: FDA Additional Information Request for 510(k) K100451 for the GamCath® High Flow Dolphin® Catheter

To Whom It May Concern:

Enclosed please find the response to the FDA request for additional information via email dated October 13, 2010, in reference to the Traditional 510(k) for GamCath® High Flow Dolphin® Catheter, submitted by Gambro Renal Products, Inc. on February 16, 2010.

The information requested from the FDA is restated followed by Gambro's response. Please contact me by telephone at 303.222.6724 or by fax at 303.222.6916 with any questions regarding this additional information. I can also be reached by email at kae.miller@us.gambro.com.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

K2

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Gambro Renal Products, Inc.

Traditional 510(k)
for
GamCath® High Flow Dolphin® Catheter

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

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ATTACHMENTS:

A Reference US Patent No. 6,500,549 B1 ..... 12 pages

B 2nd Congress of ISHD: Abstracts. Hemodialysis International, Vol. 13 No. 3 2009 Prolonged Temporary Hemodialysis Catheter Survival with Copolymer Coating in Patients with End-Stage Renal Disease: PROCOP Study. Pascal Meier ..... 2 pages

C Dialysis Catheter Polyurethane w/SMA Coating, Clinical Evaluation Code: TDJ-002-0023 Clinical Study: Evaluation of Catheter Survival, Time Course of Pressure and Blood Flow During Application of Standard and Modified Catheters, March 20, 2001, Dr. U. Heemann ..... 24 pages

D Nephrol Dial Transplant (2009) 1 of 7; doi: 10.1093/ndt/gfp638 The Role of Polymer Surface Degradation and Barium Sulfate Release in the Pathogenesis of Catheter-Related Infection ..... 7 pages

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

1.0 MEDICAL DEVICE USER FEE COVER SHEET

The completed Medical Device User Fee Cover Sheet – FDA Form 3601 is on the following page.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Form Approved: OMB No. 0910-0511 Expiration Date: January 31, 2010 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
MEDICAL DEVICE USER FEE COVER SHEET

PAYMENT IDENTIFICATION NUMBER: (b)(4)
Write the Payment Identification number on your check.

A completed cover sheet must accompany each original application or supplement subject to fees. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment and mailing instructions can be found at: http://www.fda.gov/oc/mdufma/coversheet.html

1. COMPANY NAME AND ADDRESS (include name, street address, city state, country, and post office code)

GAMBRO RENAL PRODUCTS
14143 Denver West Parkway
Suite 400
Lakewood CO 80401
US

1.1 EMPLOYER IDENTIFICATION NUMBER (EIN)
*****5786

2. CONTACT NAME
Kae Miller
2.1 E-MAIL ADDRESS
kae.miller@us.gambro.com
2.2 TELEPHONE NUMBER (Include Area code)
303-542-5045
2.3 FACSIMILE (FAX) NUMBER (Include Area code)
303-876-9264

3. TYPE OF PREMARKET APPLICATION (Select one of the following in each column; if you are unsure, please refer to the application descriptions at the following web site: http://www.fda.gov/oc/mdufma

Select an application type:
[X] Premarket notification(510(k)); except for third party
[ ] 513(g) Request for Information
[ ] Biologics License Application (BLA)
[ ] Premarket Approval Application (PMA)
[ ] Modular PMA
[ ] Product Development Protocol (PDP)
[ ] Premarket Report (PMR)
[ ] Annual Fee for Periodic Reporting (APR)
[ ] 30-Day Notice

3.1 Select a center
[X] CDRH
[ ] CBER
3.2 Select one of the types below
[X] Original Application
Supplement Types:
[ ] Efficacy (BLA)
[ ] Panel Track (PMA, PMR, PDP)
[ ] Real-Time (PMA, PMR, PDP)
[ ] 180-day (PMA, PMR, PDP)

4. ARE YOU A SMALL BUSINESS? (See the instructions for more information on determining this status)
[ ] YES, I meet the small business criteria and have submitted the required qualifying documents to FDA
[X] NO, I am not a small business
4.1 If Yes, please enter your Small Business Decision Number:

5. FDA WILL NOT ACCEPT YOUR SUBMISSION IF YOUR COMPANY HAS NOT PAID AN ESTABLISHMENT REGISTRATION FEE THAT IS DUE TO FDA. HAS YOUR COMPANY PAID ALL ESTABLISHMENT REGISTRATION FEES THAT ARE DUE TO FDA?
[X] YES (All of our establishments have registered and paid the fee, or this is our first device, and we will register and pay the fee within 30 days of FDA's approval/clearance of this device.)
[ ] NO (If "NO," FDA will not accept your submission until you have paid all fees due to FDA. This submission will not be processed; see http://www.fda.gov/cdrh/mdufma for additional information)

6. IS THIS PREMARKET APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCEPTIONS? IF SO, CHECK THE APPLICABLE EXCEPTION.
[ ] This application is the first PMA submitted by a qualified small business, including any affiliates
[ ] This biologics application is submitted under section 351 of the Public Health Service Act for a product licensed for further manufacturing use only
[ ] The sole purpose of the application is to support conditions of use for a pediatric population
[ ] The application is submitted by a state or federal government entity for a device that is not to be distributed commercially

7. IS THIS A SUPPLEMENT TO A PREMARKET APPLICATION FOR WHICH FEES WERE WAIVED DUE TO SOLE USE IN A PEDIATRIC POPULATION THAT NOW PROPOSES CONDITION OF USE FOR ANY ADULT POPULATION? (If so, the application is subject to the fee that applies for an original premarket approval application (PMA).
[ ] YES [X] NO

8. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION
(b)(4) (b)(6) 17-Nov-2009

Form FDA 3601 (05/2007)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

2.0 CDRH PRE-MARKET SUBMISSION COVER SHEET

The completed CDRH Pre-market Submission Cover Sheet is on the following pages.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Form Approval
OMB No. 0910-0120
Expiration Date: August 31, 2010.
See OMB Statement on page 5.

Date of Submission	User Fee Payment ID Number	FDA Submission Document Number *(if known)*
February 16, 2010	(b)(4)	

SECTION A — TYPE OF SUBMISSION

PMA	PMA & HDE Supplement	PDP	510(k)	Meeting
☐ Original Submission	☐ Regular (180 day)	☐ Original PDP	☑ Original Submission:	☐ Pre-510(K) Meeting
☐ Premarket Report	☐ Special	☐ Notice of Completion	☑ Traditional	☐ Pre-IDE Meeting
☐ Modular Submission	☐ Panel Track (PMA Only)	☐ Amendment to PDP	☐ Special	☐ Pre-PMA Meeting
☐ Amendment	☐ 30-day Supplement		☐ Abbreviated (Complete section I, Page 5)	☐ Pre-PDP Meeting
☐ Report	☐ 30-day Notice		☐ Additional Information	☐ Day 100 Meeting
☐ Report Amendment	☐ 135-day Supplement		☐ Third Party	☐ Agreement Meeting
☐ Licensing Agreement	☐ Real-time Review			☐ Determination Meeting
	☐ Amendment to PMA & HDE Supplement			☐ Other *(specify)*
	☐ Other			

IDE	Humanitarian Device Exemption (HDE)	Class II Exemption Petition	Evaluation of Automatic Class III Designation (De Novo)	Other Submission
☐ Original Submission	☐ Original Submission	☐ Original Submission	☐ Original Submission	☐ 513(g)
☐ Amendment	☐ Amendment	☐ Additional Information	☐ Additional Information	☐ Other *(describe submission)*:
☐ Supplement	☐ Supplement			
	☐ Report			
	☐ Report Amendment			

Have you used or cited Standards in your submission? ☐ Yes ☐ No *(If Yes, please complete Section I, Page 5)*

SECTION B — SUBMITTER, APPLICANT OR SPONSOR

Company / Institution Name	Establishment Registration Number *(If known)*		
Gambro Renal Products, Inc.	2087532		
Division Name *(If applicable)*	Phone Number *(including area code)*		
	303.222.6724		
Street Address	FAX Number *(including area code)*		
14143 Denver West Parkway, Suite 400	303.222.6916		
City	State / Province	ZIP/Postal Code	Country
Lakewood	CO	80401	USA
Contact Name			
Kae Miller			
Contact Title	Contact E-mail Address		
Regulatory Affairs Manager	kae.miller@us.gambro.com		

SECTION C — APPLICATION CORRESPONDENT (e.g., consultant, if different from above)

Company / Institution Name			
Division Name *(If applicable)*	Phone Number *(including area code)*		
Street Address	FAX Number *(including area code)*		
City	State / Province	ZIP Code	Country
Contact Name			
Contact Title	Contact E-mail Address		

FORM FDA 3514
(3/08)

PSC Graphics (301) 443-1090

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

SECTION D1 — REASON FOR APPLICATION - PMA, PDP, OR HDE

- ☐ New Device
- ☐ Withdrawal
- ☐ Additional or Expanded Indications
- ☐ Request for Extension
- ☐ Post-approval Study Protocol
- ☐ Request for Applicant Hold
- ☐ Request for Removal of Applicant Hold
- ☐ Request to Remove or Add Manufacturing Site
- ☐ Process change:
  - ☐ Manufacturing ☐ Packaging
  - ☐ Sterilization
  - ☐ Other *(specify below)*
- ☐ Response to FDA correspondence:
- ☐ Change in design, component, or specification:
  - ☐ Software / Hardware
  - ☐ Color Additive
  - ☐ Material
  - ☐ Specifications
  - ☐ Other *(specify below)*
- ☐ Labeling change:
  - ☐ Indications
  - ☐ Instructions
  - ☐ Performance Characteristics
  - ☐ Shelf Life
  - ☐ Trade Name
  - ☐ Other *(specify below)*
- ☐ Location change:
  - ☐ Manufacturer
  - ☐ Sterilizer
  - ☐ Packager
- ☐ Report Submission:
  - ☐ Annual or Periodic
  - ☐ Post-approval Study
  - ☐ Adverse Reaction
  - ☐ Device Defect
  - ☐ Amendment
- ☐ Change in Ownership
- ☐ Change in Correspondent
- ☐ Change of Applicant Address
- ☐ Other Reason *(specify)*:

SECTION D2 — REASON FOR APPLICATION - IDE

- ☐ New Device
- ☐ New Indication
- ☐ Addition of Institution
- ☐ Expansion / Extension of Study
- ☐ IRB Certification
- ☐ Termination of Study
- ☐ Withdrawal of Application
- ☐ Unanticipated Adverse Effect
- ☐ Notification of Emergency Use
- ☐ Compassionate Use Request
- ☐ Treatment IDE
- ☐ Continued Access
- ☐ Change in:
  - ☐ Correspondent / Applicant
  - ☐ Design / Device
  - ☐ Informed Consent
  - ☐ Manufacturer
  - ☐ Manufacturing Process
  - ☐ Protocol - Feasibility
  - ☐ Protocol - Other
  - ☐ Sponsor
- ☐ Report submission:
  - ☐ Current Investigator
  - ☐ Annual Progress Report
  - ☐ Site Waiver Report
  - ☐ Final
- ☐ Response to FDA Letter Concerning:
  - ☐ Conditional Approval
  - ☐ Deemed Approved
  - ☐ Deficient Final Report
  - ☐ Deficient Progress Report
  - ☐ Deficient Investigator Report
  - ☐ Disapproval
  - ☐ Request Extension of Time to Respond to FDA
  - ☐ Request Meeting
  - ☐ Request Hearing
- ☐ Other Reason *(specify)*:

SECTION D3 — REASON FOR SUBMISSION - 510(k)

- ☑ New Device
- ☐ Additional or Expanded Indications
- ☐ Change in Technology
- ☐ Other Reason *(specify)*:

FORM FDA 3514
(3/03)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

SECTION E ADDITIONAL INFORMATION ON 510(K) SUBMISSIONS

Product codes of devices to which substantial equivalence is claimed

1	MPB	2		3		4	
5		6		7		8	

Summary of, or statement concerning, safety and effectiveness information
- [x] 510 (k) summary attached
- [ ] 510 (k) statement

Information on devices to which substantial equivalence is claimed *(if known)*

	510(k) Number	Trade or Proprietary or Model Name	Manufacturer
1	K040301	GAMCATH HIGH FLOW CATHETER REF GDHK 13XXA	GAMBRO RENAL PRODUCTS, INC.
2	K991320	MEDCOMP DUO-FLOW II CATHETER WITH LUBRICIOUS HEPARIN	MEDICAL COMPONENTS, INC.
3			
4			
5			
6			

SECTION F PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

Common or usual name or classification name

catheter, hemodialysis, non-implanted

	Trade or Proprietary or Model Name for This Device	Model Number
1	GamCath® High Flow Dolphin®	(b)(4)
2	GamCath® High Flow Dolphin®	
3	GamCath® High Flow Dolphin®	
4	GamCath® High Flow Dolphin®	
5	GamCath® High Flow Dolphin®	

FDA document numbers of all prior related submissions *(regardless of outcome)*

1 K040301	2 K991320	3	4	5	6
7	8	9	10	11	12

Data included in Submission
- [x] Laboratory Testing
- [ ] Animal Trials
- [ ] Human Trials

SECTION G PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS

Product Code	C.F.R. Section *(if applicable)*	Device Class
78MPB	876.5540	☐ Class I ☑ Class II ☐ Class III ☐ Unclassified

Classification Panel

76 Gastroenterology

Indications *(from labeling)*

GamCath® High Flow Dolphin® Catheters are indicated for use in attaining short term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. GamCath® High Flow Dolphin® Catheter is not intended for use in pediatric patients.

FORM FDA 3514 (3/08)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Note: Submission of this information does not affect the need to submit a 2891 or 2891a Device Establishment Registration form.	FDA Document Number *(if known)*

SECTION H — MANUFACTURING / PACKAGING / STERILIZATION SITES RELATING TO A SUBMISSION

☑ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number: 3004367028	☑ Manufacturer ☐ Contract Manufacturer ☐ Contract Sterilizer ☐ Repackager / Relabeler

Company / Institution Name	Establishment Registration Number
Gambro Kathetertechnik Hechingen	3004367028
Division Name *(if applicable)*	Phone Number *(including area code)*: +49 7471 175023
Street Address: Linsenäcker 1	FAX Number *(including area code)*: +49 7471 175023

City	State / Province	ZIP Code	Country
HECHINGEN		DE-72379	Germany

Contact Name	Contact Title	Contact E-mail Address
Wolfgang Jentsch	Regulatory Affairs Manager	wolfgang.jentsch@gambro.com

☑ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number	☐ Manufacturer ☐ Contract Manufacturer ☑ Contract Sterilizer ☐ Repackager / Relabeler

(b)(4)

☐ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number	☐ Manufacturer ☐ Contract Manufacturer ☐ Contract Sterilizer ☐ Repackager / Relabeler

Company / Institution Name	Establishment Registration Number
Division Name *(if applicable)*	Phone Number *(including area code)*
Street Address	FAX Number *(including area code)*

City	State / Province	ZIP Code	Country

Contact Name	Contact Title	Contact E-mail Address

FORM FDA 3514
(3/08)

Add Continuation Page

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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SECTION I **UTILIZATION OF STANDARDS**

Note: Complete this section if your application or submission cites standards or includes a *"Declaration of Conformity to a Recognized Standard"* statement.

	Standards No.	Standards Organization	Standards Title	Version	Date
1	DIN EN ISO 11135-1: 2007	AMMI/ ANSI / ISO	Sterilization of health care products Ethylene oxide Part1: Requirements for the development, validation and routine control of a sterilization process for medical devices	2007-08	8/1/2007
	Standards No.	Standards Organization	Standards Title	Version	Date
2	DIN EN 556-1 2002	DIN EN	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices; German version EN 556-1:2001	2002-03	3/1/2002
	Standards No.	Standards Organization	Standards Title	Version	Date
3	ISO 594-1: 1986	ISO	Conical fittings with a 6% taper for syringes, needles an certain other medical equipment Part 1: General requirements	First edition 1986-06	6/15/1986
	Standards No.	Standards Organization	Standards Title	Version	Date
4	ISO 594-2: 1998	ISO	Conical fittings with a 6% taper for syringes, needles an certain other medical equipment Part 2: Lock Fittings	second edition 1998-09	09/01/2009
	Standards No	Standards Organization	Standards Title	Version	Date
5	DIN EN ISO 11607-1: 2006	DIN EN ISO	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems (ISO 11607-1:2006), German version EN ISO 11607-1:2009	2009-09	09/01/2009
	Standards No.	Standards Organization	Standards Title	Version	Date
6	DIN EN 868-5: 2002	DIN EN	Packaging for terminally sterilized medical devices - Part 5: Sealable pouches and reels of porous materials and plastic film construction - Requirements and test methods;	2002-02	02/01/2002
	Standards No.	Standards Organization	Standards Title	Version	Date
7	DIN EN 980: 2008	DIN EN	Symbols for use in the labelling of medical devices; German version EN 980:2008	2008-08	08/01/2008

Please include any additional standards to be cited on a separate page.

Public reporting burden for this collection of information is estimated to average 0.5 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of the Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, Maryland 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 3514
(3/08)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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	Standards No.	Standards Organization	Standards Title	Version	Date
8	DIN EN 1041: 2008	DIN EN	Information supplied by the manufacturer of medical devices; German version EN 1041:2008	2008-11	11/01/2009
9	DIN EN ISO 10555-1: 2004	DIN EN ISO	Sterile, single-use intravascular catheters Part 1: General requirements	2004-05-15	04/15/2004
10	ISO 10555-3: 1996	ISO	Sterile, single-use intravascular catheters Part 3: Central venous catheters	1996-06-15	06/15/1996
11	DIN EN ISO 10993-1: 2003	DIN EN ISO	Biologische Beurteilung von Medizinprodukten Part 1: Beurteilung und Prüfung	2003-12	08/01/2009
12	DIN EN ISO 11070: 1999	DIN EN ISO	Sterile single-use intravascular catheter introducers (ISO 11070:1998); German version EN ISO 11070:1999	1999-07	07/01/1999
13	DIN EN ISO 13485: 2007	DIN EN ISO	Medical Devices – Quality management systems – Requirements for regulatory purposes	2007-10	10/01/2007
14	DIN EN ISO: 14971:2007	DIN EN ISO	Medizinprodukte - Anwendung des Risikomanagement auf Medizinprodukte	2007-07	07/01/2007

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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3.0 510(k) COVER LETTER

Traditional 510(k) Premarket Notification Cover Letter

February 16, 2010

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 – G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

To Whom It May Concern:

Enclosed is a Traditional 510(k) Notification seeking marketing clearance for the GamCath® High Flow Dolphin® Catheter.

Administrative Information	
Type of 510(k) Submission	Traditional
Device Type	Short-Term Hemodialysis Catheter
510(k) Submitter	Gambro Renal Products, Inc. 14143 Denver West Parkway, Suite 400 Lakewood, CO 80401
Contact	Kae Miller, Regulatory Affairs Manager Phone: 303.222.6724 Fax: 222.6916
Confidentiality	Material marked "CONFIDENTIAL" is deemed by Gambro to be either trade secret or confidential commercial information. Therefore, we request that FDA apply all of the legislative safeguards pertaining to non-disclosure of such confidential material to the public. **Note: All information contained in the Attachments is CONFIDENTIAL**
Classification Name	Catheter Hemodialysis Non-Implanted
Device Trade Name	GamCath® High Flow Dolphin® Catheter
Device Variation	11,5 French 150 mm 11,5 French 200 mm 11,5 French 250 mm 13 French 150 mm 13 French 200 mm 13 French 250 mm Optional with straight or curved extension line.
Device Class	II
Product Code	78 MPB
Regulation Number	21 CFR 876.5540
Manufacturer	**Gambro Kathetertechnik Hechingen** Linsenaecker 1 Hechingen, Germany DE-72379

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Basis for Submission

The basis for this Traditional 510(k) Notification is the introduction of a new catheter for use in hemodialysis.

Design and Use of the Device

The table on the following page is provided as recommended in the FDA guidance document, *Format for Traditional and Abbreviated 510(k) s* issued on August 12, 2005.

Question	YES	NO
Is the device intended for prescription use (21 CFR 801 Subpart D)?	X	
Is the device intended for over-the-counter use (21 CFR 801 Subpart C)?		X
Does the device contain components derived from a tissue or other biologic source?		X
Is the device provided sterile?	X	
Is the device intended for single use?	X	
Is the device a reprocessed single use device?		X
If yes, does this device type require reprocessed validation data?		X
Does the device contain a drug?		X
Does the device contain a biologic?		X
Does the device use software?		X
Does the submission include clinical information?		X
Is the device implanted?		X

The premarket notification information required by 21 C.F.R. §807.87 is contained in the accompanying document in the format defined in the FDA guidance document, *Format for Traditional and Abbreviated 510(k)s* issued on August 12, 2005.

Additionally, this 510(k) includes the information recommended in the FDA *Guidance on Premarket Notification 510(k) Submission for Short-Term and Long-Term Intravascular Catheters, March 16, 1995* which is provided in Section 20.

Two copies of this traditional Premarket 510(k) notification are provided. One hardcopy and one identical duplicate on CD.

Please contact Kae Miller, Regulatory Affairs Manager at 303.222.6724 by phone or 303.222.6916 by fax for any questions regarding this submission.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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4.0 INDICATIONS FOR USE STATEMENT

The Indications for Use are identified on the following page.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Indications for Use Statement

510(k) Number (if known):_____

Device Name: GamCath® High Flow Dolphin® Catheter

Indications for Use Statement:

GamCath® High Flow Dolphin® Catheters are indicated for use in attaining short term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. GamCath® High Flow Dolphin® Catheter is not intended for use in pediatric patients.

Prescription Use ___X____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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5.0 510(k) SUMMARY

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

6.0 TRUTHFUL AND ACCURACY STATEMENT

As Required by 21 CFR 807.87(k)

I certify that, in my capacity as Regulatory Affairs Manager of Gambro, I believe to the best of my knowledge, that all data and information submitted in the pre-market notification are truthful and accurate and that no material fact has been omitted.

February 12, 2010 (b)(6)

Date **Wolfgang Jentsch**
Regulatory Affairs Manager

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

7.0 CLASS III SUMMARY AND CERTIFICATION

The GamCath® High Flow Dolphin® Catheter has been classified as a Class II medical device and therefore a Class III Summary and Certification in accordance with 21 CFR 807.87(j) and 807.94 is not applicable and therefore is not provided.

CLASSIFICATION NAME:	Catheter Hemodialysis Non-Implanted
PRODUCT CODE:	78 MPB
REGULATION NUMBER	21 CFR 876.5540
DEVICE CLASS PER 21 CFR 876:5540(b)(2)	Class II

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

8.0 FINANCIAL CERTIFICATION OR DISCLOSURE STATEMENT

No clinical trails or studies have been performed in support of this 510(k) submission and therefore no financial certification and/or disclosure statement in accordance with 21 CFR 807.87(i) have been provided in this 510(k) submission.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

9.0 DECLARATIONS OF CONFORMITY AND SUMMARY REPORTS

Certificate of Compliance with Standards the Gambro GamCath® Polyurethane Catheters are designed and manufactured by Gambro Kathetertechnik Hechingen (Germany) in compliance with the following standards regarding requirements and acceptance criteria for safety related parameters for this type of products:

Standards in regard to Quality System:

21 CFR 820	Quality System Regulation; Medical Devices; CGMP
IS0 13485	Medical devices - Quality management systems - System requirements for regulatory purposes
Directive 93/42/EEC, Annex II section 3.2:	Full Quality Assurance System

The QA system of Gambro Kathetertechnik Hechingen is regularly inspected by (b)(4)

(b)(4)

Current valid Certificate No. (b)(4)

(b)(4)

Current valid Certificate No. (b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Standards in regard to Product Specifications and Product Requirements included on the FDA From 3654

Standard	Title	FDA Recognition Number	Compliance
DIN EN ISO 11135-1: 2007	Sterilization of health care products Ethylene oxide Part1: Requirements for the development, validation and routine control of a sterilization process for medical devices	14-228	full
DIN EN 556-1: 2002	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices; German version EN 556-1:2001	No	full
ISO 594-1: 1986	Conical fittings with a 6% taper for syringes, needles an certain other medical equipment Part 1: General requirements	6-11	full
ISO 594-2: 1998	Conical fittings with a 6% taper for syringes, needles an certain other medical equipment Part 2: Look Fittings	06-129	full
DIN EN ISO 11607-1: 2006	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems (ISO 11607-1:2006); German version EN ISO 11607-1:2009	14-193	full
DIN EN 868-5: 2002	Packaging for terminally sterilized medical devices - Part 5: Sealable pouches and reels of porous materials and plastic film construction - Requirements and test methods;	No	full
DIN EN 980: 2008	Symbols for use in the labelling of medical devices; German version EN 980:2008	05-32	full
DIN EN 1041: 2008	Information supplied by the manufacturer of medical devices; German version EN 1041:2008	No	full
DIN EN ISO 10555-1: 2004	Sterile, single-use intravascular catheters Part 1: General requirements	06-161	full
ISO 10555-3: 1996	Sterile, single-use intravascular catheters Part 3: Central venous catheters	06-171	full
DIN EN ISO 10993-1: 2003	Biologische Beurteilung von Medizinprodukten Part 1: Beurteilung und Prüfung	2-98	full
DIN EN ISO 11070: 1999	Sterile single-use intravascular catheter introducers (ISO 11070:1998); German version EN ISO 11070:1999	No	full
DIN EN ISO 13485: 2007	Medical Devices – Quality management systems – Requirements for regulatory purposes	No	full
DIN EN ISO: 14971:2007	Medizinprodukte - Anwendung des Risikomanagement auf Medizinprodukte	5-40	full

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

10.0 EXECUTIVE SUMMARY

10.1 Device Description

The GamCath® High Flow Dolphin® Catheter combines the GamCath® High Flow Catheter with an additional coating based on a block copolymer. The polymer layer results in a very smooth surface structure and prevents the release of $BaSO_4$ particles. (b)(4)

(b)(4)

(b)(4) The coated catheter can be used for patient with Heparin-induced thrombocytopenia (HIT) Syndrome.

GamCath® High Flow Dolphin® Catheters are indicated for use in attaining short term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. GamCath® High Flow Dolphin® Catheter is not intended for use in pediatric patients.

The GamCath® High Flow Dolphin® Catheters manufactured by Gambro Kathetertechnik Hechingen are single use medical devices for short term use (b)(4) to obtain vascular access in patients with acute or chronic renal failure (b)(4)

(b)(4)

(b)(4) such catheters are inserted into either one of the following blood vessels: vena subclavia, vena jugularis, or vena femoralis.

(b)(4)

Catheters are equipped with small rotatable suture rings, still allowing rotation of catheter when sutured to skin

Extension lines, present on each lumen, are equipped with luer-lock connectors according to ISO 594-1 with protection caps and are provided with clamps which may be color coded to indicate the venous (blue), arterial (red).

Clamp inserts bear easily legible and permanently fixed imprints indicating usable catheter length and outer diameter of catheter shaft (in French calibration) as well as priming volumes.

Clamp inserts bear easily legible and permanently fixed imprints indicating usable catheter length and outer diameter of catheter shaft (in French calibration) as well as priming volumes.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

The Catheter is available in 13 French and 11,5 French straight and curved extension line configuration. The insertion length is available in range from 150 mm (5.906"up to 250 mm (9.843").

Dolphin Coating Description

The Dolphin coating is a co-polymer film which is applied over the catheter surface to form a continuous surface that is more biocompatible and has a smoother surface morphology than an untreated catheter. In general the copolymer film is formed by providing a hydrophobic polymer block, such as polydimethylsiloxane (PDMS) with functional –OH end groups (b)(4)

(b)(4)

Reference US Patent No. 6,500,549 B1 - Attachment A

10.2 Device Comparison Table

A detailed comparison table is provided in section 12.3.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

10.3 SUMMARY FOR PERFORMANCE TESTING

The Performance data demonstrates that the GamCath® High Flow Dolphin® Catheter is substantially equivalent to the predicate devices currently available on the market.

The tests were performed per Guidance of Premarket Notification [510(l)] Submission of Short Term and Long-Term Intravascular Catheters, dated 03/16/95.

Reference is made to section 18.0 Performance Testing – Bench

(b)(4)

Reference to publication and results below:

2nd Congress of ISHD: Abstracts. Hemodialysis International, Vol. 13 No. 3 2009
Prolonged Temporary Hemodialysis Catheter Survival with Copolymer Coating in Patients with End-Stage Renal Disease: PROCOP Study, Pascal Meier. - See Attachment B

(b)(4)

Description and Conclusion of Testing:

Testing performed on the GamCath® High Flow Dolphin® Catheter indicates that they are safe effective and perform as well as the predicate device, when used in accordance with the instruction for use.

The results of all mechanical, chemical and physical tests meet the requirements according to current applicable standards for central venous catheters. The product is qualified according to the application.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

11.0 DEVICE DESCRIPTION

11.1 Device Description

The GamCath® High Flow Dolphin® Catheters manufactured by Gambro Kathetertechnik Hechingen are single use medical devices for short term use (b)(4) to obtain vascular access in patients with acute or chronic renal failure (b)(4) (b)(4) (b)(4) such catheters are inserted into either one of the following blood vessels: vena subclavia, vena jugularis, or vena femoralis.

(b)(4)

Catheters are equipped with small rotatable suture rings, still allowing rotation of catheter when sutured to skin

Extension lines, present on each lumen, are equipped with luer-lock connectors according to ISO 594-1 with protection caps and are provided with clamps which may be color coded to indicate the venous (blue), arterial (red).

Clamp inserts bear easily legible and permanently fixed imprints indicating usable catheter length and outer diameter of catheter shaft (in French calibration) as well as priming volumes.

Clamp inserts bear easily legible and permanently fixed imprints indicating usable catheter length and outer diameter of catheter shaft (in French calibration) as well as priming volumes.

The Catheter is available in 13 French and 11,5 French straight and curved extension line configuration. The insertion length is available in range from 150 mm (5.906“) up to 250 mm (9.843”).

Catheter Assembly Setup:

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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11.2 Technical Drawing

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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11.3 Physical Specifications

(b)(4)

11.4 Mechanical Specifications

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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11.5 Biological Specifications

The catheter has to fulfill the requirements of the standard IS0 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing or comparable standards for example according USP. The catheter is classified according IS0 10993-1 as a medical device with external communicating (dialysis treatment) in usage between 24h and 30 days (less than 30 days) in circulating blood (central venous system).

Specifications which have to be fulfilled are defined in each individual standard of the required test.

11.6 Chemical Specifications

11.6.1 Composition (b)(4)

(b)(4)

- The GamCath® High Flow Dolphin® Catheter combines the GamCath® High Flow Catheter with an additional coating based on a block copolymer. The polymer layer results in a very smooth surface structure and prevents the release of $BaSO_4$ particles.

(b)(4)

(b)(4) The coated catheter can be used for patient with Heparin-induced thrombocytopenia (HIT) Syndrome.

- The Dolphin coating is a co-polymer film which is applied over the catheter surface to from a continuous surface that is more biocompatible and has a smoother surface morphology than an untreated catheter. In general the copolymer film is formed by providing a hydrophobic polymer block, such as polydimethylsiloxan (PDMS) with functional –OH end groups (b)(4)

(b)(4)

Reference US Patent 6,5000,549 B1 – See Attachment A

- (b)(4)

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11.6.2 Indicate the stability requirements (b)(4)

(b)(4)

- No additional stability requirements but those for the catheter it self with or without coating
- Recommended storage conditions: below + 30°C (+ 86°F)
- Do not store with chemicals

11.6.3 (b)(4) compatible with the following solutions, disinfections and drugs:

Compatibility with:

- Heparin
- Saline solution (NaC1 in H20) 0,9%
- Hydrogen peroxide H_2O_2
- Disinfectant iodine based
- The catheters have to fulfill the mechanical specifications according the standard IS0 10555-

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11.6.4 The complete listing of all materials, which are used for the catheter.

(b)(4)

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12.0 SUBSTANTIAL EQUIVALENCE DISCUSSION

12.1 Substantial Equivalence Claim

The GamCath® High Flow Dolphin® Catheter manufactured by Gambro Renal Products is substantially equivalent to the GamCath® High Flow Catheter, K040301 and the Medcomp®\ Duo-Flow II Catheter with Lubricious Heparin manufactured by Medical Components, Inc. K991320.

12.2 Identification of Predicate Devices

Manufacturer:	Gambro Renal Products, Inc.
Common Name:	Short-Term Hemodialysis Catheter
Trade Name:	GamCath® High Flow Catheter
510(k) Number:	K040301

Manufacturer:	Medical Components, Inc.
Common Name:	Hemodialysis Catheter, Non-Implanted
Trade Name:	Medcomp® DUO-COAT Catheter, Double Lumen
510(k) Number:	K991320

12.3 FDA 510(k) Clearance Letters for Predicate Devices

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

NOV - 1 2004

Mr. Thomas B. Dowell
Manager Regulatory Affairs
Gambro® Renal Products
10810 W. Collins Avenue
LAKEWOOD CO 80215

Re: K040301
Trade/Device Name: GamCath® High Flow Catheter
Regulation Number: 21 CFR §876.5540
Regulation Name: Blood access device and accessories
Regulatory Class: II
Product Code: 78 MPB
Dated: September 24, 2004
Received: September 27, 2004

Dear Mr. Dowell:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. However, you are responsible to determine that the medical devices you use as components in the kit have either been determined as substantially equivalent under the premarket notification process (Section 510(k) of the act), or were legally on the market prior to May 28, 1976, the enactment date of the Medical Device Amendments. *Please note:* If you purchase your device components in bulk (i.e., unfinished) and further process (e.g., sterilize) you must submit a new 510(k) before including these components in your kit. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, and labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration (21 CFR Part 807); listing (21 CFR Part 807), labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market. If you desire specific advice for your device on the labeling regulation, please contact the Office of Compliance at (301) 594-4616. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll free number (800) 638-2041 or (301) 443-6597, or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Nancy C. Brogdon

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

NOV 10 1999

Ms. Jeanne M. Cush
Technical Submissions Coordinator
Medical Components, Inc.
1499 Delp Drive
Harleysville, Pennsylvania 19438

Re: K991320
Trade Name: Medcomp® Duo-Coat Catheter, Double Lumen
Regulatory Class: II
21 CFR §876.5540/Product Code: 78 MPB
Dated: August 13, 1999
Received: August 16, 1999

Dear Ms. Cush:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. However, you are responsible to determine that the medical devices you use as components in the kit have either been determined as substantially equivalent under the premarket notification process (Section 510(k) of the act), or were legally on the market prior to May 28, 1976, the enactment date of the Medical Device Amendments. Please note: If you purchase your device components in bulk (i.e., unfinished) and further process (e.g., sterilize) you must submit a new 510(k) before including these components in your kit. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, and labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval) it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, FDA will verify such assumptions. Failure to comply with the GMP regulation may

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

result in regulatory action. In addition, the Food and Drug Administration (FDA) may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal Laws or Regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market. If you desire specific advice for your device on the labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4616. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or (301) 443-6597, or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

CAPT Daniel G. Schultz, M.D.
Acting Director, Division of Reproductive,
Abdominal, Ear, Nose and Throat,
and Radiological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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12.4 Comparison with Predicate Devices

ELEMENT OF COMPARISON SUBJECT DEVICE	NEW DEVICE GamCath® High Flow Dolphin® MS-GDHC-XXXX	PREDICATE GAMCATH® HIGH FLOW CATHETER REF: GDHK 13XX K040301	PREDICATE MEDCOMP® DUO-COAT CATHETER WITH LUBRICIOUS HEPARIN K991320
Catheter Type	Short-Term Hemodialysis Catheter Catheter Hemodialysis Non-Implanted	Short-Term Hemodialysis Catheter Catheter Hemodialysis Non-Implanted	Short-Term Hemodialysis Catheter Catheter Hemodialysis Non-Implanted
Intended Use	GamCath® catheters are indicated for use in attaining short term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. GamCath® High Flow Dolphin® Catheter is not intended for use in pediatric patients.	GamCath® catheters are indicated for use in attaining short term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. Not for pediatric use.	The Medcomp® Duo-Coat Catheter is indicated for use in attaining short term vascular access for hemodialysis and apheresis. It may be inserted percutaneous and is ideally placed in the internal jugular vein of an adult patient. Alternate insertion sites are the subclavian or femoral vein.
Mode of Operation	(b)(4)		
Material of the Catheter	The catheter shaft is made from soft aliphatic polyurethane and contains barium sulfate to be radio-opaque	The catheter shaft is made from soft aliphatic polyurethane and contains barium sulfate to be radio-opaque	The catheter shaft is made from soft aliphatic polyurethane and contains barium sulfate to be radio-opaque
Is the material of the catheter radio-opaque?	Yes, the material of the catheter is radio-opaque.	Yes, the material of the catheter is radio-opaque.	Yes, the material of the catheter is radio-opaque.

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Position of insertion of the catheter	The catheters can be used in the subclavian, jugular or femoral vein.	The catheters can be used in the subclavian, jugular or femoral vein.	The catheters can be used in the subclavian, jugular or femoral vein.
Size of the Catheter	The GamCath ® High Flow Catheter is available in 11,5 French and 13 French in straight and curved extension tube configuration. The insertion length is as follows: straight: 15, 20 and 25 centimeter.	The GamCath ® High Flow Catheter is available in 13 French in straight configuration. The insertion length is as follows: straight: 15, 17.5, 20 and 25 centimeter.	The MEDCOMP® DUO-COAT CATHETER WITH LUBRICIOUS HEPARIN is available in 9 F; 11F
Blood-flow of the Catheters	(b)(4)		Not available
Recirculation	(b)(4)		
Where used: hospital, ambulance etc.	The catheter will be implanted in the operating room. This is a sterile environment. For treatment the catheter will be used in the Dialysis centers.	The catheter will be implanted in the operating room. This is a sterile environment. For treatment the catheter will be used in the Dialysis centers.	The catheter will be implanted in the operating room. This is a sterile environment. For treatment the catheter will be used in the Dialysis centers.
Patient Population	For adult patients	For adult patients	For adult patients
Design Material			
Connector	PVC (Polyvinyl chloride)	PVC (Polyvinyl chloride)	Not available
Catheters Tube	polyurethane	polyurethane	polyurethane
Extension Line	polyurethane	polyurethane	polyurethane
Shaft Diameter	11.5 and 13 F	13 F	9 F; 11F

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Traditional 510(k) for GamCath® High Flow Dolphin® Catheter

ELEMENT OF COMPARISON SUBJECT DEVICE	NEW DEVICE GamCath® High Flow Dolphin® MS-GDHC-XXXX	PREDICATE GAMCATH® HIGH FLOW CATHETER REF: GDHK 13XX K040301	PREDICATE MEDCOMP® DUO-COAT CATHETER WITH LUBRICIOUS HEPARIN K991320
Physical Characteristics			
Catheter Type	Dual Lumen	Dual Lumen	Dual Lumen
Length Available	15 cm, 20 cm, 25 cm	15 cm, 17,5 cm, 20 cm, 25 cm	12 cm, 15 cm, 24 cm, 20 cm
Number of Lumens	2 Lumen	2 Lumen	2 Lumen
Sterility	EtO	EtO	EtO
Distal End Configuration	Staggered Tip configuration	Staggered Tip configuration	Conical Tip configuration with side holes
Intended Anatomical Location of Distal End	Vena cava superior, for jugular and subclavian access position Vena cava inferior, femoral access possition	Vena cava superior, for jugular and subclavian access position Vena cava inferior, femoral access possition	Vena cava superior, for jugular and subclavian access position Vena cava inferior, femoral access possition
Proximal End Configuration	Extension line with Luer-Lock Connector	Extension line with Luer-Lock Connector	Extension line with Luer-Lock Connector
Composition Anti-thrombotic	Surface Modified Agent. A coating base on block copolymer polyurethane and polydimethyl siloxane (PUR-PDMS Copolymer)	Not applicable	lubricious heparin

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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13.0 PROPOSED LABELS AND LABELING

13.1 Packaging insert for the GamCath® High Flow Dolphin® Catheter

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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EN Operator's manual EN

Short-term vascular access for hemodialysis, hemoperfusion and apheresis therapy with GamCath HighFlow Dolphin Catheters

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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13.2 Product Labels for the GamCath® High Flow Dolphin® Catheter

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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14.0 STERILIZATION AND EXPIRATION DATING

14.1 Sterilization Validation Method & Sal

GamCath® catheters, catheter set and accessories are sterilized with ethylene oxide (EtO).

A Validation of the sterilization of GamCath® catheters has been performed by the

(b)(4)

(b)(4)

Method: EN 550 ISO 11135:1994 Method C

(b)(4)

Summary:

The result of the validation report ensures sterility of the set with the double lumen polyurethane catheter with cuff.

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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14.2 STERILIZATION PROCESS INFORMATION

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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VALIDATION REPORT
Ethylene Oxide Sterilization Process Validation for Gambro Katheterlechnik Hechingen GmbH

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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14.3 PYROGEN TESTING

All GamCath® Catheters are pyrogen free and meet the requirements of 20.0 USP Endotoxin Units per device.

The routine pyrogen test method for all GamCath® Catheters is implemented according to USP 24 – Chapter (161): Transfusion and infusion assemblies and similar medical devices.

(b)(4)

A detailed description of the current valid test procedure is given in the following validation report from (b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

(b)(4) DATE: 14/08/02

TO: Gambro Dialysatoren GmbH & Co. KG / Abt. QW/Bio-Labor

(b)(4)

Please find here the results on the validation of the following catheters :

(b)(4)

The following report indicate the endotoxin results for each lot of product tested as Medical Devices according to USP 24 – Chapter (161) : TRANSFUSION AND INFUSION ASSEMBLIES AND SIMILAR MEDICAL DEVICES.

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

14.4 Expiration Dating

Storage Conditions:
Recommended storage conditions: below + 30°C (+ 86°F)
Do not store with chemicals

Shelf life validation:

Shelf life testing performed to show product and packaging integrity for 5 years.

Product integrity:

The following tests were performed to verify the efficiency of the SMA Dolphin coating regarding to the antibacterial properties. (b)(4)

(b)(4)

Report No.	Title
(b)(4)	Thrombogenicity of SMA-PUR coated catheters stored 3 month at room temperature
	Thrombogenicity of SMA-PUR coated catheters stored 6 month at room temperature
	Air Leakage SMA 5 years
	Liquid Leakage SMA 5 years
	Tensile Strength SMA 5 years
	Clamp Test SMA 5 years
	Delamination SMA 5 years

Summary:
The results of all mechanical, chemical and physical tests meet the requirements according to current applicable standards for central venous catheters. The product is qualified according to the application.

Packaging integrity:

Report No.	Title
(b)(4)	Packaging evaluation based on the results of the self life study performed by (b)(4)

Based on the results from (b)(4) and the investigation of the samples performed by Gambro Kathetertechnik Hechingen and of the results of packaging validation it is approved that the sterile packaging fulfils the requirements for a shelf life (b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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15.0 BIOCOMPATIBILITY

The following biological tests have been performed for a double lumen or single lumen catheter made out of aliphatic polyurethane. (b)(4)

(b)(4)

Product: (b)(4)
Article-No.:
Lot-No.:

Test	Standard	Date of report
Hemolysis	DIN 58352-3	22.08.1996
Genotoxicity	ISO 10993-3	22.07.1996
Cytotoxicity	ISO 10993-5 / EN 30993-5	21.06.1996
Systemic Injection Test	USP XXIII	22.07.1996
Intracutaneous Test (Irritation)	USP XXIII <88>	02.07.1996
Sensitization	ISO 10993-10	20.08.1996

Product: (b)(4)
Article-No.:
Lot-No.:

Test	Standard	Date of report
Muscle Implantation Test in Rabbit	ISO 10993-6	28.07.2000

Product: (b)(4)
Article-No.:
Lot-No.:

Test	Standard	Date of report
Cytotoxicity	EN 30993-5	16.05.2002
Intracutaneous Test	DIN EN ISO 10993-10	23.05.2002
Sensitization (Guinea-Pig)	EN 30993-10	04.06.2002

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Summary:

The biological testing of the catheters made out of aliphatic polyurethane passed all requirements of the individual valid standards for the final sterilized product. The results show that the products fulfill the requirements of the IS0 10993-1.

Following biological and chemical evaluations were performed in regard to Dolphin® coating:

Enclosure: Report No.	Title
(b)(4)	Biological and chemical evaluation of polyurethane catheter with SMA coating
	Biological tests of GamCath Dolphin

Summary:

The results of all biological tests meet the requirements of the ISO 10993-1 the product is qualified according to the application. There is no risk to patient of toxicity from the exposure to SMA coated catheters.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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16.0 SOFTWARE

This section is not applicable since there is no software associated with the GamCath® High Flow Dolphin® Catheter.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

17.0 ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

Not applicable to this product.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

18.0 PERFORMANCE TESTING – BENCH

Performance Data Supporting Substantial Equivalence

Terms and Definitions:

SMA Surface-Modifying Additive

(b)(4)

(b)(4) coating Dolphin®.

PDMS polydimethylsiloxane
The Abbreviation of chemical name of hydrophobic polymer block

SEM Scanning Electron Microscopy

ICG Inhibition of cell growth
Abbreviation of Toxicity screening test

PUR Polyurethane

HIT Heparin-induce thrombocytopenia (HIT)The following tests were performed to fulfill the physical, biological and chemical requirements
for central venous catheters.

Report No.	Title
(b)(4)	Viscosity behavior of 1-componet polyurethane (PUR) (b)(4)
	Toxicity screening of (b)(4) -Polyuerthane-SMA films and coatings: summary of ICG testing
	Stability of coating solution with (b)(4)
	Particle elution from coated and standard catheters
	Evaluation of mechanical properties of coated catheters in a tensile test
	Biocompatibility of coated catheters
	Reducing substance of polyurethane catheters, films and respective SMA-modifications
	Thrombogenicity of SMA-PUR coated catheters stored 3 month at room temperature
	PDMS extraction in whole blood and plasma after contact with SMA-coated catheters in comparison to standard catheters
	Thrombogenicity of heparin coated catheters

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)	Thrombogenicity of SMA-PUR coated catheters stored 6 month at room temperature
	Evaluation of mechanical properties of coated catheters in a tensile test
	Scanning electron microscopic investigation of SMA coated catheters
	Surface characterization of coated catheters after kinking (1-step coating)
	Evaluation of mechanical properties of coated catheters in a tensile test after 1-step SMA coating
	Evaluation of coating thickness by SEM
	Stability of SMA Catheter coating in a peel-off test
	Comparison: Standard dialysis catheter with dialysis catheter coated with SMA (flow measurement)
	Air Leakage SMA 5 years
	Liquid Leakage SMA 5 years
	Tensile Strength SMA 5 years
	Clamp Test SMA 5 years
	Delamination SMA 5 years

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Summary:

The results of all mechanical, chemical and physical tests meet the requirements according to current applicable standards for central venous catheters. The product is qualified according to the application.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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19.0 PERFORMANCE TESTING – ANIMAL

This section is not applicable since no animal testing was required or performed in support of this 510(k) submission for the GamCath® High Flow Dolphin® Catheter.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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20.0 PERFORMANCE TESTING – CLINICAL

Safe Medical Devices Act (SMDA) Information

Clinical Evaluation – see Attachments B, C and D

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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US006500549B1

(12) **United States Patent**
Deppisch et al.

(10) **Patent No.: US 6,500,549 B1**
(45) **Date of Patent: Dec. 31, 2002**

(54) **BIOCOMPATIBLE POLYMER FILM**

(75) Inventors: **Reinhold Deppisch**, Hechingen (DE); **Ulrich Bauer**, Hechingen (DE); **Werner Beck**, Rottenburg (DE); **Ruth Dietrich**, Hechingen (DE); **Hermann Göhl**, Bisingen-Zimmern (DE); **Katja Krämer**, Reutlingen (DE)

(73) Assignee: **Gambro AB**, Stockholm (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/415,943**

(22) Filed: **Oct. 8, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/104,001, filed on Oct. 13, 1998.

(51) **Int. Cl.**[7] **B32B 25/20**

(52) **U.S. Cl.** **428/425.5**; 525/477; 525/474; 525/464; 525/453; 428/411.1; 528/28; 528/59; 528/65

(58) **Field of Search** 525/447, 474, 525/464, 453; 428/411.1, 425.5; 528/28, 59, 65

(56) **References Cited**

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5,863,627	A	1/1999	Srycher	428/36.8

FOREIGN PATENT DOCUMENTS

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OTHER PUBLICATIONS

Costerton, J.W. et al. "Bacterial Biofilms: A Common Cause of Persistent Infections" (1999) Science 284:1318–1322.

Deppisch, R. et al. "Microdomain structure of polymeric surfaces—Potential for improving blood treatment procedures" (1998) *Nephrol., Dial. Transplant* 13:1354–1359.

Iezuka, Y. et al. "Environmentally induced Macromolecular Rearrangement on the Surface of Polyurethane–Polysiloxane Block Copolymers"; (1991) *Journal of the Chemical Society*, 87(1):147–152.

* cited by examiner

Primary Examiner—Robert Dawson
Assistant Examiner—Kuo-Liang Peng
(74) *Attorney, Agent, or Firm*—Greenlee, Winner and Sullivan, P.C.

(57) **ABSTRACT**

The present invention includes a co-polymer film which can be applied over a surface of an article to form a continuous surface that is more biocompatible and has a smoother surface morphology than an untreated article. In general the co-polymer film of the invention can be formed by providing a hydrophobic polymer block, such as polydimethylsiloxane (PDMS) with functional —OH end groups and reacting the —OH ends with a conventional monomer or prepolymer of a film-forming polymer capable of reacting with —OH groups. Such reactions are exemplified, using as reactive PDMS a triblock copolymer of the polylactone-polysiloxane-polylactone (PL-PDMS-PL) type, or silicone polyesters. The —OH groups of the polylactone blocks can react with any of a variety of isocyanates in a suitable solvent to form a polymer having PDMS incorporated with its structure. The film can be applied to the surface of an article by any convenient means of coating the article with the reaction mixture in solvent, and allowing the solvent to evaporate.

6 Claims, 4 Drawing Sheets

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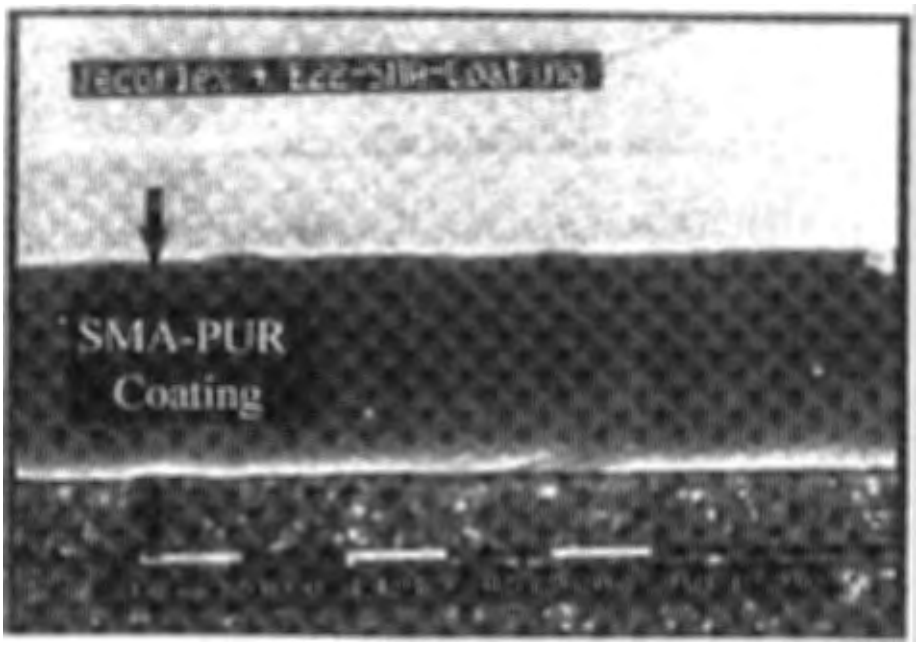

FIG. 1

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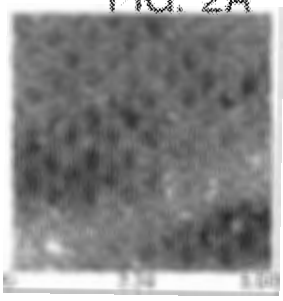
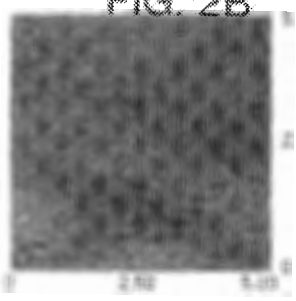
FIG. 2A

FIG. 2B

PUR
(1 comp)



height image

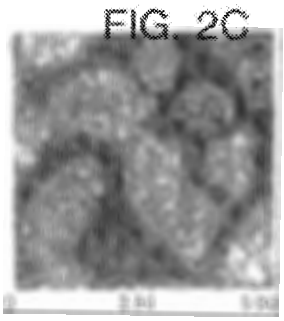


phase shift image

FIG. 2C

FIG. 2D

PUR (1 comp)
with SMA



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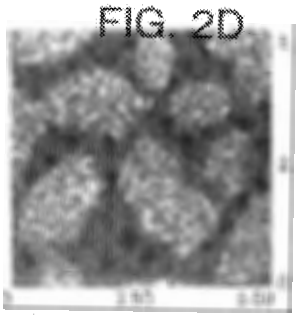

phase shift image

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FIG. 3A

FIG. 3B

PUR
(2 comp)

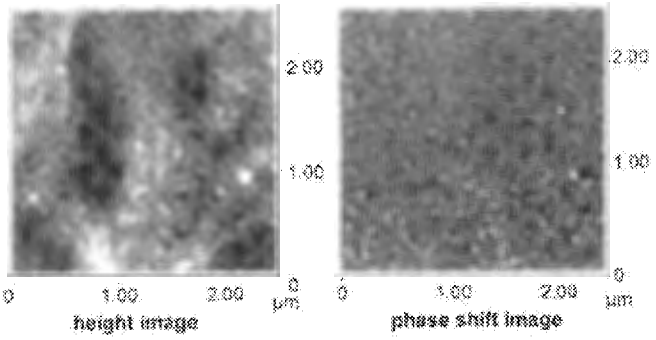
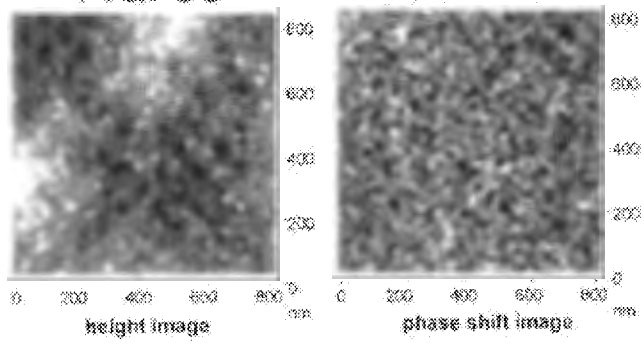


FIG. 3C

FIG. 3D

PUR (2 comp)
with SMA



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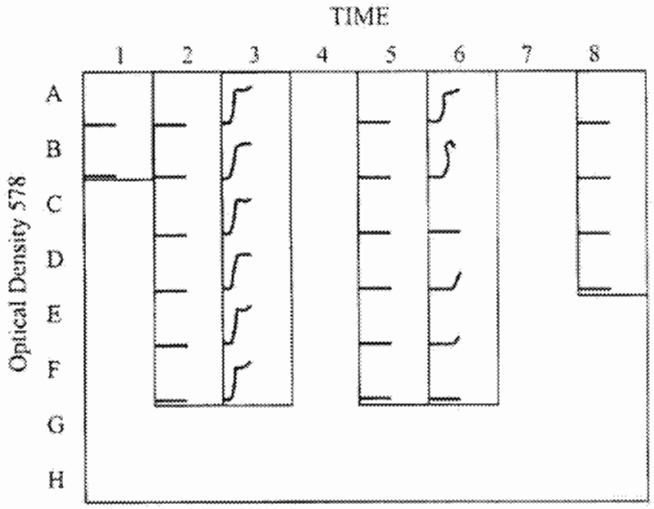

FIG. 4

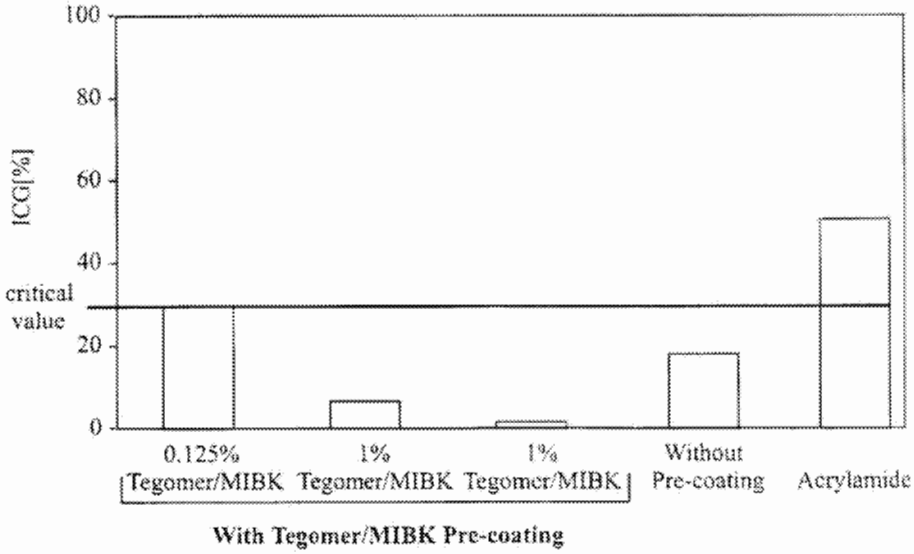

FIG. 5

Questions? Contact FDA/CDRH/OCE/Appeal CDRH FOISTATUS@fda.hhs.gov or 301-796-8118

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BIOCOMPATIBLE POLYMER FILM

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application No. 60/104,001 filed Oct. 13, 1998.

BACKGROUND OF THE INVENTION

The present invention relates to the basic problem that many of the biomedical devices used in contact with live tissue or body fluids are made of materials of synthetic or natural origin which are not biocompatible. Lack of biocompatibility can lead to blood clotting as well as various other manifestations of inflammation and tissue activation.

In addition, microbial infection can establish themselves on device surfaces. Infectious agents such as bacteria that colonize and form biofilms on surfaces can prove exceedingly difficult to eradicate, [Costerton, J. W. et al. (1999) *Science* 284:1318–1322]. Devices intended for long-term contact such as implanted stents or indwelling catheters can also serve as a surface for host cell adhesion, permitting host cells to become activated, proliferate or to alter normal physiological function and to restrict function or intended use of a device, for example by restricting fluid flow through the device.

An approach used in the prior art to improve biocompatibility has been based on modifying the surface of a device to make it more hydrophobic. On the other hand increased biocompatibility at least in part can be achieved by making a surface more hydrophilic. Although certain types of polymers, such as silicones and siloxanes, are known to possess many attributes of biocompatibility, there are no reliable physical correlates which enable one to predict biocompatibility with any degree of certainty. Generally, hydrophobic surfaces are more biocompatible than hydrophilic surfaces. Zisman's critical surface tension [Zisman, W. A., (1964) *Adv. Chem. Ser.* 43] has been used as a parameter to help assess potential biocompatibility. Materials with an optimum critical surface tension are frequently biocompatible, yet there are notable exceptions. For example, polyethylene and polypropylene have critical surface tensions well within the optimum range, but they are not predictably biocompatible. Other factors are also important. Without a clear understanding of the nature of these factors, biocompatibility remains unpredictable.

Because of the attractive structural properties of polyolefins and polyurethanes, various blending and copolymerization techniques have been developed to impart greater biocompatibility. U.S. Pat. No. 4,872,867 discloses modifying a polyurethane with a water soluble polymer and crossing them in situ with a silane-type coupling agent to form a cross-linked and intertwined polysiloxane network. U.S. Pat. No. 4,636,552 discloses a polydimethyl siloxane with polylactone side chains which are said to be useful for imparting biocompatibility when combined with a base polymer, or used to replace plasticizer. U.S. Pat. No. 4,929,510 discloses a diblock copolymer having a more hydrophobic block and a less hydrophobic block. A solution of the diblock copolymer in a solvent which swells the matrix polymer is used to introduce the diblock into an article of matrix polymer. Thereafter, the article is transferred to water, to force orientation of the incorporated diblock copolymer such that the more hydrophobic block is embedded in the matrix and the less hydrophobic block is exposed on the surface of the article. Examples of diblock copolymers included poly (ethyleneoxide-propylene oxide), N-vinyl-pyrrolidone-vinyl acetate and N-vinyl-pyrrolidone-styrene. U.S. Pat. Nos. 4,663,413 and 4,675,361 disclose segmented block copolymers, in particular polysiloxane-polycaprolactone linear block copolymers. The latter were incorporated into base polymer material to modify the surface properties thereof. Although initially blended in bulk into the base polymer, the copolymer migrates to the surface to form an exceptionally thin, possibly a monolayer film which imparts the desired surface characteristic, specifically, biocompatibility.

Triblock copolymers having a polydimethyl siloxane (PDMS) block flanked by polylactone (PL) blocks have been described, Lovinger, A. J. et al. (1993) *J. Polymer Sci. Part B. (Polymer Physics)* 31:115–123. Such triblock copolymers have been incorporated into bulk formulations, and also applied as surface coatings, to reduce thrombogenicity, as described in U.S. Pat. No. 5,702,823, incorporated herein by reference. PL-PDMS-PL triblock copolymers are commercially available, for example from Thoratec Laboratories, Berkeley, Calif., which provides a series of such polymers designated "SMA" in which the siloxane is dimethyl siloxane and the lactone is caprolactone, and also from Th. Goldschmidt AG, Essen Germany, under the name "Tegomer" (Trademark, Goldschmidt AG). The nominal molecular weights (number average) of the polysiloxane blocks suitable for use herein range from about 1000 to about 5000, while the nominal molecular weights of the caprolactone blocks range from about 1000 to about 10,000. Tsai, C-C. et al (1994) *ASAIO Journal* 40:M619–M824, reported comparative studies with PL-PDMS-PL blended into polyvinyl chloride and other base polymers or applied as a coating thereon.

Deppisch, R. et al (1998) *Nephrol. Dial. Transplant.* 13:1354–1359 reported improved thrombogenic properties for films or membrane structures of polyamide-polyvinylpyrrolidone, polyamide-polyarylethersulfone-polyvinylpyrrolidone or polyarylether-polyvinylpyrrolidone. Improved thrombogenic properties were attributed to a microdomain surface structure of hydrophobic and hydrophilic surface patches.

U.S. Pat. No. 5,589,563 discloses polymers having surface-modifying end groups, for example, polyurethanes having hard segments and soft segments covalently bonded to end groups such as PDMS or aromatic polycarbonates. The surface-modifying end groups tend to concentrate on the polymer surface to increase the surface hydrophobicity.

More recently, it has been recognized that the interactions between biological substances and man-made materials leading to clotting, inflammatory responses and microbial and host cell reactions are more complex processes in which the surface hydrophobicity of the man-made material is but one factor. Interactions between biological materials and foreign substances have been shown to include, at a minimum, molecular interactions with components of the complement system, with the kallikrein-kinin system, with the intrinsic pathway of coagulation initiation, with platelet and with other cellular components of blood including peripheral blood cells, e.g. monocytes and granulocytes.

In addition, microbial growth and host cell activation and/or proliferation on the polymer surface are problems with potentially serious consequences, especially for implanted or indwelling articles such as catheters and stents. The design of materials having improved biocompatibility must take such factors into account.

SUMMARY OF THE INVENTION

The invention includes a co-polymer film and method for improving the biocompatibility of any article of synthetic/

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polymeric, organic or metallic origin intended to contact blood, tissue or body fluids in the course of a medical treatment or procedure. Such articles include, without limitation, tubing, bags, catheters, stents, probes, feeding tubes, drainage lines, vascular grafts, artificial shunts and the like whether intended for long-term or short-term contact with blood, tissue or other body fluid or their plasma or corpuscular and cellular constituents. The co-polymer film of the invention provides reduced thrombogenicity, reduced bacterial growth and adhesion, reduced toxicity to host cells, and infiltration and seeding with inflammatory cells or host cells, when compared to articles or materials in conventional use or without the polymer film described.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1**—Scanning electron microscopy of a catheter tube cross section having $BaSO_4$ incorporated into the catheter material for enhanced x-ray contrast. The interior, blood contacting surface is uppermost. The arrow designates a PUR-SMA film applied to the inner surface of the base material.

FIG. **2**—Atomic force microscopy scans of single component PUR (top row) and PUR coated with a PUR-SMA film. Left row shows height variations, right row shows phase variations associated with drag on the probe tip. Light and dark areas have different physico-chemical characteristics, the light areas indicating a more soft and hydrophilic surface character, the dark areas indicating a surface that is relatively hard, hydrophobic and associated with a higher surface concentration of PDMS.

FIG. **3**—Atomic force microscopy comparing surfaces of a two component PUR (top row) and a coating of 2 component PUR with SMA. Height and phase images, left and right respectively, are as described for FIG. **2**.

FIG. **4**—Bacterial colonization of polyurethane test plates uncoated (row **3**) and coated with PUR-PL-PDMS-PL film (row **2**) and films of PUR (row **5**) and Pal-PL-PDMS-PL copolymer (row **6**). Horizontal axis:time (24 hrs. maximum); vertical axis, optical density at 578 nm. Letters along vertical axis identify separate test plates.

FIG. **5**—Bar graph showing cell toxicity (inhibition of cell growth) of extracts of coated catheters with and without pre-coating as described below and in Example 8.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes a co-polymer film which can be applied over a surface of an article to form a continuous surface that is more biocompatible and has a smoother surface morphology than an untreated article. In general the co-polymer film of the invention can be formed by providing a hydrophobic polymer block, such as polydimethylsiloxane (PDMS) with functional —OH end groups and reacting the —OH ends with a conventional monomer or prepolymer of a film-forming polymer capable of reacting with —OH groups. Such reactions are exemplified, using as reactive PDMS a triblock copolymer of the polylactone-polysiloxane-polylactone (PL-PDMS-PL) type, or silicone polyesters. The —OH groups of the polylactone blocks can react with any of a variety of isocyanates in a suitable solvent to form a polymer having PDMS incorporated with its structure. The film can be applied to the surface of an article by any convenient means of coating the article with the reaction mixture in solvent, and allowing the solvent to evaporate.

A polymeric film having PDMS blocks incorporated within the polymer forms over the coated surface. The resulting film is mechanically stronger than coatings of PL-PDMS-PL alone. The film integrity makes it possible to encase any structure made of any material compatible with solvents used to dissolve the starting materials. Materials can be chosen for their optimal mechanical properties, then an article made of the desired material can be encased in a polymeric film of the invention to render the article biocompatible. The polymeric films of the invention are further advantageous in that they can reduce surface roughness which may exist in the article. As an example, in polyurethane-based catheters, barium sulfate is added to provide x-ray contrast. The barium sulfate increases the surface roughness, which can degrade the biocompatibility, induce flow turbulence or enhance cellular or microbial deposits. The polymer film applied to the catheter surface not only increases the biocompatibility by changing the chemical composition of the surface, but also by reducing the roughness of the surface. Other types of surface roughness, such as are introduced during fabrication, e.g. by injection molding or by extrusion or by thermal processes during tip shaping or by mechanical manufacturing steps such as mechanical or LASER based hole drilling, can be reduced by applying a polymer film of the invention.

Without intending to be bound by a particular theory of operation, data is provided herewith demonstrating that the polymer film of the invention has surface characteristics that are consistent with current understanding regarding biocompatible surfaces. Such current understanding takes note of the fact that cells, proteins and other biological materials interact nonspecifically with surfaces in a variety of ways, including hydrophobic, hydrophilic, and ionic or electrostatic interactions, the binding often being of a cooperative nature. A review of such interactions is found in Deppisch, R. al. (1998) *Nephrol. Dial. Transplant* 13:1354–1359, which is incorporated herein by reference. The type of surface that provides the least opportunity for interaction is therefore considered to be one which presents a patchy surface with domains of varying character smaller than the corresponding interacting domains commonly found on proteins, cells and the like. The co-polymer films of the invention are characterized by a non-uniform surface having domains of varied properties. The characteristics associated with such domains include hydrophobic/hydrophilic, rough/smooth, hard/soft, and the like. Optimal sizes lie in the range from 0.1–100 nm of average diameter, although boundaries need not be regular or precisely delineated, domain size need not be uniform and domains outside the optimal range are functional. Surfaces having such optimal patchiness do not provide a sufficient contact area for any given surface trait to allow non-specific binding of biological materials. The surfaces of polymer-films of the present invention have been analyzed by atomic force microscopy (AFM). The results, presented herein, demonstrate that the exemplified such films possess a patchy surface with domains of varied hydrophobicity and hardness which have average diameters in the range 0.1–100 nm.

Also presented herewith are data demonstrating significantly increased biocompatibility of surfaces covered by a polymer film of the invention, compared to an uncoated surface.

The invention therefore includes a co-polymer film generated by reaction of a hydrophobic polymer block, for example a PDMS-containing block copolymer having reactive —OH groups, with a monomer or prepolymer of a film-forming polymer, for example, an isocyanate or isocyanate-polyol mixture. There are many ways of forming a co-polymer film according to the invention. Suitable

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hydrophobic polymer blocks include various siloxane polymers, fluoropolymers, polyethyleneglycol-polydimethylsiloxane copolymers, silicone polyesters, polyamides, polysulfones, polyaryiethersulfone, polycarbonates, polyolefins including cycloolefine-copolymers and the like. Basically all kinds of block-copolymers can be applied for coating films according to the described invention. Reactive end groups on the hydrophobic polymer block can be any sort of reactive group suitable for coupling the hydrophobic polymer block with monomer or prepolymer units of the film-forming polymer. Alternatively, coupling agents can be used to react with the hydrophobic block and then with monomer or prepolymer units of the film-forming polymer.

Examples of film-forming polymers include polyurethanes, polyolefins, polycarbonates, polyvinyl chlorides polyamides, polysulfones, polyaryleithersulfones, cellulosic polymers, cycloolefin-copolymers and the like. Preferred are polyurethanes (PUR) which can be formed by reaction of isocyanate with a polyol. PL-PDMS-PL has —OH groups which allow it to be incorporated internally into a polyurethane by reaction with free isocyanate groups.

The invention also provides a method of coating an article with a polymer film, by applying the products of the described reaction in a solvent over the surface of the article and removing the solvent, whereby the film is formed as the solvent is removed.

The invention is exemplified by two types of polymer film; using a commercially available PL-PDMS-PL block copolymer such as SMA 422, SMA 423 or SMA 425 (Trademark, Thoratec Laboratories Corp., Berkeley, Calif.) or a silicone polyester such as Tegomer H-Si 6440 (Trademark, Th. Goldschmidt A.G., Essen, Germany) in either a one component reaction with a polyurethane prepolymer (Desmodur E22 or E23, Trademark, Bayer Corp.) or a two-component reaction with an isocyanate, PL-PDMS-PL block copolymer and a polyol. In both reactions, PL-PDMS-PL blocks react as bifunctional units that become incorporated internally in the PUR polymer chain.

The reaction conditions can be varied so as to control the proportion of hydrophobic blocks to polyurethane. A preferred molar ratio of OH/NCO endgroups is in the range of 0.1 to 10. Reaction conditions which tend to increase the proportion of the hydrophobic block also tend to increase the overall hydrophobicity of the resulting film, and to increase the average diameter of the hydrophobic patches.

As a further aspect of the invention, biocompatibility, particularly reduced cell toxicity, can be improved by providing an interlayer between the surface of the article and the coating film. The interlayer can be formed of a hydrophobic material having free —OH groups such as polyol or one that is also a component of the coating film, such as PL-PDMS-PL (also referred to by tradenames herein as SMA or Tegomer). The interlayer, e.g. PL-PDMS-PL can be applied by painting or immersing the article to be coated in a solution of PL-PDMS-PL dissolved in a suitable solvent, for example methyl-isobutyl ketone, then allowing the solvent to evaporate. The process, termed pre-coating, yields a layer of PL-PDMS-PL which can subsequently be coated with a polymer film of the invention, such that the PL-PDMS-PL coating forms an interlayer between the surface of the article and the polymer coating. Formation of an interlayer can be advantageous for reducing cell toxicity of coated articles, such as catheters, especially where the catheter is made of a polyurethane base polymer having leachable isocyanates. Multilayered films can also be prepared to provide a composite of physical properties not available from a single-layer coating.

EXAMPLE 1

Step 1

25 g Methylisobutylketone

1.5 g SMA 422 (Thoratec Corp.)

Warm up to 40° C. under light stirring, approximately 5 min.

SMA 422 is a triblock co-polymer of polycaprolactone-polydimethylsiloxane-polycaprolactone blocks having nominal molecular weights of 4000, 2000 and 4000 respectively.

Step 2

Add 23.5 g Desmodur E22 (Bayer Co.)

Light stirring to avoid air bubble formation. Reaction can be carried out for up to two hours, in temperature range 0° C.–60° C.

Degassing

Desmodur E22 is a polyisocyanate prepolymer based on diphenyl methane diisocyanate. The —NCO content is 8.6% by weight. Equivalent weight is 488.

Step 3

(a) Casting a film in various thickness on glass plate with a casting knife with or without support foil, e.g. PE (Polyethylene or injection molded plates made from polyurethane); or

(b) Film forming by transporting solution through catheter tubes (ID 1–3 mm or any other geometry). The polymerized film was then examined by scanning electron microscopy (see FIG. 1).

EXAMPLE 2

Step 1

0.45 g SMA 422

23.7 g polyol (VP51 Bayer Co.)

15.9 g isocyanate (Desmodur PF Bayer Co.)

Isocyanate and SMA 422 were allowed to react together for up to 10 min. at 60° C.

Polyol was then added and the reaction further carried out as in Example 1, Step 2.

Mixing and degassing at room temperature.

Step 2

Casting as film (described above) or potting.

Other reactions of OH-groups on PL-PDMS-PL are well-known in the art and can be exploited for incorporating hydrophobic blocks into a film-forming polymer. The reaction for PL-PDMS-PL can be augmented by reaction with coupling reagents which can then react with functional groups present in other polymers or monomers. Coupling to monomers or prepolymers having —OH functional groups can be carried out using alkyl or aryl sulfonates, e.g. tosylchloride which can be reacted with the monomer or prepolymer, R—OH, then substituted by a OH-group of PL-PDMS-PL.

Monomers or prepolymers having an amine, thiol or alcohol functional group can be activated by cyanuric chloride, then coupled to PL-PDMS-PL. Monomers or prepolymers having an epoxy group can be reacted directly with the OH groups of PL-PDMS-PL. Other coupling agents include anhydrides such as maleic anhydride or maleic acid anhydride copolymer, active esters such as N-hydroxy succinimide and esters of carboxylic acids or carboxylic acids activated by various carbodiimides. In general, a wide variety of such coupling reactions is known in the art and can be exploited to incorporate hydrophobic blocks into film-forming polymers, using known reaction conditions.

EXAMPLE 3

Testing/assessing Thrombogenicity

Films or coated catheter tubes were tested for thrombogenicity assessment using freshly donated human blood.

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During contact of blood components with the material the kinetic generation of thrombin-anti-thrombin III complex (TAT) was analyzed as an indicator of thrombin formation. Thrombin is the major component in the coagulation circuit, since thrombin is a potent activator for platelets and cleaves fibrinogen to fibrin, which finally leads to a polymerized network, i.e. a clot. TAT was measured by a commercially available ELISA test according to the instruction of the manufacturer (Behring Co., Germany). The comparison of materials/surfaces is done in direct comparison of the modified versus the non-modified polymer system. Accelerated reaction kinetics for TAT indicates less biocompatible, more thrombogenic material.

For details on methodology for thrombogenicity assessment: Deppisch R. et al. (1993) *Nephrol. Dial. Transplant* Supp. 3 (1994) 17–23 and Tsai et al. (1994) *ASAIO J.* 40:M619–M624.

In vitro analysis was performed with freshly donated human whole blood. Similar results, i.e. reduction of TAT, was measured for Example 2—SMA in 2 component PUR.

TABLE I

TAT data for SMA-PUR coated tubes according to Example 1.

Type: Blood contact time	TAT (ng/ml) t = 21 min	TAT (ng/ml) t = 42 min	TAT (ng/ml) t = 63 min	TAT (ng/ml) t = 81 min
Non-treated	2	253	1570	clot already formed
Treated (60% solvent/5% SMA, 35% E22	1	75	605	1313
Treated (50% solvent/5% SMA, 45% B22	1	1	54	65

EXAMPLE 4

Si/PDMS Surface Concentration (XPS)

In order to assess the presence of Si, the central component in PDMS molecule x-ray fluorescence spectroscopy was applied. The technique used was described before, e.g. for PVC-SMA mixtures by Tsai et al. (1994) *ASAIO J.*, 40:M619–M624.

Results for films containing no or 3% SMA (related to isocyanate compound) were obtained for different take-off angles (TOA), i.e. 10, 45 and 90°. It is important to note the greater the take-off angle the higher is the penetration depth for the analysis.

TABLE II

Types	Atom (%) TOA 10°	Atom (%) TOA 45°	Atom (%) TOA 90°
Ex. 1 product non-treated	0	0	0
Ex. 1 product treated 3% SMA	17.0	12.4	9.62

These data show that Si, due to the presence of PDMS-content in the SMA-PUR, increased with decreasing TOA which indicates enrichment of SMA-PUR when cast as described above. In the given example an approximate 20-fold enrichment was realized. This experiment demonstrates that enrichment of the PDMS occurs in the surface.

TABLE III

Types	Atom (%) TOA 10	Atom (%) TOA 45	Atom (%) TOA 90
PUR 2 component non-treated	0	0	0
PUR 2 component treated (3% SMA)	15.7	8.2	6.0

These data confirm the enrichment of SMA-PUR polymer chains to the uppermost surface.

EXAMPLE 5

Scanning Electron Microscopy (SEM)

Non-modified and SMA-modified films on catheter tubes prepared as cross-cuts were sputter coated with a thin Pt/Au layer and analyzed in a Philips electron microscope. As shown in FIG. **1** a coating film of approximately 20 μm forms labeled "SMA-PUR coating." The coating process allows variation of the film thickness optimally from about 0.1 μm to several 100 μm. Furthermore, SEM also identifies small white spots which are due to the addition of $BaSO_4$ into the catheter material. $BaSO_4$ gives a change in emission of electrons in SEM. FIG. **1** shows a clear separation of the $BaSO_4$ from the blood contacting surface. As a conclusion: coated, blood-contacting surface lacks roughness due to $BaSO_4$ crystals, there is no release of $BaSO_4$ into blood, instead $BaSO_4$ remains in the catheter material.

EXAMPLE 6

AFM Pictures in Tapping Mode

The next issue in analysis was the confirmation of hypothesized nano-domains. Atomic force microscopy (AFM) is the most powerful technique to analyze nano-structures consisting of patches with different chemical or physico-chemical properties.

The AFM analysis was performed applying tapping mode technique with low forces on the tip of the cantilever (reference for methods: Magonov et al. (1996) in *Surface Analysis with STM and AFM*, VCH, Weinheim), see FIG. **2** and FIG. **3**.

The pictures of the surfaces taken or generated by AFM in tapping show different spots in the size of nanometers (10–100 nm in diameter). The picture defined as height image shows a kind of depth profile, whereas the picture defined as phase shift image shows the phase shift when the cantilever or tip is 'scratching' or moving on the surfaces (e.g. due to chemical forces or different softness). Light areas are more soft and hydrophilic. Darker areas have higher PDMS and are harder. By varying the molecular

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weight or chain length of the coating polymers, the person of ordinary skill in the art can readily modify the lateral structure of the nanodomain morphology.

EXAMPLE 7

Bacterial Adhesion

Evaluation of bacterial adhesion to co-polymer films and coated test plates was conducted by the method of Bechert, T. et al. (1998), XI[th] Aachen Colloquium on Biomaterials, Poster 26., German Offenlegung DE 19751581 A1. Adhesion of *Staphylococcus epidermis* on the material surface was quantified by means of photometry using an ELISA reaction to fix a dye to cells adhering on the surface of the material. Optical density measurements provide a relative quantitative measurement of adherent bacteria, under standardized conditions.

Various combinations of polyurethane (PUR) films, co-polymer films of PUR and PL-PDMS-PL, polyurethane test plates uncoated and coated with co-polymer films were tested.

Test plates were made of Tecoflex EG60DB20 (Thermedics, Inc., Woburn, Mass.) a thermoplastic, aliphatic polyurethane synthesized of methylene bis (cyclohexyl) diisocyanate (40%), polytetramethylene ether glycol (9.6%) and 1,4 diol chain extender (30.4%) with barium sulfate (20.0%) to impart x-ray opacity. Coating material was a one-component polyurethane essentially as in Example 1 formed from 35% Demodur E22, 5% PL-PDMS-PL (Tegomer) and 60% methyl isobutyl ketone (MIBK), cast as a film or coated on the Tecoflex test plates.

Test plates or films were exposed to a viable culture of *S. epidermis* for a period of 48 hours, with absorbance readings every twenty minutes.

Results are shown in FIG. **4**. Optical density is plotted on the vertical axis against time on the horizontal axis, for a series of test replicates A–F. Uncoated plates (row **3**) rapidly and reproducibly supported increasing density of adherent bacteria. Coated plates over the same time interval did not support measurable bacterial adherence. Films formed of polyurethane alone did not support measurable adherence. Co-polymer films of PUR and PL-PDMS-PL significantly retarded the adherence of bacteria compared to uncoated test plates, by an average of about 30 hours for the same optical density. Surprisingly the presence of PDMS at the surface reduces in a dose-dependent manner the bacterial adhesion and proliferation.

EXAMPLE 8

Cell Toxicity Studies

The toxicity of various combinations of test plate materials, film coatings and film-coated test plates was evaluated by measuring inhibition of cell growth (ICG). ICG was measured by making aqueous eluates of the various test materials, then incubating growing mammalian cells in culture medium containing the eluate, then evaluating cell viability by neutral red uptake.

The ICG test was begun by seeding a 96-well tissue culture plate with 1500–2000 mouse fibroblast cells (strain L-929) previously grown to subconfluence for 48–72 h in complete Eagles MEM. The plates were incubated for 24 h at 37° C. The medium was then removed and test eluates were added. The test eluates were made by incubating test plates or films in distilled water (1 ml for each 10 cm^2 test material) at 70° C. for 24 h.

For each plate, 250 μl 0.4% Neutral red solution was mixed with 20 ml of complete Eagle's MEM. The eluate incubation medium was removed and 200 μl/well of neutral red containing medium was added. The plates were then incubated for 3 h at 37° C. The solution was then discarded, the plates rinsed with 200 μl PBS/well. After that, 200 μl/well of 50% (v/v) ethanol and 1% (v/v) acetic acid in distilled water was added. After a 10 min wait the absorbance at 540 nm of each well was measured. ICG% was calculated as

$$\frac{A_E - A_T}{A_E} \times 100$$

where A_E=mean absorbance in test solution minus mean absorbance in blank, A_E=mean absorbance in control (no cells) minus mean absorbance in blank. The materials are deemed non-toxic if ICG is <30% as described by Wieslander et al. (1991) *Kidney International* 49:77–79.

The following materials were employed:

Completed Eagles MEM:

500 ml Eagles MEM

50 ml Fetal calf serum

5 ml 200 m ML-Glutamine

5 ml Non-Essential Amino Acid solution.

0.5 ml Gentamycin 50 mg/ml

PBS (10xstock solution):

NaCl	80 g
KCl	2 g
KH_2PO_4	2 g
Na_2HPO_4	11 g

dissolve in H_2O to 1000 ml final volume.

The stock solution is diluted 10-fold and pH adjusted to 7.2.

50% ethanol, 1% acetic acid solution:

500 ml ethanol (96%)

490 ml water

10 ml Glacial acetic acid

4% Neutral red stock solution:

4g Neutral red (Merck No.1376)

100 ml distilled water

Diluted 10-fold with water prior to use.

In parallel experiments uncoated Tecoflex catheters and co-polymer films were non-toxic, i.e. ICG<30% compared to water or saline solution as reference. However, catheters and test plates coated with co-polymer films were toxic. Substituting Desmodur E23 for Desmodur E22 resulted in co-polymer films which were non-toxic as films and non-toxic when applied to a catheter or test plate. Desmodur E23 has 15%-NCO groups.

Toxicity was also reduced or eliminated by interposing an interlayer of polyol or PL-SMA-PL over the test material, prior to applying the co-polymer film. Test catheters were pre-coated with either 0.125% or 1.0% PL-PDMS-PL by applying the pre-coating in a solution of methyl-isobutyl ketone and curing at 40° C. to remove the solvent. Test catheters were then coated with co-polymer essentially as described in Example 1 except the co-polymer starting solution was 45% Desmodur E23, 5% PL-PDMS-PL and 50% MBK. The data are shown in FIG. **5**. Catheters pre-coated with a PL-PDMS-PL interlayer had significantly reduced toxicity although catheters coated without an interlayer were also below the 30% ICG threshold for toxicity. Therefore, toxicity can be reduced either by interposing an

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interlayer having free-OH groups, or by employing rapidly reacting components to form the co-polymer film. Either strategy avoids or minimizes the possibility of reaction between the reaction components of the co-polymer film and the base polymer of which the article to be coated is formed. This multilayer concept as described above allows a great flexibility in composing the polymers.

EXAMPLE 9

Non-attachment of Mammalian Cells

The failure of mammalian cells, such as fibroblasts, to attach and overgrow articles coated with a co-polymer film of the present invention was demonstrated in the following way: Fibroblast cells were inoculated on a tissue culture plate pre-coated on the bottom with a co-polymer film of the invention, a portion of which was overlaid by a glass plate with the entire apparatus bathed in growth medium. Growth on the co-polymer surface was compared to growth on the glass surface. Cells grew on the glass surface but failed to attach or proliferate on the co-polymer surface. The failure of cells to attach or proliferate on co-polymer film surfaces of the invention indicates that such surfaces are unlikely to be damaged when implanted, by ingrowth or overgrowth of host cell tissue.

The invention having been described by examples of specific embodiments of the operating principals of the invention, other embodiments will be recognized by those skilled in the art following the general teachings and principles taught or suggested herein. Those variations that fall within the scope of the invention include the use of alternative materials for forming the co-polymer films of the invention, alternative reaction conditions for film formation and/or coating, alternatives for interlayer formation or combinations thereof.

SUMMARY OF THE RESULTS

The described SMA-PUR films show a series of improvements in terms of properties:

1. Mechanical stability of the film compared to a simple coating of PL-PDMS-PL;
2. Reduced roughness below 0.1 nm compared to technology used up to now;
3. Micro/Nano-domains in the range of 5–100 nm as proven by AFM;
4. Reduced thrombogenicity: lower TAT generation kinetics; and
5. Enrichment of PDMS to the surface as documented by ESCA and XPS analysis.

We claim:

1. An article having a surface intended to contact blood, tissue or body fluids, said article having a co-polymer film covering said surface, the co-polymer film comprising a film-forming polymer component and a hydrophobic polymer block having reactive end groups, said film having a non-uniform surface characterized by domains of varied properties of hydrophobicity, roughness or hardness, said domains having average diameters in the range 0.1 nm–100 nm, wherein the film-forming polymer is selected from the group consisting of polyurethanes, polyolefin, polycarbonates, polyvinylchlorides, polysulfones, polyethersulfones, and polyamides and the hydrophobic polymer block is selected from the group consisting of siloxane polymers, fluoropolymers, ptyethyleneglycol-polydimethyl siloxane co-polymers, silicone polyesters and polylactone-polysiloxane-polylactone triblock co-polymers.

2. An article according to claim **1** wherein the film-forming polymer is a polyurethane and the hydrophobic polymer block is a polylactone-polysiloxane-polylactone triblock co-polymer.

3. An article according to claim **1** wherein the film-forming polymer is a polydiphenyl methane diisocyanate prepolymer and the hydrophobic block is a polycaprolactone-polydimethylsiloxane-polycaprolactone triblock co-polymer.

4. An article according to claim **3** wherein prior to condensation, the proportion of —OH groups on the hydrophobic block to —NCO groups on the film-forming polymer is in the range of 0.1 to 10.0.

5. An article according to claim **1** having a first coating comprising a polyol or a polylactone-polysiloxane-polylactone triblock co-polymer, said first coating underlying the co-polymer film.

6. An article according to claim **5** further comprising an interlayer film overlying the first coating and underlying the co-polymer film.

* * * * *

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,500,549 B1
DATED : December 31, 2002
INVENTOR(S) : Deppisch et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10,
Line 15, replace "A_c=mean absorbance" with -- A_t=mean absorbance --.

Column 12,
Line 21, replace "plyethyleneglycol-" with -- polyethyleneglycol- --.

Signed and Sealed this

Twenty-fifth Day of March, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

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Annex 1:

Clinical Study: Evalauation of catheter survival, time course of pressure and blood flow during application of standard and modified catheters March 20, 2001
Dr. U. Heemann

Annex 2:

Pronologed Catheter Survival in Intermitted Hemodilaysis
Using a less throbogenic micropatterened polymer modification
ASAIO Journal 2003
Dr. U. Heemann

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Study report

Clinical study

Evaluation of catheter survival, time course of pressure and blood flow during application of standard and modified catheters in intermittent dialysis

Priv Doz. Dr. U. Heemann

Universitätsklinikum Essen
Zentrum für Innere Medizin

March 20, 2001

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Prolonged Catheter Survival in Intermittent Hemodialysis Using a Less Thrombogenic Micropatterned Polymer Modification

Marcus Baumann,* Oliver Witzke,* Ruth Dietrich,† Ulrike Haug,† Reinhold Deppisch,† Jens Lutz,‡ Thomas Philipp,* and Uwe Heemann‡

Adequate vascular access is a major prerequisite for hemodialysis treatment. Catheter related complications, in particular thrombus formation, are frequent, difficult to handle, and cost intensive. We investigated whether a new surface modified catheter containing a microdomain structure is beneficial for catheter survival. Surface thrombogenicity of standard double lumen catheters (STD-DC) and surface modified film-coated domain structured double lumen catheters (FCDS-DC) consisting of a novel reactive polyurethane copolymer coating was assessed by measurement of thrombin-antithrombin (TAT) III complex *in vitro*. Furthermore, in a randomized observational study with 20 patients on hemodialysis, we analyzed catheter survival of either STD-DC (GamCath GDK 11 French, length 12.5 or 15 cm) or FCDS-DC (GamCath Dolphin GDK 11 French, length 12.5 or 15 cm). Catheter care protocol was identical, and dialysis treatment parameters were kept constant in both groups. *In vitro* measured surface thrombogenicity was reduced in the modified catheter compared with standard catheter. The clinical investigation revealed that both number of days before catheter removal according to clinical requirements and number of treatments per catheter were significantly higher with the modified catheter as compared with the standard catheter (14.5 *vs.* 10.3 days; 7 *vs.* 4 treatments; $p < 0.03$, Fisher-Yates test). Micropatterned surface coating with a polyurethane polymer significantly increased catheter survival and the number of treatments per catheter. *ASAIO Journal* 2003; 49: 708–712.

In hemodialysis, catheter complications are a matter of substantial concern. Thrombus formation is a major source of clinical complications, in addition to bacterial adhesion, biofilm formation, and subsequent infections, and leads eventually to early treatment failure. Thus, short catheter survival also induces high costs. Several antimicrobial coating techniques have been developed to reduce bacterial adhesion and infection.[1,2] Although thrombus formation is acknowledged as the key problem for short catheter survival, only a few studies have investigated this entity, mainly on the basis of the impact of blood–material contact. Surface properties turned out to play a key role for activation of the coagulation system and adhesion of clot components such as fibrin net or platelet aggregates.[3–5]

We hypothesized that the improvement of blood–surface interaction by a reactive polymer film coating used *in vitro* might reduce thrombogenic events in the vascular access device and subsequently lead to prolonged catheter survival in the clinical setting. We therefore compared, in a randomized observational study, the clinical application of conventional and surface modified catheters with identical geometry and flow design with respect to catheter survival as the primary endpoint.

A novel coating technology provides the surface with a micropatterned structure of hydrophilic-hydrophobic domains in a polymer system containing hydrophobic polydimethylsiloxane (PDMS) blocks in a polyurethane net.[6] Micropatterned surfaces have been shown to improve blood compatibility.[7,8] As depicted in **Figure 1**, atomic force microscopy analysis shows a substantial difference between the standard catheter surface and the domain structured reactive polymer film.

Methods and Patients

In Vitro *Assessment of Thrombogenicity*

Surface thrombogenicity of the standard and modified catheters was assessed simultaneously in an *in vitro* recirculation perfusion system at 37°C with freshly donated platelet rich human ACD plasma. The shear rates provided in the experimental setting were comparable with the clinical situation (200 ml/min). Calcium was added to trigger coagulation, and plasma samples were taken at different points of time up to 90 minutes and frozen at −70°C until analysis. The formation of thrombin-antithrombin (TAT) III complex was measured in once-thawed samples to assess the extent of surface induced coagulation activation using a commercially available enzyme linked immunoabsorbent assay kit (Behring, Marburg, Germany) according to the manufacturer's instructions.

Study Population

Twenty patients treated in Essen University Hospital who required intermittent hemodialysis therapy for acute (n = 9) or chronic (n = 11) renal failure were randomly assigned to application of a standard or a surface modified catheter. Five

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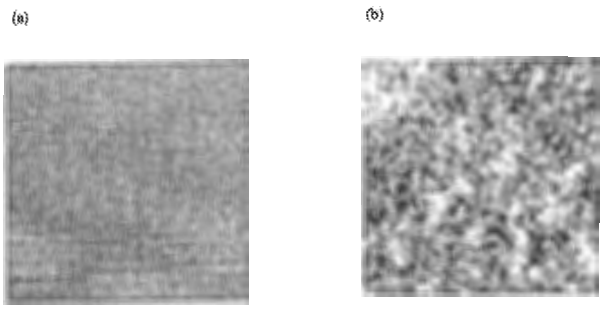

Figure 1. Atomic force microscopy of (A) standard and (B) modified catheter surface.

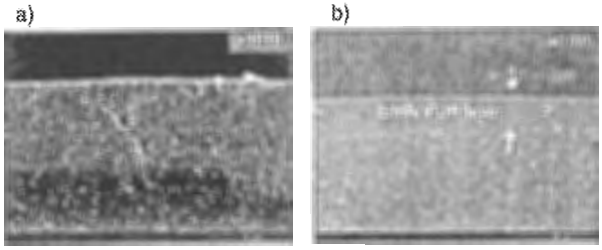

Figure 2. Cross section of (A) standard double lumen catheters (STD-DC) and (B) modified film-coated domain-structured double lumen catheter (FCDS-DC) by scanning electron microscopy.

patients dropped out because of accidental catheter removal (n = 1) or transfer to another department (n = 4). Patient characteristics of the remaining 15 patients are summarized in **Table 1**.

Standard or low molecular weight heparin was used for anticoagulation according to body weight. Exclusion criteria were drug therapy affecting coagulation (*e.g.*, vitamin K antagonists, fibrinolytic therapy), continuous hemodialysis modes, hemodynamic instability, and age less than 18 or greater than 80 years.

Catheters

The following catheter types with a length of 12.5 or 15 cm were applied during the clinical observation: standard double lumen catheters (STD-DC) (GamCath GDK-1112.5 or GDK-1115, Gambro, Hechingen, Germany) and film coated domain structured double lumen catheters (FCDS-DC) (GamCath Dolphin GDK-1112.5/SMA or GDK-1115/SMA, Gambro, Hechingen, Germany). All catheters were was inserted into the right vena jugularis.

Table 1. Patient Characteristics

Feature	STD-DC (n = 7 patients)	FCDS-DC (n = 8 patients)
Age, y	56 ± 11	54 ± 17
Weight, kg	58 ± 13	74 ± 7*
Dropouts	3/10	2/10
Origin of acute renal failure		
Prerenal	3	3
Intrarenal	0	1
Origin of chronic renal failure		
Autoimmune disease	1	2
Glomerulonephritis	1	1
Diabetes mellitus	2	1
Anticoagulation		
Heparin bolus (IU)	1,017 ± 383	1,147 ± 493
Continuous heparin dose (IU/h)	793 ± 190	1,000 ± 398*
Coagulation factors		
AT III (%)	92.7 ± 10.1	84.6 ± 12.7*
Fibrinogen (mg/dl)	436 ± 58	381 ± 103*
Thrombocyte count (1,000/μl)*	243 ± 130	204 ± 52
ACT (s)	144 ± 20	146 ± 19

STD-DC, standard double lumen catheter; FCDS-DC, film coated domain structured double lumen catheter; AT III, antithrombin III; ACT, activated clotting time.
* $p<0.05$ by t-test.

As depicted in **Figure 2**, modified catheters are standard double lumen catheters coated with a 5 to 50 μm layer of a novel reactive polyurethane copolymer. This coating provides a surface with micropatterned hydrophobic and hydrophilic domains, markedly reducing the interaction with proteins and cells.[7] The coating is applied on all surfaces of the catheter, both outer and inner.

Treatment Modes and Monitoring

Intermittent hemodialysis was performed using a volume controlled Fresenius 4002 machine (Fresenius, Bad Homburg, Germany) with either a high flux (F60, surface area 1.3 m^2) or a low flux polysulfone hemodialyzer (F6, surface area 1.3 m^2) (Fresenius, St. Wendel, Germany). Technical setup and type of blood lines were kept constant throughout the study period. Blood flow rates and blood pressures were recorded at start and end of each treatment. In addition, thrombocyte counts, fibrinogen, antithrombin III (AT-III), and activated clotting time (ACT) were determined on each day of treatment to assess the patients' state of coagulation. Catheter thrombosis was defined as continuous blood flow drop below 200 ml/min. Patients routinely received volume expansion and repositioning of the catheter. If blood flow remained below 200 ml/min, catheters were removed for electron microscopic studies.

Statistics

If not otherwise specified, data are given as means ± standard deviation. To assess statistically significant differences, t-tests and Fisher-Yates tests were performed. $p < 0.05$ was considered statistically significant.

Results

In Vitro *Assessment of Surface Thrombogenicity*

As depicted in **Figure 3**, the formation of TAT complex is markedly reduced and delayed in the modified (FCDS-DC) compared with the standard catheter (STD-DC).

Clinical Evaluation

Twenty patients were included in the study. During the study period, five patients dropped out. Of these, four were transferred to other units, and one patient accidentally removed the catheter himself. Reasons for drop out were thus not catheter related.

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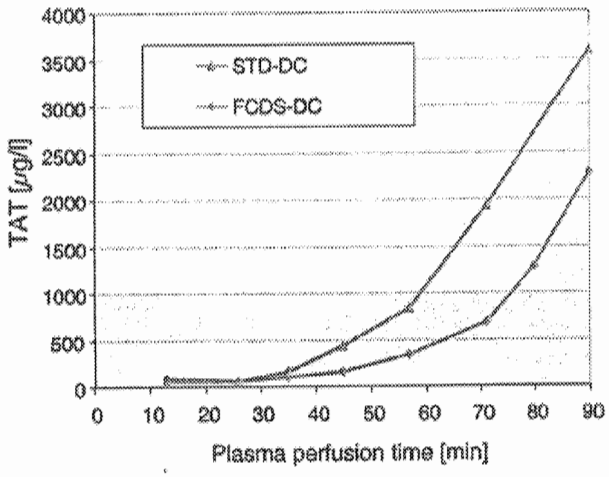

Figure 3. Surface thrombogenicity of standard (STD-DC) (A) and modified catheter (FCDS-DC) (B) as assessed *in vitro* by thrombin-antithrombin (TAT) III complex measurement in human plasma.

Data were evaluated from seven patients during treatment with the standard catheter (STD-DC) and from eight patients treated with the surface modified catheter (FCDS-DC). Hemodialysis in patients with chronic renal failure was performed three times a week. In patients with acute renal failure, the frequency was modified. However, overall hemodialysis sessions per days of inserted catheter were comparable (STD-DC 0.38 *vs.* FCDS-DC 0.41; $p > 0.05$).

Catheter survival was significantly prolonged with FCDS-DC compared with STD-DC (14.5 ± 11.7 days, range 2–39 *vs.* 10.3 ± 11 days, range 3–30; $p < 0.05$) as assessed with the Fisher-Yates test (categories: catheter survival < 7 days and ≥ 7 days). Significantly more treatments could be performed with a single catheter when using FCDS-DC compared with STD-DC (7.1 ± 3.4, range 2–12 *vs.* 4.3 ± 4.6, range 1–12; $p < 0.05$) (Fisher-Yates test, categories: < 4 and ≥ 4 treatments).

Duration of treatments (4.5 ± 0.22 hours, range 4–5 hours *vs.* 4.3 ± 0.15 hours, range 4–5 hours; $p > 0.1$), venous pressures (start 103 ± 30 mm Hg *vs.* 93 ± 41 mm Hg, $p > 0.1$; end 95 ± 37 mm Hg *vs.* 81 ± 39 mm Hg, $p > 0.1$), and blood flow rates (start 209 ± 29 ml/min *vs.* 210 ± 43 ml/min, $p > 0.1$; end 203 ± 24 ml/min *vs.* 202 ± 36 ml/min, $p > 0.1$) were similar with FCDS-DC and STD-DC. Reasons for catheter removal were a representative cross section of usual clinical requirements.

Concerning anticoagulation, the heparin bolus at start of dialysis was not significantly different with FCDS-DC and STD-DC (1,147 ± 493 *vs.* 1,017 ± 383 IU; $p > 0.2$). The continuous heparin dose was significantly higher with FCDS-DC compared with STD-DC (1,000 ±398 IU/h *vs.* 793 ± 190 IU/h; $p < 0.02$). However, in relation to body weight, the difference was no longer significant (**Table 1**). Furthermore, there was a mismatch in the distribution of single values between the treatment groups (FCDS-DC 51 *vs.* STD-DC 29 single value). In the FCDS-DC group, more patients received more than three treatments as compared with those treated with STD-DC.

To assess the state of coagulation, we investigated AT III, fibrinogen, thrombocyte counts, and ACT. As depicted in **Table 1**, no significant differences between patients treated with FCDS-DC and STD-DC were observed for thrombocyte counts (204 ± 52 × 1,000/µl *vs.* 243 ± 130 × 1,000 /µl; $p > 0.1$) or ACT (146 ± 19 s *vs.* 144 ± 20 s; $p > 0.6$), whereas AT III and fibrinogen were significantly different in the two study groups. However, all means were in the normal range (AT III 80–120%, fibrinogen 200–400 mg/dl, thrombocyte count 150–350 × 10^3/µl, ACT 96–152 s). AT III and fibrinogen were lower with FCDS-DC compared with STD-DC (84.6 ± 12.7% *vs.* 92.7 ± 10.1%, $p < 0.03$; 381 ± 103 mg/dl *vs.* 436 ± 58 mg/dl, $p < 0.04$). Again, the distribution of single values between the groups was nonequal (*e.g.*, fibrinogen: FCDS-DC 27 *vs.* STD-DC 21 single values) because more patients treated with FDCS-DC received more than three treatments as compared with those treated with STD-DC.

Discussion

In the present prospective observational pilot study, we compared two different types of central venous double lumen catheters with respect to functional application characteristics (*i.e.*, number of hemodialysis sessions and catheter survival). Patients included in the study had their first vascular access because of need for dialysis treatment. When analyzing the number of treatments performed with a single catheter, the surface modified catheter was superior to the standard catheter. In addition, the mean application period until catheter removal was significantly elevated with the surface modified catheter. Although the study was performed with a limited number of patients, the difference with respect to number of possible treatments as well as catheter lifetime were both statistically significant, which points to an obvious difference in clinical behavior of these two materials. It is known that many factors can affect catheter survival and thrombosis of the access site. Therefore, great care has been taken to limit the number of possibly interacting confounding factors (*e.g.*, technical setup and anticoagulation regime were similar in both groups). To investigate patients with acute and chronic renal failure, we had a special interest in patients with similar characteristics, including altered dialysis strategy in acute and chronic renal failure, origin of renal failure, and hemodynamic stability.

To assess the state of coagulation in each patient and at each treatment, we investigated AT III, fibrinogen, thrombocyte counts, and ACT. No significant difference was noted for ACT and thrombocyte counts. Small but statistically significant differences were found for AT III and fibrinogen levels. These data were collected for each individual treatment, and, therefore, they contain a bias with respect to patients being treated for different periods of time. Distribution of single values between the groups was unequal because more patients received more than three treatments in the group with modified catheters compared with those treated with standard catheters. Furthermore, it is important to note that all means of the parameters assessing coagulation—AT III, fibrinogen, thrombocyte counts, and ACT—remained in the normal range.

The quality of central venous catheters as temporary vascular access is of incremental importance because of increasing incidences of renal replacement therapies in acute renal failure or of comorbid conditions such as bad vascular situations (*e.g.*, in patients with diabetes). Catheter related clinical complica-

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tions such as occlusive events, severe infections, and subsequent prolongation of hospital stay are a considerable strain for affected patients and an important expense factor in health care.

It is known from a number of publications that interaction of blood components (*i.e.*, plasma proteins from coagulation and complement cascades) as well as thrombocytes or polymorphonuclear cells with synthetic materials trigger a sequence of events leading to proinflammatory and procoagulatory signals.[8–10] It has not been considered before what role catheter modifications might play in improving vascular access situations in the clinical setting. Vanholder and Ringoir[11] describe the dilemma of finding suitable polymer modifications for catheter materials. Polyurethane is known to be quite a biocompatible material, especially with respect to activation of the intrinsic and extrinsic pathways of the coagulation system. Over the past years, different modifications have been proposed to improve catheter materials. Impregnation of catheters with antimicrobial as well as with anticoagulatory substances such as heparin did not bring significant improvements in the clinical setting.[12] Canaud[13] recently called for actions to improve hemodialysis related complications, especially infections, and stressed the need for developing new technology for polymer and catheter manufacturing with thromboresistant and infection-resistant properties. In our protocol, great care is taken to handle catheters aseptically, and catheter handling and protocol of catheter care were identical in both groups.

It is not an easy task to balance the different sources of biologic responses to nonphysiologic surfaces in contact with blood.[14] The catheter modification tested in this clinical study for the first time consists of a domain patterned structure of hydrophilic-hydrophobic domains in a polymer system containing hydrophobic PDMS blocks in a polyurethane net. Atomic force microscopy analyses showed a substantial difference between the standard catheter surface and the domain structured reactive polymer film. *In vitro* studies revealed that the new polymer coating shows lower and delayed start of thrombin formation, indicating thrombosis resistance. Thrombogenicity in an extracorporeal circuit depends on many factors that may confound the final result of fibrin or platelet deposits. In contrast with bioactive modifications by heparin or other anticoagulatory substances, the microdomain approach used here is likely to prevent the deposition of protein and cells at the surface and, by this, clot formation in the catheter.

Twardowski and Moore[5] recently demonstrated that, because of manufacturing conditions, side holes and surfaces of industrially manufactured catheters show quite significant pyrogenic surfaces in the range of several micrometers because of mechanical shaping of the catheter design.[5] In the catheters tested here, a polymer film of approximately 5 to 50 μm is applied in a final step to the standard catheter geometry. Because of this procedure, the surface is more smooth and prevents the deposition or damage of blood cells that is observed in areas with sharp edges in uncoated devices. The initial clinical findings support the concept that improvement of surface roughness as well as introducing a nonadhesive biopassive surface may result in significant improvement of catheter characteristics in the clinical setting.

In 1985, Hecker[15] had already identified roughness as a leading cause of enhanced thrombogenic behavior of catheter surfaces, mainly caused by the use of radio-opaque particles (*i.e.*, barium sulfate in catheters). The approach selected for catheter modification for this new type also reduces a possible release of particles by sealing the surface with a continuous and closed polymer film. Schwab and Beathard[16] recently reviewed the catheter situation in an article entitled "Hate Living with Them, but Can't Live without Them." Catheters for vascular access in hemodialysis are essential in the maintenance of acute and chronic renal disease. Thrombotic complications are difficult to treat, and their treatment should be the first measure in preventing thrombus deposition. Surface design and structuring of less thrombogenic surfaces to prevent intrinsic thrombosis is therefore of major concern. Although our study reports only experience with a limited number of patients at one dialysis unit with homogeneous catheter care protocols, it is important to facilitate the progress and clinical research toward improved access solutions.

Further prospective clinical studies with higher patient numbers at different study sites need to be performed to assess the relative importance of surface modification *versus* catheter care protocols to better control vascular access complications that may not be adequately addressed by clinical nephrology research.

Acknowledgment

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Original Article

The role of polymer surface degradation and barium sulphate release in the pathogenesis of catheter-related infection

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Abstract

Background. Susceptibility to infection and thrombosis of intravascular catheters is increased by surface irregularities, which might be prevented by coating.

Methods. BaSO4 release from conventional haemodialysis catheters (CC) and modified catheters (MC) which had been coated with a surface-modifying additive (SMA) was assessed *in vivo* and *in vitro*. For the *in vivo* part, patients were randomized to receive a temporary CC or MC, with crossover after 1 week. After retrieval, catheters were examined using scanning electron microscopy to assess surface integrity, and an *in vitro* model of catheter exposure to the bloodstream was used to evaluate surface morphology and susceptibility to bacterial adhesion and proliferation.

Results. $BaSO_4$ moieties covered 14.7 ± 3.7% of the surface of unused CC. After *in vivo* use in 16 patients, 62.7 ± 32.9 × 10^3 holes/mm^2 were detected, indicating $BaSO_4$ detachment from 3.3 ± 1.7% of the catheter surface. No defects were observed in unused CC and in MC, whether used or unused. After incubation of four catheters (two of each type) with *Staphylococcus epidermidis*, the two degraded CC showed an immediate and strong bacterial growth as indicated by an increase in medium impedance of 0.512%/10 min compared to −0.021%/10 min in MC ($P < 0.001$).

Conclusions. Short-term exposure of CC to the bloodstream causes $BaSO_4$ particle release, resulting in surface irregularities predisposing to bacterial proliferation. $BaSO_4$ release can be prevented by SMA coating.

Keywords: catheter infection; haemodialysis; polydimethylsiloxane; surface modification; surface roughness

Introduction

Central venous catheters are widely used in clinical practice for therapeutic purposes such as extracorporeal blood purification, drug administration, fluid replacement and parenteral nutrition. Haemodialysis catheters provide a fast access for renal replacement therapy in both acute and chronic kidney failure [1]. Blood stream infection remains the most important complication accounting for morbidity, mortality and cost [2,3]. A major culprit for this complication is roughness of the catheter surface due to microscopic irregularities which promotes thrombogenicity [3] as well as biofilm formation [4]. One of the factors potentially contributing to roughness is the addition to the polymer formulation of radio-opaque materials, such as barium sulphate ($BaSO_4$), allowing the verification of position [5,6]. In addition, implanted polymers may undergo biodegradation and breakdown caused by local hydrolytic or proteolytic conditions at sites of leukocyte activation and adhesion or ingrowth of germs colonizing the biofilm on the polymer surface [7,8].

We hypothesized that in haemodialysis catheters areas of $BaSO_4$ aggregation make catheters prone to surface degradation after prolonged exposure to the bloodstream. Release of $BaSO_4$ particles due to biodegradation at the surface in turn increases surface irregularity which as such might act as a promoting factor for aggregation of bacteria [4,8–10].

Improvements in design of biomaterials over the past decade include the development of surface-modifying additives (SMA). SMA are a family of polysiloxane-containing copolymers that exhibit a microdomain structure containing areas with opposing physicochemical properties in the nanoscale range [11,12]. Surface-coating films composed by these copolymers have a lower potential for coagulation activation and platelet adhesion and activation [13].

In the present study, we compared a commercially available SMA-coated polyurethane catheter with a conventional polyurethane catheter in a prospective randomized crossover clinical trial to test our hypothesis that $BaSO_4$ moieties are released from the catheter surface *in vivo* and that the resulting roughness of the catheter surfaces contributes to susceptibility to bacterial adhesion and proliferation. Scanning electron microscopy was used

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to assess catheter surface integrity, and an *in vitro* model of catheter exposure to the bloodstream was used to evaluate surface morphology and susceptibility to bacterial adhesion and proliferation. Because of the randomized crossover design, the study was limited to clinical conditions requiring a temporary catheter and the evaluation of changes after short-term exposure to the bloodstream.

Materials and methods

Catheters

Conventional polyurethane catheters (CC) and surface-modified catheters with a polyurethane-based block copolymer coating (MC) but otherwise identical (GamCath® and GamCath® Dolphin, Gambro Kathetertechnik, Hechingen, Germany) were compared in both the *in vivo* and *in vitro* study. MC were produced using a reactive polymeric film-coating process as final manufacturing step. Single- and double-lumen catheters were available. Although the initial choice for each patient was left to the attendant nephrologist, the same number of lumina was to be used throughout the entire study period. All catheters were CE-marked.

Patients

Patients aged 18–80 years and undergoing intermittent haemodialysis for acute kidney injury or stage 5 (end-stage) kidney disease with a need for a central venous catheter as vascular access were eligible for the study. Pregnancy, treatment with vitamin K antagonists or the need for continuous renal replacement therapy were exclusion criteria. After inclusion, patients were randomly assigned to be dialysed initially with the MC or CC, with a crossover after 7 ± 1 days. The investigator in charge of patient inclusion, catheter insertion and clinical data collection was blinded to the type of catheter. Intermittent haemodialysis was performed at a constant blood flow rate (range 100–300 ml/min) for at least three haemodialysis sessions per catheter, without changing the type of dialysis machine, dialyser, tubings or anticoagulation lock. The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

Catheter application

Catheters were inserted into the internal jugular or femoral vein. After 7 ± 1 days, the catheter was exchanged using a guidewire. Seven days later, the second catheter was withdrawn as well and replaced by a conventional catheter when still required as vascular access. Immediately after removal, the catheters were rinsed with a 50-mL flush of a 0.9% sterile saline solution through the inlet and outlet tubings, applying a low infusion rate. The external catheter surface was rinsed in a bath of 0.9% sterile saline using an appropriate container. After rinsing, the catheter was fixed by flushing 50 mL of 2% glutaraldehyde in 0.9% saline through the inlet and outlet tubings. Subsequently, the catheter tip with side holes was stored at 4°C in a 50-mL container filled with 2% glutaraldehyde until analysis.

In vitro model investigations for $BaSO_4$ release

Catheter surfaces were exposed to hydrogen peroxide to simulate the clinical situation of biodegradation by an oxidative, hydrolyzing agent. Surface contact with oxidants was pursued by incubation of the catheters in rotating tubes, filled with 3% hydrogen peroxide at 37°C for a period of 8 days. To simulate *in vivo* conditions with respect to proteolytic surface degradation, catheters were incubated in freshly donated human serum under the same conditions. After incubation, the catheters were fixed with 2% glutaraldehyde (GDA) and processed for scanning electron microscopic analysis.

The fixation procedure per se did not induce any increase in surface roughness nor hole formation in unused CC and MC.

Morphological studies

Surface and cross-section characterization with scanning electron microscopy. New unused catheters and fixed samples after *in vivo* use or *in vitro* degradation were rinsed with distilled, sterile-filtered water, dried and sputter-coated with gold using an SCD 040 equipment (Bal-Tec, Witten, Germany).

Cross-sections and surfaces of new catheters, and surfaces of used or *in vitro*-degraded catheters were analysed in a scanning electron microscope (SEM, Philips SEM 515, Eindhoven, The Netherlands). Thin layer sputter coating (carbon-Pt target) was applied to investigate the polymeric specimen. Secondary electron emission was used to identify material contrasts, i. e. bright electron-dense areas embedded in the grey matrix area were identified as barium collections whereas dark spots were considered as holes devoid of barium sulphate. Validation was performed by energy-dispersive X-ray spectroscopy (EDX) as described below.

Identification of $BaSO_4$. $BaSO_4$ was identified with EDX. Spots with bright appearance and grey matrix as displayed in the SEM image were analysed for elemental composition.

Surface characterization with atomic force microscopy. In analogy to the catheter-coating process, plain polyurethane films with and without block copolymer were produced. These films were analysed by atomic force microscopy (AFM, NanoScope, Veeco Inc., USA) without preceding sample conditioning, in tapping mode with phase detection to obtain material contrast. Standard silicium tips with a nominal radius of 10–50 nm were used. Measurement was performed at the natural resonance of the cantilever.

Quantification of $BaSO_4$ release. SEM images were used to assess the number of holes at the surface after *in vivo* use of the catheters. The evaluated display window area was 334 μm^2.

Greyscale analysis of the SEM images with the Zeiss KS400 software (version 3.0) was used to distinguish between bright areas of high electron density and dark areas of low electron density appearing as holes embedded in the matrix. The respective areas were quantified by grey value segmentation to generate binary regions (bright/dark). From this analysis, the percentages of surface areas covered by bright electron-dense $BaSO_4$ moieties and by holes at the surface which had released $BaSO_4$ were calculated.

Assessment of susceptibility of degraded catheter surfaces to bacterial proliferation. As reported previously in other centres [14,15], also in our hospital, *Staphylococci* species are responsible for most catheter-related infections. Therefore, we chose an experimental setup where *in vitro* serum-exposed catheter surfaces were brought into contact with *Staphylococcus epidermidis* (ATCC 12228; concentration of McF = 0.01 corresponding to ~3×10^5/mL) under controlled closed-system conditions, avoiding any contamination, for a period of 4 h. Bacterial metabolic activity on the catheter surfaces was investigated by measurement of medium impedance during an additional catheter incubation with trypticase soy bouillon (Bio Mérieux, Nürtingen, Germany) in a BacTrac 4110 device (Sy-Lab, Neupurkersdorf, Austria). The impedance of such a suspension changes when ions are formed through metabolic cleavage of molecules with low or no electric charge by live/proliferating bacteria

Table 1. Characteristics of patients and dialysis modalities

Male (%)	44	
Age (year)	69 ± 10	
Indication (no. of patients)		
ESRD	12	
ARF	4	
Position (no. of patients)		
Jugular	12	
Femoral	4	
	CC	MC
Sessions/patient (no.)	57	35
Duration (hours)	3.6 ± 0.9	3.9 ± 0.8
Blood flow rate (mL/min)	202 ± 35	199 ± 20
Units of LMWH per session	5346 ± 3890	6214 ± 3465

Data are mean ± SD or numbers. ESRD, end-stage renal disease (CKD stage 5); AKI, acute kidney injury; LMWH, low-molecular weight heparin. To facilitate comparison, units of different LMWHs are summed; within each patient, the same type of LMWH was used.

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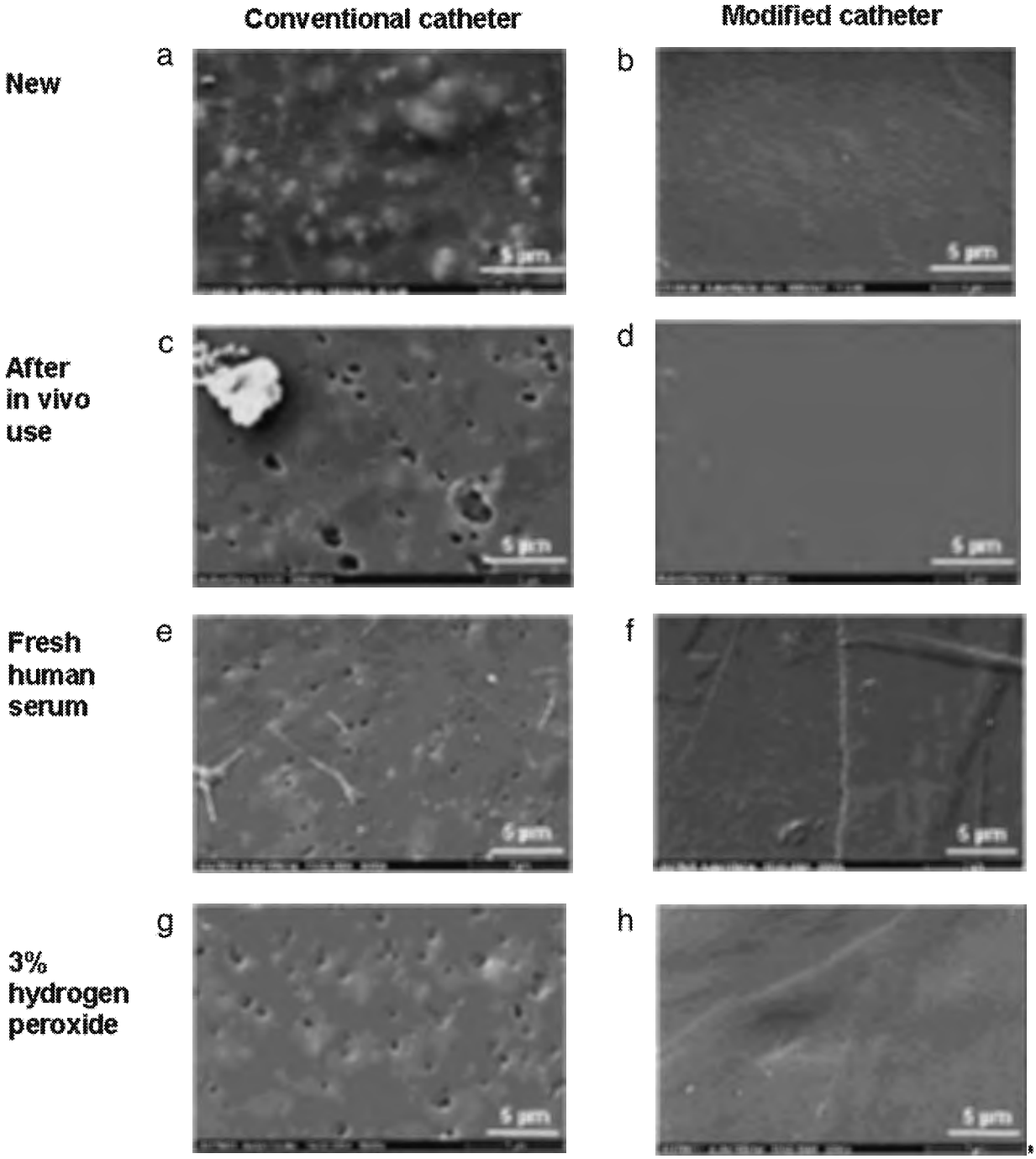

Fig. 1. Inner surface morphology of a CC (left) and an MC (right) assessed with SEM, before (a, b) and after (**c, d**) contact with blood *in vivo*; after *in vitro* incubation with fresh human serum (**e, f**) and hydrogen peroxide (**g, h**). Before use, electron-dense areas are seen in the CC (**a**) but not in the MC (**b**). After *in vivo* use or *in vitro* degradation, holes of different sizes are observed in the CC (**c, e, g**) but not in the MC (**d, f, h**).

[16]. The rate of change in impedance depends on the number and type of bacteria adhered to the surface during the preceding incubation step. Duplicate experiments were performed in parallel, i.e. with serum-exposed CC and MC, respectively.

Statistics

Data were tested for normal distribution with the Shapiro–Wilk test. Normally distributed data are presented as mean ± SD, and non-normally distributed data are given as median and range if not otherwise stated. The change in impedance over time after bacterial exposure was assessed using linear regression analysis with a dummy variable used for the type of catheter (MC = 0; CC = 1). An interaction term of time by catheter type was used to test for a difference in slopes between the two catheters.

Results

In vivo study

Sixteen patients were included in whom 92 haemodialysis sessions were performed during the study period. The ma-

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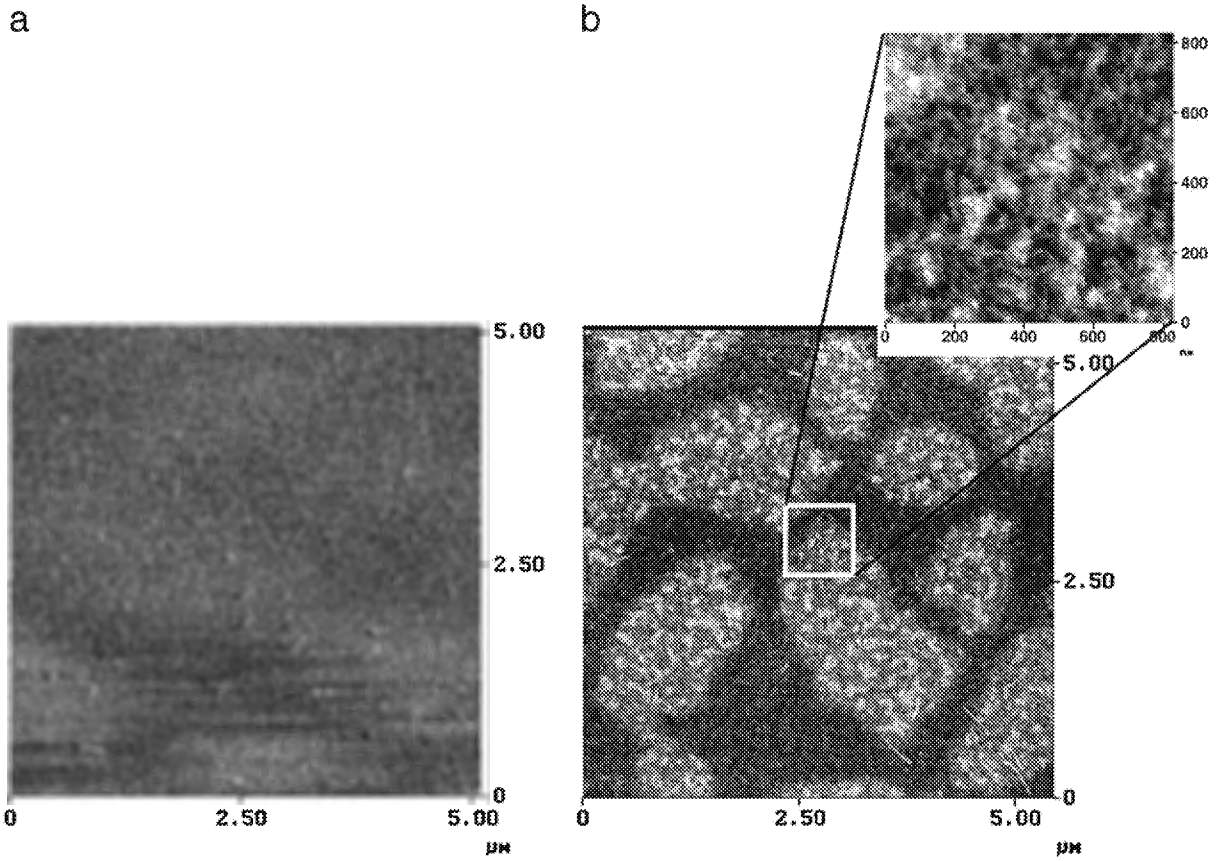

Fig. 2. AFM of the surface of a CC (**a**) and an MC (**b**) depicting hydrophilic–hydrophobic microdomain structure on the CC but not on the MC surface.

jority were chronic haemodialysis patients who needed a temporary catheter because of vascular access problems. Characteristics of patients and dialysis modalities are shown in Table 1. Two patients received daily dialysis during the week while they were on the CC whereas they were treated by alternate day dialysis while on MC, and three other patients dropped out of the study while on CC before the MC study period was started, resulting in a larger number of dialysis sessions with the CC. Otherwise both catheters were comparable regarding ease of insertion, duration of dialysis sessions, blood flow rates and anticoagulation use.

Analysis of the catheter surfaces by SEM revealed no holes at the surface of the unused CC (Figure 1a) whereas, after 1 week of haemodialysis, multiple holes were obvious at the CC surface (Figure 1c). Neither before use (Figure 1b) nor after *in vivo* use (Figure 1d), were any holes detected on the MC surface. Multiple bright areas corresponding to barium sulphate in new CC (Figure 1a) were replaced by dark areas corresponding to hole formation, suggesting that a substantial amount of barium sulphate had been lost in used CC (Figure 1c).

Quantification of $BaSO_4$ release. Through quantification by greyscale analysis of the SEM images, it was estimated that bright electron-dense areas, corresponding to $BaSO_4$ moieties, covered 14.7 ± 3.7% of the surface of the new CC (n = 8). After exposure to blood *in vivo*, many of these electron-dense areas disappeared in CC, and multiple defects in the catheter surface appeared as holes of variable size, as depicted in Figure 1c. In used CC, 62.7 ± 32.9 × 10^3 holes/mm^2 surface area were detected, with diameters ranging from 0.1 to 1.0 μm (n = 13 used catheters). The percentage area of holes as assessed with greyscale analysis was 3.3 ± 1.7%, ranging from 0 to 4.6% (median 4.0%).

In a representative imaging experiment, the SEM image of the CC surface after *in vivo* use displayed a dark area fraction of 4.4%, corresponding to the zone of barium sulphate particle release, and a bright area fraction of 9.0%, totaling 13.4% which is in the range of the average 14.7% of area corresponding to $BaSO_4$-containing surface in CC mentioned above.

Neither bright electron-dense areas nor holes were visible at the surface of the new MC (Figure 1b) or *in vivo* used MC (Figure 1d). Thus, no greyscale analysis or evaluation of number of holes was performed with MC.

In vitro studies

Identification of $BaSO_4$. Characterization of the CC surface by EDX for elemental composition revealed that the spots with bright appearance on the SEM image consist of Ba, C, O and S whereas C, O and N were identified in the dark matrix which thus represents the polyurethane base material.

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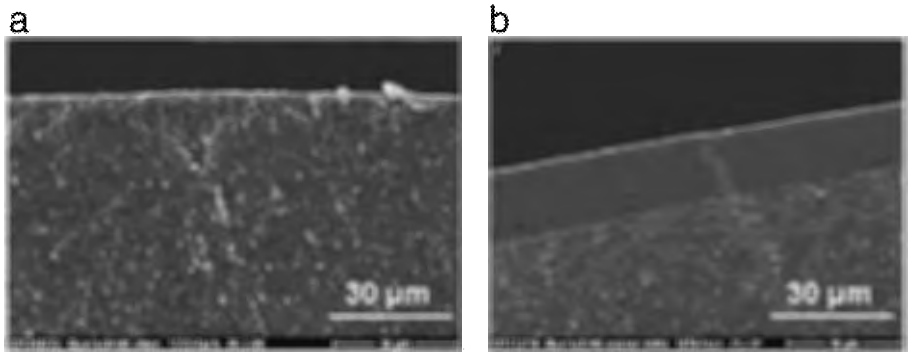

Fig. 3. Cross-section of CC (**a**) and MC (**b**) assessed with SEM, showing a smoother surface for MC.

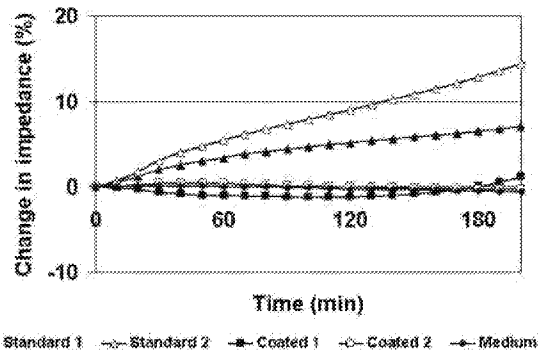

Fig. 4. Bacterial proliferation on two CC catheters (open triangles and filled triangles), and two MC catheters (open squares and filled squares), after *in vitro* treatment with serum and subsequent incubation with *S.epidermidis* for 4 h. A serum-treated catheter maintained in medium (diamonds) alone was used as a control experiment.

Analysis by SEM of surface degradation. A series of *in vitro* studies was performed to further elucidate underlying mechanisms: incubation in fresh human serum to simulate proteolytic degradation; incubation with 3% hydrogen peroxide to simulate oxidative polymer surface degradation. As depicted in Figure 1e and 1g, holes of similar diameter range as seen *in vivo* after 1 week of dialysis with CC (Figure 1c) were found on the CC but not on the MC surface (Figure 1f and 1h).

Microscopic characterization of surface structure and catheter cross-section. AFM applied to plain polyurethane films confirmed the presence of microdomains in the surface structure of the block copolymer containing polyurethane (MC) (Figure 2b) which were absent in the pure polyurethane (CC) (Figure 2a).

Cross-sectional analysis with SEM revealed the characteristic surface with improved smoothness of the MC (Figure 3b) compared to the CC (Figure 3a).

Quantification of $BaSO_4$ release. Greyscale analysis of SEM images of *in vitro*-degraded CC surfaces revealed hole formation due to release of $BaSO_4$ moieties of 5.65% (range 4.7 to 6, $n = 4$) of surface area after contact with hydrogen peroxide and 7.65% (range 4.4 to 8.2, $n = 4$) after incubation with human serum which is in the same range as found for CC after *in vivo* use. Bright electron-dense $BaSO_4$ moieties covered 5.2% (range 1.2 to 33.6%) of the surface after incubation with hydrogen peroxide and 6.15% (range 1.9 to 19.5) after incubation with serum.

Bacterial adhesion and growth on degraded catheter surfaces. Two catheters of each type that had been in contact with serum were challenged with *S. epidermidis* for 4 h and subsequently analysed by the BacTrac method to assess the influence of surface degradation on bacterial adherence and activity.

As depicted in Figure 4, a continuous linear increase in impedance is observed for CC but not MC, indicating ion formation from cleavage of molecules with low or no electric charge by the metabolic activity of proliferating bacteria. MC revealed a markedly delayed bacterial activity, whereas on the surface of the degraded CC, an immediate and strong bacterial growth was observed. In two parallel experiments, impedance with CC increased by 6.47 and 12.81% after 180 min. In contrast, on MC, the change in impedance after 180 min of 0.03 and −0.20% was indistinguishable from that of medium alone (−0.45%).

Multiple linear regression analysis indicated a significant time by catheter interaction, with an increase in impedance of 0.512%/10 min in CC compared to −0.021%/10 min in MC catheters ($P < 0.001$ for interaction; model $R^2 = 0.87$, $P < 0.001$).

Discussion

The present study identifies the release of $BaSO_4$ as an important factor contributing to irregularities of the catheter surface after contact with blood. Summing up the areas covered with holes and with bright electron-dense $BaSO_4$ moieties, as identified with EDX, results in a percentage area that closely corresponds to the area covered by $BaSO_4$ moieties at the new CC surface, as assessed with greyscale analysis. Based on these findings, we conclude that release of $BaSO_4$ might be the predominant mechanism leading to surface defects.

Moreover, we were able to demonstrate that these defects are related to an increased susceptibility to bacterial growth. Coating of the catheter with a thin polyurethane/SMA layer prevented the release of $BaSO_4$ and conferred protection against bacterial proliferation. From these results, we hypothesize that catheter-related infections, one

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of the two major complications of haemodialysis catheters and a major cause of morbidity and mortality among dialysis patients, can be preceded by surface irregularities as a common pathway and that the release of $BaSO_4$ plays an important role in this process. Likewise, and although not addressed in the present study, also thrombogenicity might be enhanced by this roughness due to surface irregularities. Bacterial adhesion and biofilm formation, however, may start very rapidly after catheter insertion, so that roughness should be considered as one of the many factors that may play a role in this complex process.

The finding of this study that catheter surface irregularities result from the release of $BaSO_4$ from the catheter surface provides new insights in the mechanisms involved in the thrombogenicity and susceptibility to infection of artificial surfaces. Many other medical devices such as pacemaker leads, vascular ports and arterial catheters contain $BaSO_4$ moieties. Therefore, these results may be relevant for a wide range of medical disciplines and may have large implications on future evolutions in design and development of biomaterials in medicine, especially since this effect can be prevented by adequate coating of the catheter surface.

Previous studies have shown that catheters with rougher surfaces are more thrombogenic than those with smooth surfaces because surface irregularities play a major role in the initiation of thrombosis in and on intravascular catheters [5]. The reason why some catheters have smoother surfaces than others has not been well evaluated. Manufacturing processes such as drilling of side holes [10] as well as the physicochemical properties of the material may play a role. Polyethylene catheters tend to be less thrombogenic than polyurethane catheters that have a rough and irregular surface [17,18]. Our study revealed for the first time the release of $BaSO_4$ moieties during contact with blood as an important mechanism contributing to surface irregularities. This explains the previously observed association of roughness with the presence of radio-opaque particles. In one study, irregularities were concentrated into radio-opaque tracer strips [5]. A recent case report of a broken haemodialysis catheter implicated irregular $BaSO_4$ powder lumps that formed elongated cavities on extrusion [19]. These aggregates of $BaSO_4$ were very similar to those observed in our study. Another study described a very irregularly arranged structure at distance marks containing radio-opaque admixtures, which were placed on the surface and parts of the catheter wall [6]. Moreover, it was demonstrated in these studies that these parts of the catheter wall were much more prone to adhesion of formed elements of the blood and bacteria or spores than other areas of the wall. An SEM study of Franson *et al.* revealed lodgment of bacteria into surface irregularities in both infected catheters *in vivo* and unused catheters *in vitro* [20]. Irregularities of artificial surfaces thus also favour the adhesion of microorganisms, either directly or indirectly by adhesion to conditioning films formed by the precipitation of proteins such as fibrinogen, fibronectin and laminin. Bacterial adhesion subsequently triggers the expression of genes responsible for biofilm formation [9].

Besides damage to the catheter surface, the release of $BaSO_4$ may also exert deleterious effects related to the toxicity of the compound itself. At clinically relevant concentrations, $BaSO_4$ causes a deactivation of the phagocytic response upon stimulation [21]. Due to the sustained release of $BaSO_4$ from the catheter surface, local $BaSO_4$ concentrations could be reached that are sufficient to produce a similar effect thus lowering the immunologic defence against bacterial colonization and biofilm formation.

The recognition of the adverse effects of surface irregularities stimulated the development of devices with microdomain-structured synthetic polymer surfaces. These block copolymers, also called SMAs, are blended in a reactive mixture with polyurethane polymer resins and coated on device surfaces, as was the case for the SMA dialysis catheter (MC) we used (US patent 6841255). SMAs improve biocompatibility by delaying contact activation and reducing thrombin–antithrombin complex generation [12], and diminish the thrombogenicity by hampering adhesion of platelets [22,23]. The SMA-coated catheters we used had a very smooth surface compared to the conventional catheters, and more importantly, this coating prevented the release of $BaSO_4$ by sealing the surface with a continuous and closed polymer film. Hence, SMA coating confers an additional benefit of preventing damage to the catheter surface induced by $BaSO_4$ release. The *in vitro* model we used allowed us to confirm that coating with SMA also protects against bacterial proliferation, even after an important bacterial load. Obtaining a smoother surface by SMA coating thus reduces susceptibility to bacterial adhesion. Surface irregularities resulting from the release of $BaSO_4$ may represent a common causative pathway for these complications.

A drawback of the present study is that, although it is partly based on catheter samples collected *in vivo*, it does not evaluate hard clinical endpoints. Before starting a clinical study of sufficient power, we needed, however, to evaluate whether our hypothesis of barium moiety loss and creation of surface irregularity indeed could be corroborated morphologically. By adding bacteriological studies on catheters which had been treated by serum, and which showed the same characteristics as catheters extricated *in vivo*, we could in addition show that these irregularities indeed were linked to increased susceptibility to bacterial growth. For ethical reasons, we could only perform this randomized crossover study in clinical conditions where a temporary catheter was needed. Although long-term indwelling catheters are protected by the barrier of the subcutaneous trajectory, they also contain barium and are exposed to the bloodstream for much longer periods than in the present study. Therefore, we expect that the changes observed in temporary catheters after only 1 week, also occur in indwelling catheters. The clinical impact of $BaSO_4$ release, both in tunnelled-cuffed catheters and in temporary catheters, remains to be determined.

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Conflict of interest statement. This study was sponsored by Gambro.

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May 18, 2010

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14143 DENVER WEST PARKWAY SUITE 400
LAKEWOOD, COLORADO 80401
UNITED STATES
ATTN: KAE MILLER

510k Number: K100451

Product: GAMCATH HIGH FLOW DOLPHIN MS-G

Extended Until: 06/18/2010

Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information (AI) is not received by the "Extended Until" date shown above, your premarket notification will be considered withdrawn (21 CFR 807.87(l)). If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

Marjorie Shulman

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Section
Office of Device Evaluation
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Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name Jeffrey Coggins

Subject: 510(k) Number K100451

To: The Record

Please list CTS decision code AT

- ☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)
- ☑ Hold (Additional Information or Telephone Hold).
- ☐ Final Decision (SE, SE with Limitations, NSE, Withdrawn, etc.).

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*		
510(k) Summary /510(k) Statement	*Attach Summary*		
Truthful and Accurate Statement.	*Must be present for a Final Decision*		
Is the device Class III?			
If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)			
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			
Is this device intended for pediatric use only?			
Is this a prescription device? (If both prescription & OTC, check both boxes.)			
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			
Is clinical data necessary to support the review of this 510(k)? Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If not, then applicant must be contacted to obtain completed form.)			
Does this device include an Animal Tissue Source?			
All Pediatric Patients age<=21			
Neonate/Newborn (Birth to 28 days)			
Infant (29 days -< 2 years old)			
Child (2 years -< 12 years old)			
Adolescent (12 years -< 18 years old)			
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)			

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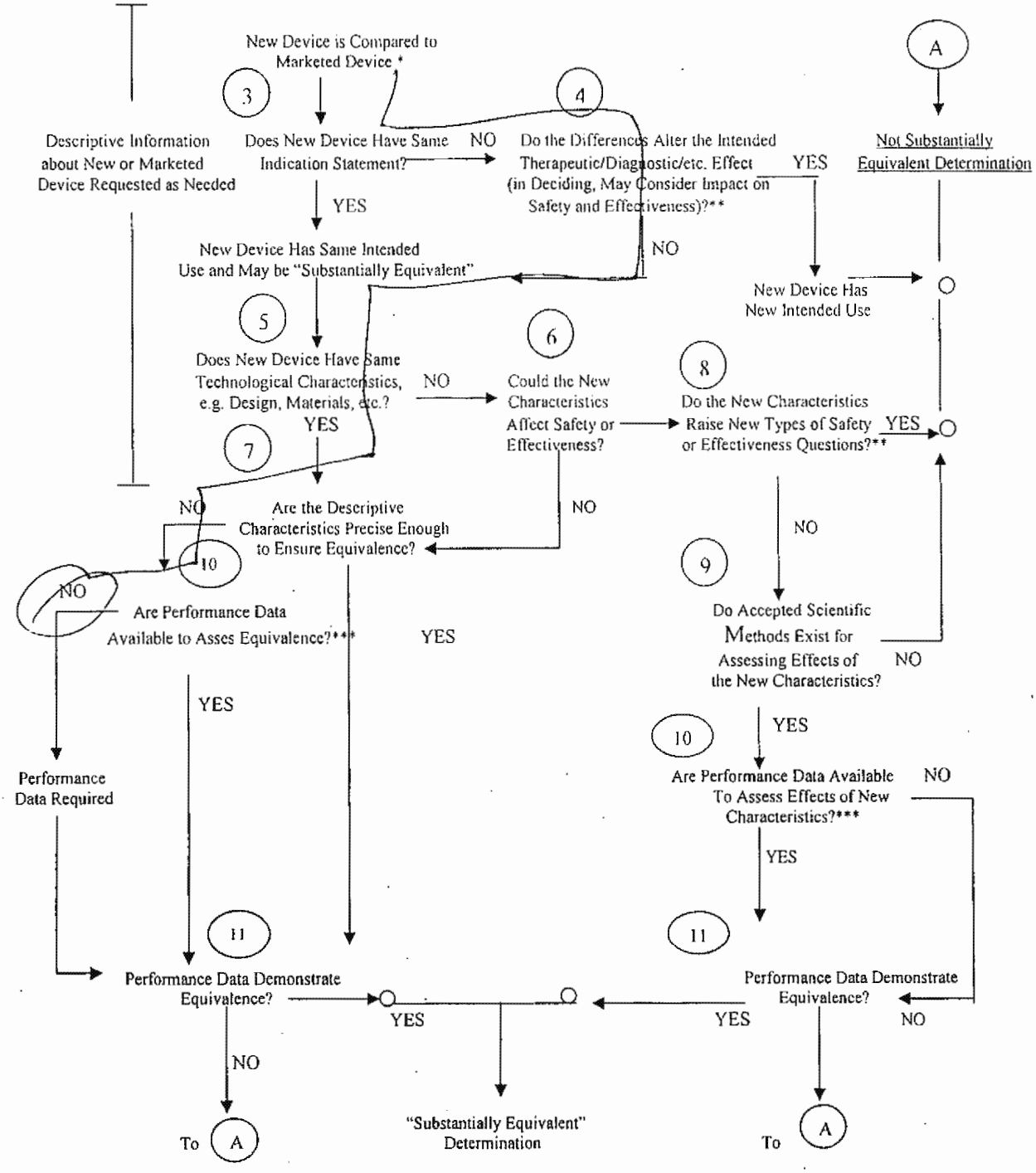
510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



❖ 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

❖❖ This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

❖❖❖ Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

606

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old) Nanotechnology Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html)	*Contact OC.*

Regulation Number **Class*** **Product Code**

(*If unclassified, see 510(k) Staff)

Additional Product Codes:

Review: Carolyn Y Neuland (Branch Chief) GRDB (Branch Code) 4/19/10 (Date)

Final Review: (Division Director) (Date)

469

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

Premarket Notification [510(k)] Review
Traditional/Abbreviated

K100451

Date: April 6, 2010
To: The Record
From: Jeffrey Cooper, DVM

Office: ODE
Division: DRARD

510(k) Holder: Gambro Renal Products, Inc.
Device Name: GamCath® High Flow Dolphin® Catheter
Contact: Kae Miller, Regulatory Affairs Manager
Phone: 303 222-6724
Fax: 303 222-6916
Email:

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

Reviewer

4/16/10
Date

Branch Chief

4/19/10
Date

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

419

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-15-2024

Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name JEFFREY Cooper DM

Subject: 510(k) Number K100451/S1

To: The Record

Please list CTS decision code JH

- ☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)
- ☐ Hold (Additional Information or Telephone Hold)
- ☐ Final Decision (SE, SE with Limitations, NSE, Withdrawn, etc.).

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*		
510(k) Summary /510(k) Statement	*Attach Summary*		
Truthful and Accurate Statement.	*Must be present for a Final Decision*		
Is the device Class III? If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)			
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			
Is this device intended for pediatric use only?			
Is this a prescription device? (If both prescription & OTC, check both boxes.)			
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			
Is clinical data necessary to support the review of this 510(k)? Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If not, then applicant must be contacted to obtain completed form.)			
Does this device include an Animal Tissue Source?			
All Pediatric Patients age<=21			
Neonate/Newborn (Birth to 28 days)			
Infant (29 days -< 2 years old)			
Child (2 years -< 12 years old)			
Adolescent (12 years -< 18 years old)			
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)			

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)			
Nanotechnology			
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html)	*Contact OC.*		

Regulation Number **Class*** **Product Code**

(*If unclassified, see 510(k) Staff)

Additional Product Codes: _____

Review: David Ruch GRDB 10/13/10
acting (Branch Chief) for CYN (Branch Code) (Date)

Final Review: _____
(Division Director) (Date)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Cooper, Jeffrey (CDRH)

From: Cooper, Jeffrey (CDRH)
Sent: Wednesday, October 13, 2010 6:44 PM
To: 'Miller, Kae'
Subject: K100451-S1

DAP acting for CYN 10/13/10

Thank you for completely answering the previous questions. I am placing your submission on hold for these additional questions.

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Jeffrey Cooper, M.S., D.V.M.
Veterinary Medical Officer
Center for Devices & Radiological Health (CDRH)
Office of Device Evaluation (ODE)
Division of Reproductive, Gastro-Renal, and Urological Devices (DRGUD)
Gastroenterology and Renal Devices Branch (GRDB)
WO66 G228
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
(301) 796-6517
jeffrey.cooper@fda.hhs.gov

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

Premarket Notification [510(k)] Review
Traditional/Abbreviated

K100451-S1

Date: July 6, 2010, September 23, 2010 and October 13, 2010
To: The Record
Office: ODE
From: Jeffrey Cooper, DVM
Division: DRARD

510(k) Holder: Gambro Renal Products, Inc.
Device Name: GamCath® High Flow Dolphin® Catheter
Contact: Kae Miller, Regulatory Affairs Manager
Phone: 303 222-6724
Fax: 303 222-6916
Email:

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(5)

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(b)(5)

Reviewer

10/8/10
Date

acting for Carolyn Neuland, PhD
Branch Chief

10/13/10
Date

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Cooper, Jeffrey (CDRH)

From: McBryde, Kevin D
Sent: Friday, September 24, 2010 10:47 AM
To: Cooper, Jeffrey (CDRH)
Cc: Neuland, Carolyn Y.; Lerner, Herbert P.
Subject: K100451/S001

Attachments: Nephrology Consult K100451 S001 09.24.10.pdf

Dear Jeff,

Here is my clinical consultation for the Gambro GamCath High Flow Dolphin Catheter for short-term use.

Nephrology Consult K100451 S00...

(b)(5)

Please let me know if you should have any questions for me.

Sincerely,

Kevin

Kevin D. McBryde, MD
Medical Officer
Pediatric Nephrology
Gastroenterology & Renal Devices Branch (GRDB)
Division of Reproductive, Gastro-Renal and Urological Devices (DRGUD)
Office of Device Evaluation (ODE)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration (FDA)
White Oak Office Building 66 (WO66)
Room G222
10903 New Hampshire Avenue
Silver Spring, MD 20993
Telephone: (301) 796-5590
Fax: (301) 847-8111
E-mail: kevin.mcbryde@fda.hhs.gov

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at kevin.mcbryde@fda.hhs.gov.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

67

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Office of Device Evaluation
Division of Reproductive, Abdominal, and Radiological Drug Products

From: Kevin D. McBryde, MD
Medical Officer
FDA/CDRH/ODE/DRGUD/GRDB

To: Jeffrey W. Cooper, DVM
Veterinary Medical Officer
FDA/CDRH/ODE/DRGUD/GRDB

Through: Carolyn Y. Neuland, Ph.D.
Branch Chief
Gastroenterology & Renal Devices Branch
FDA/CDRH/ODE/DRGUD

Copy to: Herbert Lerner, MD
Acting Division Director
FDA/CDRH/ODE/DRGUD

Subject: K100451/S001, Gambro Renal Products, Inc. GamCath® High Flow Dolphin® Catheter

Date: September 24, 2010

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

Kevin D. McBryde, MD
FDA/CDRH/ODE/DRGUD/GRDB

DAP
acting for
CYN
10/13/10

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K100451/A3

GAMBRO Renal Products

14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 222 6500

December 8, 2010

FDA CDRH DMC
DEC 09 2010
Received K40

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 – G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: FDA Additional Information Request for 510(k) K100451 for the GamCath® High Flow Dolphin® Catheter

To Whom It May Concern:

Enclosed please find the response to the FDA request for additional information via email dated October 13, 2010, in reference to the Traditional 510(k) for GamCath® High Flow Dolphin® Catheter, submitted by Gambro Renal Products, Inc. on February 16, 2010.

The information requested from the FDA is restated followed by Gambro's response. Please contact me by telephone at 303.222.6724 or by fax at 303.222.6916 with any questions regarding this additional information. I can also be reached by email at kae.miller@us.gambro.com.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GAMBRO.

Annex #9

(b)(4)

(b)(4)

Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test

Report

Author: (b)(4)

Sponsor: Gambro Lundia AB
MTC Department
PO Box 10101
SE 220 10 Lund /Sweden

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name Jeffrey Cooper DVM

Subject: 510(k) Number K100451/S2

To: The Record

Please list CTS decision code SE

- ☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)
- ☐ Hold (Additional Information or Telephone Hold).
- ☑ Final Decision (SE, SE with Limitations, NSE, Withdrawn, etc.).

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*	✓	
510(k) Summary /510(k) Statement	*Attach Summary*	✓	
Truthful and Accurate Statement.	*Must be present for a Final Decision*	✓	
Is the device Class III? If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		✓
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)		✓	
Is this a combination product? (Please specify category N, see http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			✓
Is this device intended for pediatric use only?			✓
Is this a prescription device? (If both prescription & OTC, check both boxes.)		✓	
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			✓
Is clinical data necessary to support the review of this 510(k)? Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If not, then applicant must be contacted to obtain completed form.)			✓
Does this device include an Animal Tissue Source?			✓
All Pediatric Patients age<=21			
Neonate/Newborn (Birth to 28 days)			
Infant (29 days -< 2 years old)			
Child (2 years -< 12 years old)			
Adolescent (12 years -< 18 years old)			
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)			

4

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)	—
Nanotechnology	—
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html) *Contact OC.*	—

Regulation Number	Class*	Product Code
876.5540	II	MPB

(*If unclassified, see 510(k) Staff)

Additional Product Codes: _____

Review: Mega M Shackelford for C/N (Branch Chief) GRDB (Branch Code) 12/21/10 (Date)

Final Review: _____ (Division Director) 12/21/10 (Date)

6

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GAMBRO Renal Products

K100451/S1

14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 232 6800

August 27, 2010

FDA CDRH DMC

AUG 30 2010

Received

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 – G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

FDA CDRH DMC
AUG 30 2010
Received

K-49

Re: FDA Additional Information Request for 510(k) K100451 for the GamCath® High Flow Dolphin® Catheter

To Whom It May Concern:

Enclosed please find the response to the FDA request for additional information via email dated July 16, 2010, in reference to the Traditional 510(k) for GamCath® High Flow Dolphin® Catheter, submitted by Gambro Renal Products, Inc. on February 16, 2010.

The information requested from the FDA is restated followed by Gambro's response. Please contact me by telephone at 303.222.6724 or by fax at 303.222.6916 with any questions regarding this additional information. I can also be reached by email at kae.miller@us.gambro.com.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

GAMBRO Renal Products

14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 222 6500

December 6, 2010

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 – G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: FDA Additional Information Request for 510(k) K100451 for the GamCath® High Flow Dolphin® Catheter

To Whom It May Concern:

Enclosed please find the response to the FDA request for additional information via email dated October 13, 2010, in reference to the Traditional 510(k) for GamCath® High Flow Dolphin® Catheter, submitted by Gambro Renal Products, Inc. on February 16, 2010.

The information requested from the FDA is restated followed by Gambro's response. Please contact me by telephone at 303.222.6724 or by fax at 303.222.6916 with any questions regarding this additional information. I can also be reached by email at kae.miller@us.gambro.com.

Sincerely,

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Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

FDA Request for Additional Information via Email Dated October 13, 2010:

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

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Indications for Use Statement

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-PQISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

510(k) SUMMARY

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852 Released by CDRH on 09-13-2024

Short-term vascular access for hemodialysis, hemoperfusion and apheresis therapy with GamCath HighFlow Dolphin Catheters

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-EOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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11.6.4 The complete listing of all materials, which are used for the catheter.

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-PQISTATUS@fda.hhs.gov or 301-796-8118

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Attachment #5: revised Instructions for use (detailed changes)

(b)(4)

(b)(4)

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Short-term vascular access for hemodialysis, hemoperfusion and apheresis therapy with GamCath HighFlow Dolphin Catheters

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-EOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

June 09, 2010

GAMBRO RENAL PRODUCTS, INC.
14143 DENVER WEST PARKWAY SUITE 400
LAKEWOOD, COLORADO 80401
UNITED STATES
ATTN: KAE MILLER

510k Number: K100451
Product: GAMCATH HIGH FLOW DOLPHIN MS-G

Extended Until: 08/17/2010

Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information (AI) is not received by the "Extended Until" date shown above, your premarket notification will be considered withdrawn (21 CFR 807.87(l)). If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

Marjorie Shulman

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room W-O66-0609
Silver Spring, MD 20993-0002

APR 19 2010

Ms. Kae Miller
Regulatory Affairs Manager
Gambro® Renal Products, Inc.
14143 Denver West Parkway, Suite 400
LAKEWOOD CO 80401

Re: K100451
Trade/Device Name: GamCath® High Flow Dolphin® Catheter
Dated: February 16, 2010
Received: February 17, 2010

Dear Ms. Miller:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above. We cannot determine if the device is substantially equivalent to a legally marketed predicate device based solely on the information you provided. To complete the review of your submission, we require the following additional information:

(b)(4)

399

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

(b)(4)

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act (Act) for determining substantial equivalence of your device.

You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Act.

You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations (21 CFR 812).

If the information, or a request for an extension of time, is not received within 30 days, we will consider your premarket notification to be withdrawn and your submission will be deleted from our system. If you submit the requested information after 30 days it will be considered and processed as a new 510(k)(21 CFR 807.87(l)); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete. For guidance on 510(k) actions, please see our guidance document entitled, "FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment" at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089738.pdf

If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the additional information request.

The purpose of this document is to assist agency staff and the device industry in understanding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee and Modernization Act. .

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

The requested information, or a request for an extension of time, should reference your above 510(k) number and should be submitted in duplicate to:

U.S. Food and Drug Administration
Center for Devices and Radiological Heath
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning the contents of the letter, please contact Jeffrey Cooper, D.V.M., at (301) 796-5590. If you need information or assistance concerning the IDE regulations, please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or at (301) 796-7100, or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Carolyn Y Neuland

Carolyn Y. Neuland, Ph.D.
Chief, Gastroenterology and Renal
Devices Branch
Division of Reproductive, Abdominal,
and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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K100451 – Gambro Renal Products, Inc.

Div/Branch	Last Name	Date	Div/Branch	Last Name	Date
DRARD/GRDB	[signature]	4/19/10			
DRARD/GRDB	[signature]	4/19/10			

cc: DMC
ODE – DRARD/GRDB – Cooper

DRAFT:JeffCooper:lrm:4.14.2010
REVISED CarolynNeuland:4.13.2010
FINAL: JeffCooper:4.16.2010
RevisedFinal:JeffCooper:CarolynNeuland:lrm:4.19.2010

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center ¿ WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

August 31, 2010

GAMBRO RENAL PRODUCTS, INC.
14143 DENVER WEST PARKWAY SUITE 400
LAKEWOOD, COLORADO 80401
UNITED STATES
ATTN: KAE MILLER

510k Number: K100451

Product: GAMCATH HIGH FLOW DOLPHIN

The additional information you have submitted has been received.

We will notify you when the processing of this submission has been completed or if any additional information is required. Pleaseremember that all correspondence concerning your submission MUST be sent to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. On August 12, 2005 CDRH issued the Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s. This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so in 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.

Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely,

510(k) Staff

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

DEC 2 1 2010

510(k) SUMMARY

Submitter's Name	Gambro Renal Products, Inc.
Address	14143 Denver West Parkway, Suite 400 Lakewood, Colorado 80401
Establishment Registration Number	2087532
Contact Person	Kae Miller, Regulatory Affairs Manager
Telephone Number	303.222.6724
Fax Number	303.222.6916
Date Summary Was Prepared	December 02, 2010

Device Information	
Name of the Device	GamCath® High Flow Dolphin® Catheter
Common or Usual Name	Short-Term Hemodialysis Catheter
Classification Name	Catheter Hemodialysis Non-Implanted
Device Class	II
Product Code	MPB
Regulation Number	21 CFR 876.5540

Predicate Device Information (1)	
Name of the Device	GamCath® High Flow Catheter
510(k) Number	K040301
Classification Name	Catheter Hemodialysis Non-Implanted
Device Class	II
Product Code	MPB
Regulation Number	21 CFR 876.5540

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Predicate Device Information (2)	
Name of the Device	Medcomp Duo-Flow II Catheter with Lubricious Heparin
510(k) Number	K991320
Classification Name	Catheter Hemodialysis Non-Implanted
Device Class	II
Product Code	MPB
Regulation Number	21 CFR 876.5540

DEVICE DESCRIPTION

The GamCath® High Flow Dolphin® Catheters are single use medical devices for short term use to obtain vascular access in patients with acute or chronic renal failure. The GamCath® High Flow Dolphin® Catheter combines the GamCath® High Flow Catheter with an additional coating based on a block copolymer. The polymer layer results in a surface structure that locks in barium sulfate particles. The coated catheter is free of heparin, therefore the use of the catheter is not contraindicated in patients with HIT syndrome.

Catheters made of Polyurethane are equipped with small rotatable Polypropylene suture rings, still allowing rotation of catheter when sutured to skin. Polyurethane Extension lines, present on each lumen, are equipped with PVC luer-lock connectors according to ISO 594-1 with Polyethylene protection caps and are provided with clamps which may be color coded to indicate the venous (blue), arterial (red). Clamp inserts bear easily legible and permanently fixed imprints indicating usable catheter length and outer diameter of catheter shaft (in French calibration) as well as priming volumes. The Catheter is available in 13 French and 11,5 French straight and curved extension line configuration. An inner dilator made of FEP is provided in the venous lumen for insertion. The insertion length is available in range from 150 mm (5.906") up to 250 mm (9.843"). The Dolphin coating is a co-polymer film which is applied over the catheter surface to form a continuous surface that has a smoother surface morphology than an untreated catheter. The copolymer film is formed by providing a hydrophobic polymer block, such as polydimethylsiloxan (PDMS) with functional –OH end groups.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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INDICATIONS FOR USE

GamCath® High Flow Dolphin® catheters are indicated for use in attaining short term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. GamCath® High Flow Dolphin® Catheter is not intended for use in pediatric patients.

TECHNOLOGICAL CHARACTERISTICS COMPARED TO PREDICATE DEVICE

The GamCath® High Flow Dolphin® Catheter is substantially equivalent to the GamCath® High Flow Catheter, K040301 and the MedComp Duo-Flow II Catheter with Lubricious Heparin manufactured by Medical Components, Inc. K991320.

Substantial equivalency was shown by detailed comparisons of Intended Use, Patient Population, Mode of Operation, Labeling and Catheter Type. Technological characteristics showed substantial equivalency with respect to material of the catheter (Connector, Catheters Tube, Extension Line), position of insertion of the catheter, sizes of the catheter, design/physical characteristics (number of lumens, sterility, distal end configuration, intended anatomical location of distal end, proximal end configuration).

Both GamCath® High Flow Dolphin® Catheter and MedComp Duo-Flow II Catheter are having a coating. The materials used differ. MedComp Duo-Flow II Catheter uses a lubricious heparin coating whereas GamCath® High Flow Dolphin® Catheter uses the Dolphin® coating. The Dolphin coating is a co-polymer film which is applied over the catheter surface to form a continuous surface. In general the copolymer film is formed by providing a hydrophobic polymer block, such as polydimethylsiloxan (PDMS) with functional –OH end groups. The reliance of Dolphin coating was placed on testing against recognized standards to evaluate safety and performance (see section non-clinical performance data below). GamCath® High Flow Dolphin® catheter coating is free of heparin; therefore the use of the catheter is not contraindicated in patients with HIT syndrome.

NON-CLINICAL PERFORMANCE DATA

The non-clinical tests submitted included biocompatibility data as per ISO 10993-1 (including Cytotoxicity, Sensitization, Intracutaneous reactivity, Acute Systemic toxicity, Genotoxicity, and Hemolysis). Ethylene Oxide sterilization was validated as per ISO 11135-1 and 10993-7. Package integrity testing was done successfully.

Substantial equivalence versus the predicate device was shown by the following tests: Integrity of the catheter was shown by testing for air leakage and liquid leakage as per ISO 10555-1. Clamping tests up to 300 cycles were done to prove absence of visible delamination or visible detachable particles. Pressure in the catheter was measured over the range of flow rates. Performance data was collected to verify tensile strength according ISO 10555-1 of Connector to extension line, Extension line to hub (bifurcation), Hub to catheter shaft, and Catheter shaft to tip.

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CONCLUSION OF SAFETY AND EFFECTIVENESS

The comparison of technological characteristics demonstrated that GamCath® High Flow Dolphin® Catheters are substantially equivalent to the predicate devices. The GamCath® High Flow Dolphin® Catheters met all performance criteria of the test performed and is safe and effective when used as intended.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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Silver Spring, MD 20993-0002

Ms. Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.
14143 Denver West Pkwy, Suite 400
LAKEWOOD CO 80401

DEC 2 1 2010

Re: K100451
Trade/Device Name: GamCath® High Flow Dolphin® Catheter
Regulation Number: 21 CFR §876.5540
Regulation Name: Blood access device and accessories
Regulatory Class: II
Product Code: MPB
Dated: December 6, 2010
Received: December 7, 2010

Dear Ms. Miller:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Herbert P. Lerner, M.D., Director (Acting)
Division of Reproductive, Gastro-Renal
and Urological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GAMBRO Renal Products

Traditional 510(k) for GamCath® High Flow Dolphin® Catheter

Indications for Use Statement

510(k) Number (if known): K100451

Device Name: GamCath® High Flow Dolphin® Catheter

DEC 2 1 2010

Indications for Use Statement:

GamCath® High Flow Dolphin® catheters are indicated for use in attaining short term vascular access for hemodialysis, hemoperfusion and apheresis therapy via the jugular, subclavian or femoral vein. GamCath® High Flow Dolphin® Catheter is not intended for use in pediatric patients.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Reproductive, Gastro-Renal, and Urological Devices
510(k) Number K100451

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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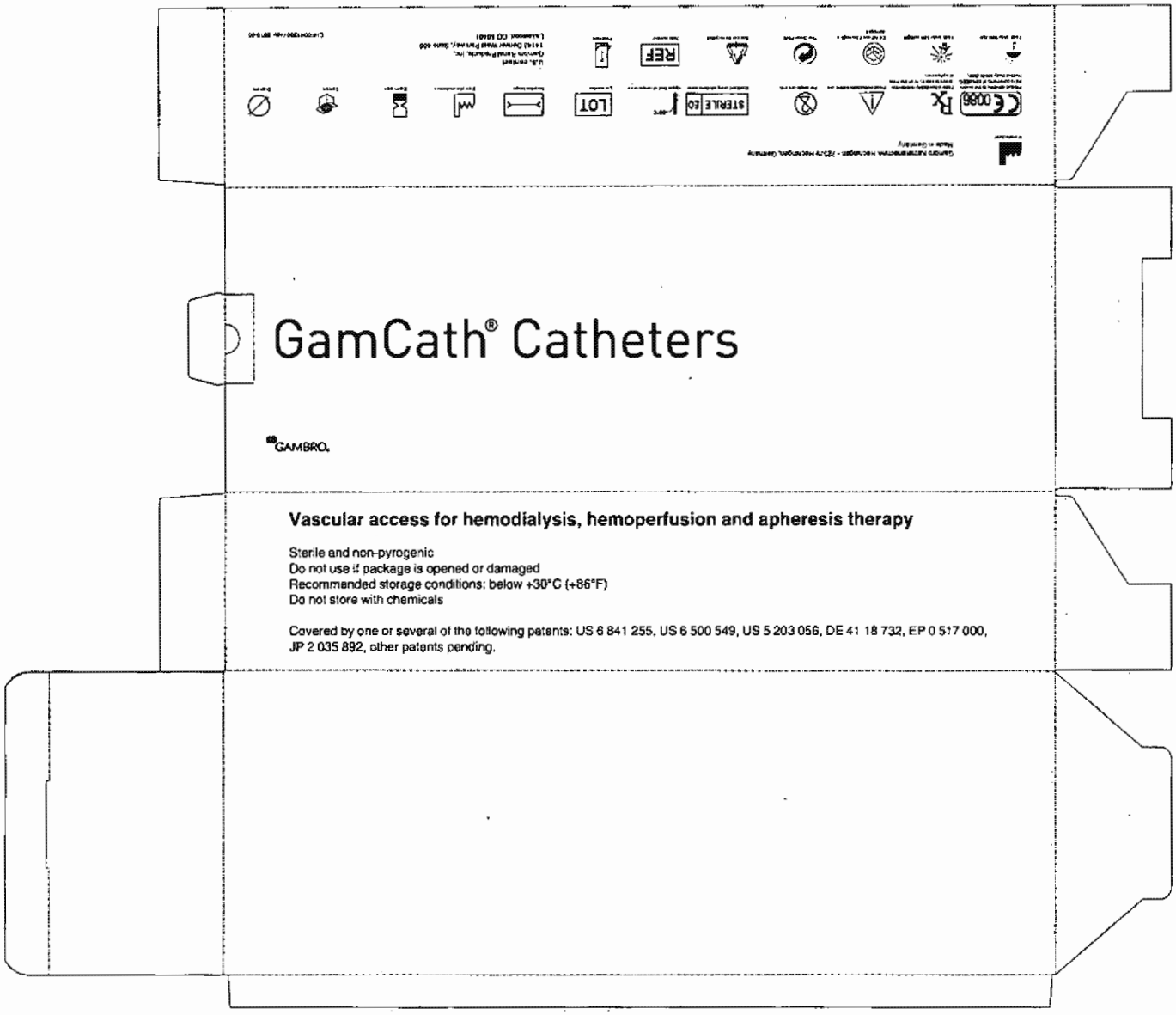

ANNEX 8 - 1

359

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Vascular access for hemodialysis, hemoperfusion and apheresis therapy

Sterile and non-pyrogenic
Do not use if package is opened or damaged
Recommended storage conditions: below +30°C (+86°F)
Do not store with chemicals

Covered by one or several of the following patents: US 6 841 255, US 6 500 549, US 5 203 056, DE 41 18 732, EP 0 517 000, JP 2 035 892, other patents pending.

Manufacturer

Gambro Kathetertechnik Hechingen • 72379 Hechingen, Germany
Made in Germany

ANNEX 8 - 2

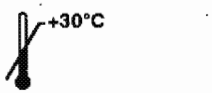
Product confirms to the essential requirements of 93/42/EEC. Notified Body #0086 (BSI).

Federal law (USA) restricts this device to sale by or on the order of a physician.

Read instructions before use

For single use only

Sterilized using ethylene oxide



Upper limit of temperature

Keep away from rain

Keep away from sunlight

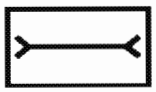
Do not use if package is damaged

The Green Point

Box can be recycled

Code number

Lot number


Insertion length

Date of manufacture

Expiry date

Content

Diameter

Peel here

U.S. contact
Gambro Renal Products, Inc.
14143 Denver West Parkway, Suite 400
Lakewood, CO 80401

CHF0042640 / rev. 2010-05

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center ¿ WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

October 15, 2010

GAMBRO RENAL PRODUCTS, INC.
14143 DENVER WEST PARKWAY SUITE 400
LAKEWOOD, COLORADO 80401
UNITED STATES
ATTN: KAE MILLER

510k Number: K100451
Product: GAMCATH HIGH FLOW DOLPHIN MS-G

We are holding your above-referenced Premarket Notification (510(k)) for 30 days pending receipt of the additional information that was requested by the Office of Device Evaluation. Please remember that all correspondence concerning your submission MUST cite your 510(k) number and be sent in duplicate to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm.

The deficiencies identified represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm.

If after 30 days the additional information (AI), or a request for an extension of time, is not received, we will discontinue review of your submission and proceed to delete your file from our review system (21 CFR 807.87(l)). Please note our guidance document entitled, "Guidance for Industry and FDA Staff, FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment". If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request. The purpose of this document is to assist agency staff and the device industry in understanding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee and Modernization Act. You may review this document at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089735.htm. Pursuant to 21 CFR 20.29, a copy of your 510(k) submission will remain in the Office of Device Evaluation. If you then wish to resubmit this 510(k) notification, a new number will be assigned and your submission will be considered a new premarket notification submission.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Please remember that the Safe Medical Devices Act of 1990 states that you may not place this device into commercial distribution until you receive a decision letter from FDA allowing you to do so.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center - WO66-G609
Silver Spring, MD 20993-0002

Ms. Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.
14143 Denver West Pkwy, Suite 400
LAKEWOOD CO 80401

DEC 21 2010

Re: K100451
Trade/Device Name: GamCath® High Flow Dolphin® Catheter
Regulation Number: 21 CFR §876.5540
Regulation Name: Blood access device and accessories
Regulatory Class: II
Product Code: MPB
Dated: December 6, 2010
Received: December 7, 2010

Dear Ms. Miller:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related

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adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Herbert P. Lerner, M.D., Director (Acting)
Division of Reproductive, Gastro-Renal
and Urological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GAMBRO Renal Products

14143 Denver West Parkway, Suite 400
Lakewood, Colorado 80401
USA

Tel 303 232 6800

August 27, 2010

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 – G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: FDA Additional Information Request for 510(k) K100451 for the GamCath® High Flow Dolphin® Catheter

To Whom It May Concern:

Enclosed please find the response to the FDA request for additional information via email dated July 16, 2010, in reference to the Traditional 510(k) for GamCath® High Flow Dolphin® Catheter, submitted by Gambro Renal Products, Inc. on February 16, 2010.

The information requested from the FDA is restated followed by Gambro's response. Please contact me by telephone at 303.222.6724 or by fax at 303.222.6916 with any questions regarding this additional information. I can also be reached by email at kae.miller@us.gambro.com.

Sincerely,

(b)(6)

Kae Miller
Regulatory Affairs Manager
Gambro Renal Products, Inc.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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FDA Request for Additional Information via Email Dated July 16, 2010:

(b)(4)

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ANNEXES

Annex 1: Additional information supporting Anti-Thrombogenicity of GamCath® High Flow Dolphin® Bench test data

Annex 2: Pascal Meier, MD, FASN
Less thrombogenic modified catheter surface improves temporary hemodialysis catheter survival
(PROlonged hemodialysis catheter survival with COPolymer coating)
Study Synopsis 2005: 1-4

Annex 3: J. F. Hecker, L. A. Scandrett
Roughness and thrombogenicity of the outer surfaces of intravascular catheters
Journal of Biomedical Material Research 1985; Vol 19: 381-395

Annex 4: A. Levin, M. Rocco
2006 Updates Clinical Practice Guidelines and Recommendations KDOQI
National Kidney Foundation 2006

Annex 5: E. Hecking, J. L. Bragg-Gresham, H. C. Rayner, R. L. Pisoni, V. E. Andreucci, C. Combe, R. Greenwood, K. McCullough, H. I. Feldman, E. W. Young, P. J. Held, F. K. Port
Haemodialysis prescription, adherence and nutritional indicators in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)
Nephrol Dial Transplant (2004); 19: 100–107

Annex 6: J. Tordoir, B. Canaud, P. Haage, K. Konner, A. Basci, D. Fouque, J. Kooman, A. Martin-Malo, L. Pedrini, F. Pizzarelli, J. Tattersall, M. Vennegoor, C. Wanner, P. Wee, R. Vanholder
European Best Practice Guidelines (EBPG) on Vascular Access
Nephrol Dial Transplant (2007); 22 [Suppl 2]: ii88–ii117

Annex 7: L. M. Moist, B. R. Hemmelgarn, C. E. Lok
Relationship between Blood Flow in Central Venous Catheters and Hemodialysis Adequacy
Clinical Journal of the American Society of Nephrology 2006; 1: 965–971

Annex 8: A. Davenport, K. Neng Lai, J. Hertel, R. J. Caruana
Anticoagulation
Handbook of Dialysis Fourth Edition: 204-205

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GAMBRO Renal Products

14143 Denver West Parkway,
Suite 400
Lakewood, Colorado 80401
USA

Tel 303 222 6500

August 18, 2010

Additional information supporting Anti-Thrombogenicity of GamCath® High Flow Dolphin®

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Less thrombogenic modified catheter surface improves temporary hemodialysis catheter survival

(b)(4)

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Roughness and thrombogenicity of the outer surfaces of intravascular catheters

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Thirty-seven types of catheters made from plastics including silicone rubber, polyvinylchloride, polyethylene, and polyurethane were tested for thrombogenesis in the cephalic vein of sheep. The range in the mass of thrombus on the catheters at autopsy 9 days after insertion was 20-fold. There was considerable variation when catheters made from the same types of plastic were compared, but polyethylene catheters tended to be more thrombogenic than other types. Scanning electron microscopy (SEM) revealed a variety of surfaces ranging from very smooth to very rough. Roughness was frequently associated with the presence of radio-opaque particles which in several catheters were concentrated into radio-opaque tracer strips. Within types of plastics, catheters with rougher surfaces were usually more thrombogenic than those with smooth surfaces.

INTRODUCTION

The most common reaction of blood in contact with foreign surfaces is the formation of thrombus.[1-3] The plastic intravascular catheter is probably where blood most commonly contacts a foreign surface *in vivo* as catheters are inserted into a high proportion of patients in hospitals. Thrombus which forms on a catheter is usually not seen as it strips off and remains in the vessel when the catheter is withdrawn. While thrombus may adhere to the vessel wall and can block the vessel,[4] it may also embolize to cause infarction of organs.[5] Deaths have been ascribed to such embolized thrombus in kidneys, intestines, legs, and spinal cords of babies.[6-9]

We have developed a model for measuring thrombogenicity of catheters in which lengths of catheter tubings are inserted into veins of sheep for a predetermined number of days and then amounts of thrombus are determined at autopsy.[10,11] Results have indicated marked differences in the mass of thrombus on set lengths of these tubings.

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Roughness may be a cause of these differences in thrombogenicity. In a separate experiment,[12] we investigated the thrombogenicity of one batch of polyvinylchloride resin which had been extruded into tubing at five temperatures ranging between 110 and 205°C. Tubing extruded at the lower temperatures had incomplete melting of the resin and as a consequence was rougher as determined by inspection in a scanning electron microscope. We were able to show that the rougher surfaces were associated with significantly greater amounts of thrombus in both arteries and veins of sheep confirming that roughness is one factor in thrombogenesis. We have also demonstrated a probable connection between roughness of tips of umbilical artery catheters and thrombus formation.[13]

In this article, we report on data obtained when catheters were tested in veins of sheep and on the relation between thrombogenicity and the roughness of these catheters.

MATERIALS AND METHODS

The sheep were mature Merino ewes of 30–40 kg body weight from the flock of the University of New England. Anesthesia for catheterization was induced with pentobarbitone sodium and maintained after tracheal intubation with a halothane-oxygen mixture. Catheters supplied sterile were not resterilized. Otherwise silicone rubber was sterilized by autoclaving after washing with a soft white soap (as recommended by Dow Corning Corp.) and other materials with ethylene oxide allowing at least 7 days for escape of residual traces of sterilant. Before insertion, each catheter was cut to a length of 28–30 cm and one end was sealed by turning about 3 mm back on itself and holding it there with a ligature. The skin adjacent to the cephalic vein was incised for about 15 mm at about 4 cm above the knee and the vein was located, freed and incised. The open end of the catheter was inserted up to the closed end which was held in place with another ligature placed around it and the vein. Finally the skin was closed burying the catheter to avoid the possibility of infection passing through the skin. Both cephalic veins were used but in no animal was the same type of catheter used twice.

All but one of the catheters were 1.5–2.2 mm o.d. The exception was the Vygon catheter which was only 1.2 mm o.d. and only 16 cm long. It was intended that 12 of each type would be tested but there were only 11 lengths available of the Extracorporeal catheter, Extracorporeal (silver), Angiodan EVA and Wallace catheters and only 5 for each of the Extracorporeal (natural) and Extracorporeal (barium) tubings. The results were similar for the last two and so they were combined.

After 9 days, each animal was anesthetized with pentobarbitone and given 5000 *i.u.* of heparin to prevent coagulation of blood. Animals were then killed by exsanguination caused by severing the carotid arteries. Catheterized vessels were dissected free and held up so that any free blood could drain. They were then slit open and thrombus associated with the 25 cm of

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tubing from the point of insertion was removed and weighed (about 15 cm for Vygon catheters). Before statistical analysis by analysis of variance, square root transformations were done to normalize the distributions and to produce homogeneity of variances.[3] Significant differences between types of catheters at the 0.05 level were identified with Duncan's test.[14] No correction was made for the reduced numbers in some groups or the shorter length of the Vygon catheters.

For SEM, samples of catheters were coated with gold in a E5100 series 2 Cool Sputter Coater (Polaron Equipment Ltd., Watford, Herts, England) and examined in a Jeol JSM 35 scanning microscope at magnifications of up to 2000X. Samples were mounted on pins affixed to the centers of stubs, tilted by up to 60° and then rotated so that all of the surface could be examined.

RESULTS

Representative photomicrographs of surfaces are shown in Figures 1 through 9 while data for thrombogenicity and observations on surface appearances are given in Table I. Catheters are arranged in the table into four groups according to type of plastic and then in increasing thrombogenicity. There were statistically significant differences in thrombogenicity between catheters in each group ($F = 7.2–11.0$; $p < 0.001$). The range in thrombogenicity was greater than three-fold for the polyethylene and silicone rubber groups and greater than fivefold for the polyvinylchloride and "other plastics" groups. There also were differences between groups as all but one catheter in the polyethylene group had more thrombus than those in the silicone rubber group.

Figure 1. Two of a series of marks along one side of Dow-Corning silicone rubber. The remainder of the surface was smooth. Bar = 100 μm.

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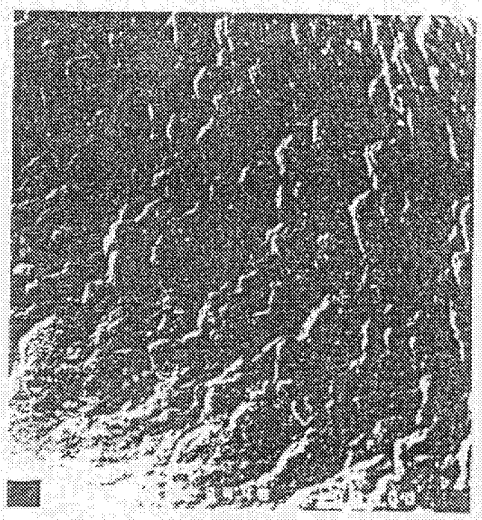

Figure 2. Surface of Pudenz Cardiac catheter showing ridges. Bar = 100 μm.

Inspection in the electron microscope showed that many surfaces were smooth or had only slight irregularities and it was difficult to differentiate between them in smoothness even when stereo pairs of photomicrographs were viewed in a stereo viewer. Catheters with these smooth surfaces included the Braun PEAA, Dow-Corning silicone rubber and radio-opaque silicone rubber, Avcomat, Angiodan and the non-tracer strip of many of the catheters with tracer strips. Other catheters such as the Bard I-Cath, and

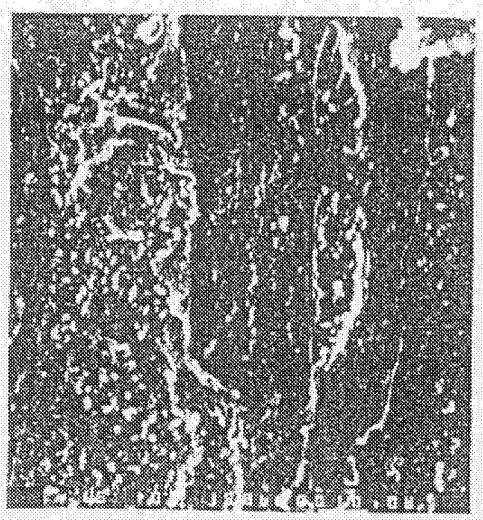

Figure 3. Surface over the tracer strip of a Sorenson I-V Intrafusor. Bar = 10 μm.

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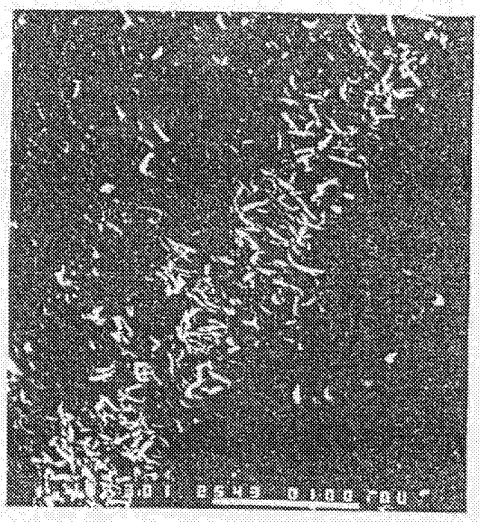

Figure 4. Appearance of an Argyle Umbilical Catheter over the tracer strip showing flakes of material. The remainder of the surface was similar to the top left and bottom right-hand corners. Bar = 100 μm.

Deseret Subclavian/E-Z Cath and the nontracer strip portions of polyvinylchloride catheters with tracer strips had distinct rippled patterns which were shallow and nonjagged when stereophotomicrographs were viewed. When the catheters were separated into plastic types, all but one of the catheters of which all of the circumference was smooth or only slightly irregular had comparatively low values for thrombogenicity. The exception was the

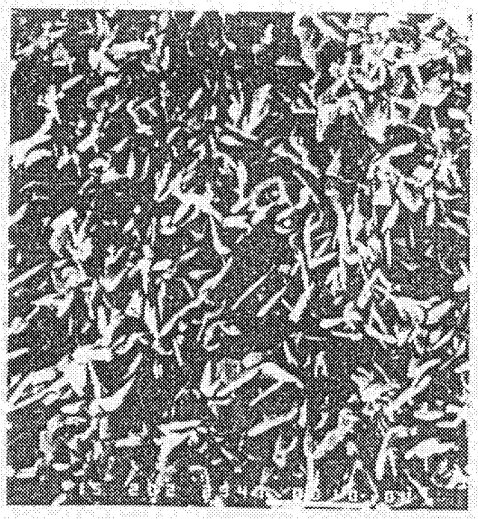

Figure 5. Tracer strip of Argyle Intramedicut Catheter. Bar = 10 μm.

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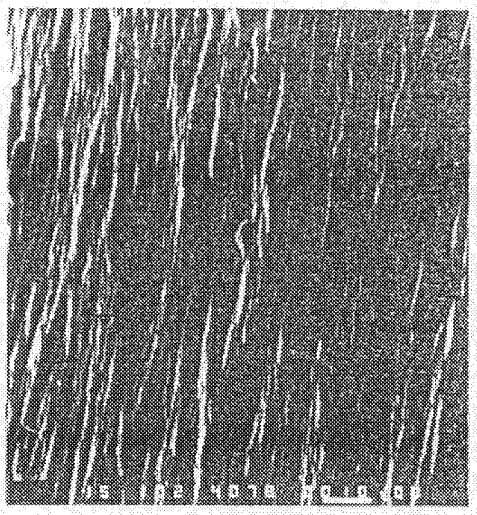

Figure 6. Surface of Vygon Leader-catheter showing longitudinal striations. Some samples were considerably rougher. Bar = 10 μm.

Pharma-Plast umbilical catheter which was the most thrombogenic of the polyvinylchloride group.

Other catheters either showed rough sections on the circumference which corresponded to tracer strips or were rough over the entire surface. A relation was evident between the roughness and thrombogenicity. This relation was particularly noticeable with several comparisons:

Pudenz catheter compared with other silicon rubber catheters,

Figure 7. Surface of Kifa Polyethylene tubing. Bar = 10 μm.

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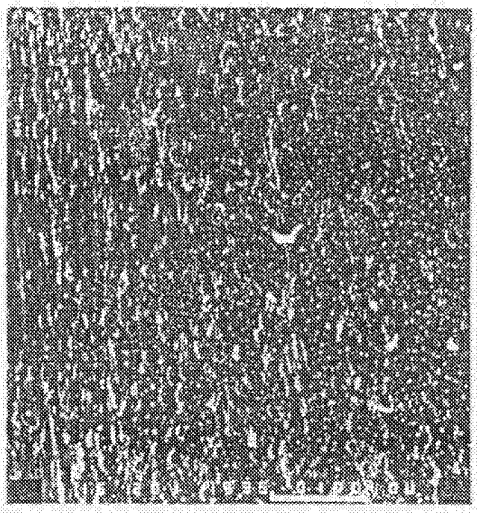

Figure 8. Surface of Surgimed radio-opaque polyethylene tubing Bar = 100 μm.

Swan-Ganz and Argyle Intramedicut compared with the Portex umbilical and Dural polyvinylchloride,
radio-opaque compared with non-radio-opaque polyethylene catheters,
Wallace compared with the Avcomat catheters, and
Portex nylon No 30 compared with Portex nylon No 36 catheters.
Within each of the four groups, significant differences between catheters

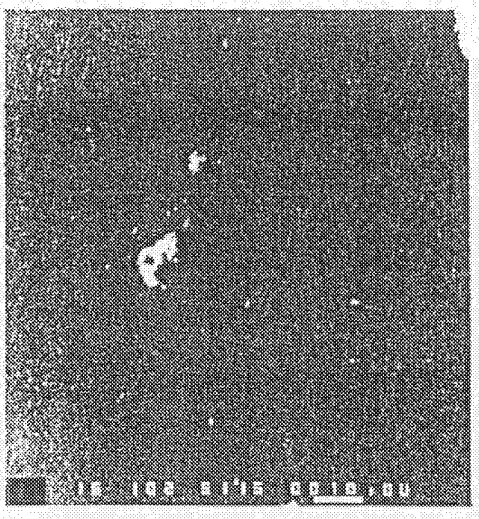

Figure 9. Smooth surface of Avcomat polyurethane tubing. The white material was dust. The two diagonal lines are an artifact produced by the microscope. Bar = 10 μm.

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were associated, with the exception of the Pharma-Plast catheter, with noticeable differences in roughness.

DISCUSSION

It would be preferable to be able to present measurements quantifying the degree of surface irregularity of each catheter. Methods which measure the deflection of lightly loaded styluses slowly drawn over materials are available for measuring surface irregularity. They are designed for use on hard materials and, when used on catheters, are affected by the deformability of plastics (Hecker, unpublished). There appears to be no method readily available for measuring roughness of plastics and so observation in a scanning electron microscope is the only method that a manufacturer or research worker can use to assess smoothness or roughness of a plastic.

The regular marks on one side of the Dow-Corning silicone rubber catheters (Fig. 1) but not on silicone rubber from other manufacturers are apparently due to a production process. The tubing is very soft when extruded and is laid on a stainless-steel mesh so that it can be cured by heat. The marks are formed where the tubing contacts the mesh. A very thin rough line can be seen on one side of other silicone rubbers and these are probably laid on a tray instead.

Many catheters, especially those made from polyvinylchloride, had gently rippled patterns. If roughness is a factor in thrombogenesis, the rippled patterns would appear to be of little importance as most with such rippled patterns had relatively little thrombus. A manufacturer suggested in discussion that, as two smooth surfaces tend to adhere, a rippled pattern could be desirable for assisting a catheter to slip inside an enclosing sheath.

Some catheters, particularly the Pudenz catheter, had surface patterns which are likely to be caused by the tubing sticking slightly to the extruded

TABLE I
Thrombus Formation and Comments on Scanning Electron Microscope Appearance of Catheters Tested in the Cephalic Vein of Sheep

No.	Catheter	Size	Thrombus mg	Thrombus $\sqrt{mg}$	Surface appearance and comments
Silicone rubber					
1.	Extracorporeal[a] infusion catheter	16 Ga	116	10.0[a]	Surface smooth. Contained barium sulfate.
2.	Dow-Corning[a] tubing (plain)	1.5 mm	219	13.3[ab]	Surface smooth except for pairs or triads of defects at regular intervals along one side (Fig. 1).
3.	Dow-Corning[a] tubing (radio-opaque)	1.5 mm	203	13.9[b]	Contained barium sulfate. Surface similar to 2.
4.	Extracorporeal[a] tubing (silver)	1.5 mm	353	18.5[c]	Contained silver chloride. Surface was dimpled and more irregular than 1–3.
5.	Extracorporeal[a] tubing (natural or barium)	1.5 mm	367	18.9[c]	Half contained barium sulfate (see text). Surface similar to 4.

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TABLE I *(Continued from the previous page.)*

No.	Catheter	Size	Thrombus mg	Thrombus $\sqrt{mg}$	Surface appearance and comments
6.	Pudenz[c] cardiac catheter	2.2 mm	385	19.2[c]	Surface had ridges 50–200 μm apart (Fig. 2) and was appreciably rougher than the other silicone rubber catheters.
Polyvinylchloride					
7.	Deseret[d] E-Z Cath and Subclavian	16 Ga	161	11.7[a]	Had shallow undulations (10–20 μm between peaks).
8.	Bard[e] I-Cath	16 Ga	284	14.4[ab]	Surface was indistinguishable from 7.
9.	Dural[f] PVC tubing	1.5 mm	215	14.1[ab]	Three sets were tested. Surfaces had fine gentle undulations and occasional shallow extrusion grooves.
10.	Dural[f] PVC tubing	1.5 mm	271	15.6[ab]	
11.	Dural[f] PVC tubing	1.5 mm	347	17.5[ab]	
12.	Sorenson[g] I-V Intrafusor	15 Ga	306	16.7[ab]	Most of the circumference was relatively smooth but it was rougher over the tracer strip (Fig. 3).
13.	Argyle[h] umbilical catheter	5 F Ga	295	16.8[ab]	Similar to No. 12 except that some were very rough over the tracer strip (Fig. 4).
14.	Abbott[i] Drum Cartridge catheter	5 F Ga	336	17.5[ab]	Similar to 12.
15.	Portex[j] umbilical catheter	6 F Ga	332	17.8[ab]	Both the tracer strip and nontracer strip parts were relatively smooth.
16.	Pharmaseal[k] umbilical catheter	5 F Ga	358	18.5[b]	Surface had shallow undulations. No tracer strip present.
17.	Swan-Ganz[l] flow-directed catheter	5 F Ga	676	24.5[c]	Surface was irregular. Particles were dispersed through the plastic.
18.	Argyle[h] Intramedicut catheter	14 Ga	691	25.5[c]	Very rough over the tracer strip (Fig. 5), otherwise relatively smooth.
19.	Pharma-Plast[m] umbilical catheter	5 F Ga	813	26.5[c]	Two batches were tested. No. 19 had fine shallow irregularities.
20.	Pharma-Plast umbilical catheter	5 F Ga	873	28.6[c]	No. 20 also had some longitudinal extrusion ridges.
Polyethylene					
21.	Dural[f] polyethylene tubing	1.5 mm	398	18.7[a]	Surface was smooth except for several shallow longitudinal grooves.
22.	Vygon[n] Leader-catheter	1.2 mm	472	21.3[ab]	Had numerous deep longitudinal striations (Fig. 6).
23.	Braun[o] catheters	1.7 mm	695	25.5[bc]	Had several tracer strips over some of which the surface was rough. Remainder of surface was smooth. No. 23 had been treated with heparin (see text).
24.	Braun catheters	1.7 mm	730	26.2[bc]	
25.	Cook[p] radio-opaque tubing	4.6 F Ga	761	26.9[bc]	Surface irregular to rough. Particles dispersed throughout plastic.
26.	Braun[o] Cavafix catheters	1.7 mm	857	27.4[bc]	Similar to No. 23.
27.	Kifa[q] tubing	Red	1031	31.6[bc]	Similar to No. 25 (Fig. 7).

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TABLE I *(Continued from the previous page.)*

No.	Catheter	Size	Thrombus mg	Thrombus $\sqrt{mg}$	Surface appearance and comments
28.	Surgimed[r] radio-opaque tubing	1.58 mm	1457	37.6[st]	Similar to No. 25 (Fig. 8).
Other Polymers					
29.	Braun[e] polyurethane catheter	1.7 mm	55	5.7[a]	Surface was very smooth.
30.	Avcomat 100[o] tubing (polyurethane)	1.65 mm	111	9.3[ab]	Surface very smooth (Fig. 9).
31.	Portex[j] nylon intravenous cannula	1.65 mm	228	12.4[bc]	Smooth except for some material which may not have been firmly attached to the surface.
32.	Bard[f] Advanset (Teflon)	16 ga	310	16.6[cd]	Surface had some extrusion marks and bumps up to 4 μm diameter.
33.	Angiodan[r] EVA umbilical catheter	1.8 mm	357	18.3[de]	Surface was smooth and similar to Fig. 9.
34.	Braun[e] PEAA tubing	1.7 mm	357	19.5[ef]	Tubing No. 23 which had been coated with PEAA (see text). Surface was very smooth (similar to Fig. 9).
35.	Wallace[w] Piggy-back central venous catheter (polyurethane)	16 Ga	597	23.5[fg]	Surface irregular. Contains radio-opaque particles.
36.	Deseret[d] E-Z Cath (Teflon)	16 Ga	620	24.6[g]	Has some extrusion marks and bumps up to 10 μm diameter.
37.	Portex[j] Nylon Intravenous Cannula	1.65 mm	733	24.9[g]	This was made several years before No. 31. Surface was rough with short rods and larger particle aggregates.

Note. Data are presented as mean mass of thrombus (mg) and as mean mass after a square root transformation ($\sqrt{mg}$). Within each group of plastics, significant differences ($p < 0.05$) exist between catheters not sharing the same lower case superscripts.

[a]Extracorporeal Medical Specialities Inc., King of Prussia, PA.
[b]Dow Corning Corp., Midland, MI.
[c]Heyer Schule Inc., Goleta, CA
[d]Deseret Pharmaceutical Co. Inc., Sandy, UT.
[e]C. R. Bard International Ltd., Sunderland, England.
[f]Dural Plastics Ltd., Dural, N.S.W. Australia.
[g]Sorenson Research Co., Salt Lake City, UT.
[h]Sherwood Medical Inds., Inc., St. Louis, MO.
[i]Abbott Laboratories, North Chicago, IL.
[j]Portex Ltd., Hythe, Kent, England.
[k]Pharmaseal Lab., Glendale, CA.
[l]Edwards Lab. Inc., Santa Anna, CA.
[m]Pharma-Plast (Australia Pty. Ltd., Sydney, N.S.W. Australia. (This catheter is no longer available.))
[n]Vygon S.A., 95 Ecouen, France.
[o]B. Braun A.G., Melsungen, West Germany.
[p]Cook Inc., Bloomington, IN.
[q]Kifa, Solna, Sweden.
[r]Surgimed Pty. Ltd., Frankston, Victoria, Australia.
[s]C. R. Bard, Inc., Murray Hill, NJ.
[t]AVCO MEDICAL Products, U.S.A.
[w]H. G. Wallace Ltd., Colchester, England.

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nossle during extrusion. Such patterns suggest that less than optimum extrusion conditions had been used. Many individual catheters had one or more shallow longitudinal grooves which were probably caused by a particle of dirt sticking to the extruder nozzle. The Vygon catheters however had a multitude of deep grooves. Diameter is a factor affecting the amount of thrombus that forms in this test[11] and, if the Vygon catheters had been of similar diameter and length to other catheters, it is likely that the amount of thrombus measured on them would have been greater. The older batch of nylon catheters which had the greater thrombogenicity (No 36) had a covering of small rods which were possibly particles of nylon. A characteristic of all of the rougher catheters was that they lacked the gloss of the smooth catheters when viewed by the naked eye.

The most common form of surface irregularity was associated with the presence of particles containing elements with high atomic numbers which had been incorporated to provide radio-opacity. The particles in some catheters had been coextruded in polymer together with particle-free polymer in order to provide one or more tracer strips. In other catheters, the particles had been dispersed throughout the plastic. This permitted greater radio-opacity but prevented viewing of blood in the lumen. Particles of 0.4–4 μm could be seen in the cut ends of most radio-opaque plastics other than silicone rubber and it is likely that colloidal barium sulphate produced by precipitation had been used in silicone rubber catheters containing this substance. With the exceptions of Portex Umbilical catheters and a few Argyle Umbilical catheters in which the tracer strips did not come near the surface, these radio-opaque particles were associated with surface irregularities in all plastics other than silicone rubber.

Sawyer et al.[15] in patients and in dogs compared a PEAA catheter (similar to No 33) with other catheters including a polyethylene catheter (similar to No 23) and found fewest complications with the PEAA catheter. Loffler and Bauer[16] also compared in dogs seven plastics, some of which were similar to catheters tested here (No 23, 24, 29, 34) and obtained similar results for thrombogenicity except that a PEAA catheter was amongst the least thrombogenic. PEAA is a copolymer of 15% polyacrylic acid and 85% polyethylene and had been applied to polyethylene catheters (No 23) by dip coating. This covered the tracer strips and produced a smooth surface. In contrast to Sawyer et. al. who inferred thrombogenicity from complications and in contrast to Loffler and Bauer who did measure the amounts of thrombus that formed, it had high thrombogenicity in this experiment. Of similar smoothness were the two polyurethane catheters (No 29 & 30) which had low thrombogenicity.

Several authors have noted that the surface of many types of vascular catheters, especially those used for radiography, are rough[17–20] but only two references have been made to roughness of tracer strips. Clawson and Boros[21] showed that barium sulphate in tracer strips of Argyle Umbilical catheters caused roughness whereas it did not when dispersed throughout an experimental silicone rubber catheter (the latter may have had the colloidal particles referred to above). Libsak and Kollmeyer[22] also demon-

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strated roughness of tracer strips of Argyle umbilical catheters but in short-term experiments in dogs were unable to show that this roughness increased thrombogenicity.

Several papers report on investigations on thrombus formation in short-term experiments of one or two hours.[23–24] However, no one except Sawyer et al.[15] and Idezuk et al.[25] has previously tested in animals a range of catheters over time spans similar to those which many catheters are used in humans. Thrombus formation is a variable phenomenon and use of only small numbers of animals as others have done is likely to produce misleading results. By using sufficient replications, it was possible with the data presented here to grade catheters statistically on the basis of thrombogenicity.

The main exception to the relation between thrombus formation and roughness was the Pharma-Plast umbilical catheter (No 19) which has also been shown to be relatively thrombogenic in new born lambs.[24] Other factors such as chemical composition are probably causing its increased thrombogenicity.

Sheep were selected for this study as they were readily available and cheap but also they are more similar in size than many animals used for testing thrombogenicity and have coagulation indices that are not greatly dissimilar to those of man.[27,28] The most significant apparent difference is the plasminogen level but this difference has been shown to be artifactual.[27] Sheep platelets are more similar to those of man in reactions to foreign surfaces than are dog or rabbit platelets.[30] In general, these thrombus results parallel the performance of catheters in humans. For example, polyethylene catheters used for radiology induce thrombus in humans in minutes[4,17,20,28] and were the most thrombogenic types tested here and Swan Ganz catheters were seen to have formed appreciable thrombus during open heart surgery.[31] The Pudenz catheter has been associated with thrombus-related problems on that portion inserted into the right atrium, whereas transvenous pacemaker electrodes are sheathed with Dow-Corning silicone rubber and are associated with fewer problems. Also catheters such as the Deseret, Bard and Abbott catheters are used satisfactorily in humans for several days although investigation has shown that thrombus does form on them.[32,33]

Although chemical and physical differences have effects, these results point to roughness as a significant cause of thrombogenesis in commonly used device. We suggest the following as an explanation why roughness results in increased thrombus in this test: many of the relatively non-thrombogenic catheters tested may initiate platelet aggregation but relatively smooth surfaces would discourage the adhesion of platelet aggregates and fibrin and so allow these to be swept away as microemboli. In contrast, rougher surfaces would facilitate adhesion and consequently the build up of thrombus. The presence of a catheter in an animal can result in a shorter half life for platelets and it would be expected that testing these catheters for their effects on parameters such as platelet turnover could produce different results (*e.g.*, see Ref. 34). However, in the clinical situation, thrombus which

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adheres to the actual catheter is likely to be more important than changes in such blood parameters.

This research highlights three points. First, it confirms that roughness is one of the factors which can cause thrombogenicity. Second, it demonstrates the need for both by research workers and manufacturers for a satisfactory method for quantifying roughness. Until such a method is developed, we suggest for research purposes that the practice (evident in this journal) be continued of presenting scanning electron photomicrographs of surfaces under study. Last, it shows that manufactureres should consider the quality control of roughness of catheters as it has been demonstrated that many are rough. Not one of several manufacturers contacted had investigated roughness of their products. Possible methods of making smoother catheters include use of finely ground or colloidal particles, burying tracer strips under the surface, and coating catheters with a thin layer of another suitable polymer.

We wish to thank Portex Ltd for the supply of umbilical artery catheters (No. 15) and the "new" nylon catheters (No. 31), Braun A. G. for tubings (No. 23, 24, 29 and 34), Dow Corning Corp. for the radio-opaque tubing (No. 3) and Extracorporeal Corp. for tubings (Nos 4 and 5).

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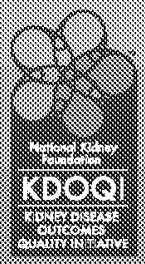

- Hemodialysis Adequacy
- Peritoneal Dialysis Adequacy
- Vascular Access

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Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these CPGs and CPRs is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

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The National Kidney Foundation makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group.

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Vascular Access
Acronyms and Abbreviations

aOR	Adjusted odds ratio
AMI	Acute myocardial infarction
AUC	Area under the curve
AV	Arteriovenous
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BFR	Blood flow rate
BP	Blood pressure
BTM	Body Thermal Monitor
CDC	Centers for Disease Control and Prevention
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CLS	Catheter lock solution
CMS	Centers for Medicare & Medicaid Services
CPG	Clinical Practice Guideline
CPM	Clinical performance measure
CPR	Clinical Practice Recommendation
CQI	Continuous quality improvement
CRB	Catheter-related bacteremia
CrCl	Creatinine clearance
CVC	Central venous catheter
CVD	Cardiovascular disease
DD	In line dialysance
DDU	Duplex Doppler ultrasound
DOPPS	Dialysis Outcomes and Practice Patterns Study
DOQI	Dialysis Outcomes Quality Initiative
DRIL	Distal revascularization—interval ligation
DSA	Digital subtraction angiography
DU	Doppler ultrasound
DVP	Dynamic venous pressures
FDA	Food and Drug Administration
FFBI	Fistula First Breakthrough Initiative
GFR	Glomerular filtration rate
GPT	Glucose pump infusion technique
Hct	Hematocrit
HD	Hemodialysis

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HDM	Hemodynamic monitoring
HTN	Hypertension
IAP	Intra-access pressure
IgG	Immunoglobulin G
INR	International normalized ratio
IV	Intravenous
IVC	Inferior vena cava
IVUS	Intravascular ultrasound
KDOQI	Kidney Disease Outcomes Quality Initiative
KLS	Kidney Learning System
KRT	Kidney replacement therapy
LVH	Left ventricular hypertrophy
MAP	Mean arterial (blood) pressure
MRA	Magnetic resonance angiography
N	Number of subjects
NCC	Noncuffed catheter
nd	No data reported
NKF	National Kidney Foundation
NS	Not significant
NVAII	National Vascular Access Improvement Initiative
OABF	Optodilution by ultrafiltration
ORX	Optodilutional recirculation measurement technique
ΔP	Pressure gradient
PAVA	Proximal arteriovenous anastomosis
PD	Peritoneal dialysis
PE	Pulmonary embolism
PFSS	Percutaneous fibrin sheath stripping
P_{IA}	Intra-access pressure
PICC	Peripherally inserted central catheter
PSV	Peak systolic velocity
PTA	Percutaneous angioplasty
PTFE	Polytetrafluoroethylene
PU	Polyurethane
PVD	Peripheral vascular disease
Q_A	Access blood flow
QA/CQI	Quality assurance/continuous quality improvement
Q_B	Blood pump flow delivered to the dialyzer
Q_{BP}	Blood pump flow
Qf	Ultrafiltration rate
QIP	Quality improvement project
QOL	Quality of life
RCT	Randomized controlled trial
ROC	Receiver operating characteristic

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RR	Relative risk
rTPA	Recombinant tissue plasminogen activator
SGA	Subjective global assessment
SVC	Superior vena cava
SVR	Systolic velocity ratio
TCC	Tunneled cuffed catheter
TD	Thermal dilution
tPA	Tissue plasminogen activator
TQA	Transcutaneous optodilution flow method
UDT	Ultrasound dilution technique
UK	Urokinase
UOP	Urine output
UreaD	Urea dialysance
UrCl	Urea clearance
URR	Urea reduction ratio
US	Ultrasonography
USRDS	United States Renal Data System
VAT	Vascular access team
VDP	Venous drip chamber pressure
VFDU	Variable flow Doppler ultrasound

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Glossary

Anastomosis: An opening created by surgical, traumatic, or pathological means between 2 normally separate spaces or organs.

Aneurysm: An abnormal blood-filled dilation of a blood vessel wall (most commonly in arteries) resulting from disease of the vessel wall.

Pseudoaneurysm: A vascular abnormality that resembles an aneurysm, but the outpouching is not limited by a true vessel wall, rather by external fibrous tissue.

Angioplasty: The repair of a blood vessel abnormality.

Percutaneous transluminal angioplasty: The repair of a lesion using an endoluminal approach, usually with a balloon that can be inflated to pressures up to 30 atmospheres.

Antibiotic lock: Instillation of an antibiotic solution into the lumen of a dialysis catheter for the entire interdialytic period; antibiotics tested include vancomycin, aminoglycosides, and minocycline.

Antimicrobial lock: Instillation of an antimicrobial solution into the lumen of a dialysis catheter for the entire interdialytic period; antimicrobial solutions include high-concentration citrate, high-concentration EDTA, and taurolidine.

Antimicrobial: Any agent capable of destroying or inhibiting the growth of microorganisms.

Antiseptic: Any agent capable of preventing infection by inhibiting the growth of microorganisms.

Cannulation: The insertion of cannulae (by definition, a needle with a lumen) or angiocaths into a vascular vessel.

Buttonhole technique or constant-site technique: The repeated cannulation into the exact same puncture site so that a scar tissue tunnel track develops. The scar tissue tunnel track allows the needle to pass through to the outflow vessel of the fistula following the same path with each cannulation time. Only used in fistulae. Should not be used for accessing grafts.

Catheter: A device providing access to the central veins or right atrium, permitting high-volume flow rates.

Exit site: The location on the skin that the catheter exits through the skin surface.

Insertion site: Location at which the catheter enters the vein, for example, the right internal jugular vein is the preferred insertion site.

Long-term catheter: Also known as tunneled cuffed catheter (TCC); a device intended for use for longer than 1 week that typically is tunneled and has a cuff to promote fibrous ingrowth to prevent catheter migration and accidental withdrawal.

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Port catheter system: Subcutaneous device for hemodialysis access that is cannulated with needles; the device contains a ball-valve system that is connected to 1 or more central venous catheters (CVCs).

Short-term catheter: A device intended for short-term use (<1 week) that typically is not tunneled. Intended for use in hospitalized patients; not for outpatient maintenance dialysis.

Diagnostic testing: Specialized testing that is prompted by some abnormality or other medical indication and that is undertaken to diagnose the cause of the vascular access dysfunction.

Dialysance: The number of milliliters of blood completely cleared of any substance by an artificial kidney or by peritoneal dialysis in a unit of time, usually a minute, with a specified concentration gradient.

Distal revascularization—interval ligation (DRIL): A surgical procedure to reduce ischemia to the hand caused by steal syndrome.

Elastic recoil: The recurrence of stenosis following angioplasty.

Fistula (plural, fistulae): Autogenous autologous arteriovenous fistula, also referred to as native.

Brescia-Cimino (radiocephalic) fistula: An autologous fistula constructed between the radial artery and the cephalic vein at the wrist.

Gracz fistula: An autologous fistula constructed between the brachial artery and a branch of the medial antecubital vein, the perforating vein, below the elbow.

Snuff-box fistula: An autologous fistula constructed between a branch of the radial artery and an adjacent vein in the anatomic snuff box of the hand.

Fistula maturation: The process by which a fistula becomes suitable for cannulation.

Rule of 6s: A fistula in general must be a minimum of 6 mm in diameter with discernable margins when a tourniquet is in place, less than 6 mm deep, have a blood flow greater than 600 mL/min, and should be evaluated for nonmaturation if, after 6 weeks from surgical creation, it does not meet these criteria.

Flow: The amount of blood flowing through a system.

Q_A: Access blood flow.

Qf: Ultrafiltration rate.

Q_B: Blood pump flow delivered to the dialyzer.

Flow measurement methods:

Crit line: Using changes in hematocrit (Hct) induced by ultrafiltration.

GPT: Glucose pump (infusion) technique.

HDM: Hemodialysis monitor using magnetic detection of differential conductivity.

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Ionic dialysance: A method that uses a change in dialysis fluid sodium concentration to calculate flow.

ORX: Optodilutional recirculation measurement technique.

TD: Thermal dilution method.

TQA: Direct transcutaneous optodilutional flow method.

UDT: Ultrasound dilution technique.

VFDU: Variable flow Doppler ultrasound.

Graft: A conduit of synthetic or biological material connecting artery to vein.

Synthetic: Made of plastic polymers, such as polytetrafluoroethylene (PTFE), polyurethane (PU).

Biological: Made of biological materials, such as bovine carotid artery, cryopreserved human femoral veins, etc.

Tapered: Grafts for which internal diameter varies from the arterial to the venous end.

Untapered: Grafts with a uniform diameter, usually 6 mm.

Kt/V: A dimensionless quantity that assesses the amount of dialysis delivered.

Monitoring: The evaluation of the vascular access by means of physical examination to detect physical signs that suggest the presence of dysfunction.

Magnetic resonance angiography (MRA): A technique to visualize the arterial and venous systems using gadolinium as the imaging agent.

Neointimal hyperplasia: The myoendothelial proliferation of cells and matrix that produces stenosis, primarily in grafts.

Online: The conductance of a test during a hemodialysis procedure.

Physical examination (of the access): Inspection, palpation, and auscultation of the access.

Pressure: Force applied uniformly over a surface, measured as force per unit of area; stress or force acting in any direction against resistance.

Mean arterial pressure (MAP): Usually recorded in the arm opposite the vascular access.

P_{LA}: Pressure in the access when there is no external blood flow for dialysis, also referred to as the "static pressure."

Venous drip chamber pressure (VDP): Also referred as dynamic venous pressure (DVP). Measured in the venous tubing and equal to the pressure required to infuse blood back into the vascular access at the blood pump flow set.

Recirculation: The return of dialyzed blood to the systemic circulation without full equilibration.

Cardiopulmonary recirculation: Resulting from the return of dialyzed blood without full equilibration with all systemic venous return.

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Access recirculation: Resulting from the admixture of dialyzed blood with arterial access blood without equilibration with the systemic arterial circulation. Occurs under conditions in which blood pump flow is greater than access flow.

Receiver operating characteristic (ROC) curve: A technique to evaluate the sensitivity and specificity of a diagnostic test to detect/predict the presence of a disease state.

Steal syndrome: Signs and symptoms (pain, coldness, cyanosis, necrosis) produced by an access as a result of the diversion of arterial blood flow into the fistula.

Acronecrosis: Gangrene occurring in the distal part of the extremities, usually fingertips and toes.

Stenosis: A constriction or narrowing of a duct or passage; a stricture.

Cephalic arch stenosis: A common site for stenosis of the cephalic vein at an anatomic site where there is a narrowing of the cephalic vein as it arches over the shoulder in the region of the deltopectoral groove before the vein junction with the axillary vein.

Surveillance: The periodic evaluation of the vascular access by means of tests, which may involve special instrumentation and for which an abnormal test result suggests the presence of dysfunction.

Tissue plasminogen activator (tPA): A natural lytic used to dissolve fibrin or nonorganized thrombus.

Transposition: The movement of a vein from its normal position either by elevation to bring the vein closer to the skin or laterally to permit easier cannulation.

Ultrasound: The use of ultrasonic waves for diagnostic or therapeutic purposes, specifically to image an internal body structure.

Doppler ultrasound (DU): Ultrasound that uses the Doppler effect to measure movement or flow in the body and especially blood flow; also referred to as Doppler ultrasonography.

Duplex Doppler ultrasound (DDU): Combines Doppler and B-mode (grayscale) imaging to provide diagnostic ultrasound used for quantitative color velocity imaging, also referred to as Doppler sonography.

Systolic velocity ratio (SVR): The ratio of velocity in an abnormal vessel relative to a normal vessel.

Urokinase: A natural lytic used to dissolve fibrin or nonorganized thrombus.

Vascular access team (VAT): Patient and group of professionals involved in management of vascular access (includes caregivers who construct, cannulate, monitor, detect problems in, and repair vascular accesses). Caregivers include nephrologist, nephrology nurse, patient care technician, nurse practitioner, physician assistant, interventionalist, surgeons, and vascular access coordinator.

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Foreword

The publication of the second update of the Clinical Practice Guidelines (CPGs) and Clinical Practice Recommendations (CPRs) for Vascular Access represents the second update of these guidelines since the first guideline on this topic was published in 1997. The first set of guidelines established the importance of placing fistulae in long-term hemodialysis patients. Several of these guidelines have been selected as clinical performance measures by regulatory agencies to drive the process of quality improvement in long-term dialysis patients, and an initiative in the United States called "Fistula First" recently was started in an effort to increase the percentage of patients who have an arteriovenous fistula placed for long-term hemodialysis therapy.

Several major changes have occurred since the publication of the first set of guidelines. First, a number of clinical trials have been performed to determine the efficacy of different methods of identifying an access that is beginning to fail. Thus, this update of the guideline includes a substantial revision of accepted methods for access dysfunction detection. Second, cannulation techniques have been updated to include the importance of training staff in cannulation techniques and the appropriate uses of the buttonhole technique for arteriovenous fistulae. Finally, urokinase was removed from the market and other thrombolytic agents have been developed to assist with reestablishing patency in dialysis catheters. The use of these newer agents is addressed in this update.

This document has been divided into 3 major areas. The first section consists of guideline statements that are evidence based. The second section is a new section that consists of opinion-based statements that we are calling "clinical practice recommendations," or CPRs. These CPRs are opinion based and are based on the expert consensus of the Work Group members. It is the intention of the Work Group that the guideline statements in Section I can be considered for clinical performance measures because of the evidence that supports them. Conversely, because the CPRs are opinion based, and not evidence based, they should not be considered to have sufficient evidence to support the development of clinical performance measures. The third section consists of research recommendations for these guidelines and CPRs. We have decided to combine all the research recommendations for the guidelines into 1 major section and also have ranked these recommendations into 3 categories: critical importance, high importance, and moderate importance. Our intended effect of this change in how the research recommendations are presented is to provide a guidepost for funding agencies and investigators to target research efforts in areas that will provide important information to benefit patient outcomes.

This final version of the Clinical Practice Guidelines and Recommendations for Vascular Access has undergone extensive revision in response to comments during the public review. While considerable effort has gone into their preparation during the past 2 years and every attention has been paid to their detail and scientific rigor, no set of guidelines and clinical practice recommendations, no matter how well developed, achieves its

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purpose unless it is implemented and translated into clinical practice. Implementation is an integral component of the Kidney Disease Outcomes Quality Initiative (KDOQI) process and accounts for the success of its past guidelines. The Kidney Learning System (KLS) component of the National Kidney Foundation is developing implementation tools that will be essential to the success of these guidelines.

In a voluntary and multidisciplinary undertaking of this magnitude, many individuals make contributions to the final product now in your hands. It is impossible to acknowledge them individually here, but to each and every one of them, we extend our sincerest appreciation. This limitation notwithstanding, a special debt of gratitude is due to the members of the Work Group and their co-chairs, Anatole Besarab of Henry Ford Hospital and Jack Work of Emory University. It is their commitment and dedication to the KDOQI process that has made this document possible.

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INTRODUCTION

More than 300,000 individuals in the United States rely on a vascular access to receive hemodialysis (HD) treatment.[1] Vascular access continues to be a leading cause for hospitalization and morbidity in patients with chronic kidney disease (CKD) stage 5.[2] Appropriate care of HD patients with CKD stage 5 requires constant attention to the maintenance of vascular access patency and function. An ideal access delivers a flow rate to the dialyzer adequate for the dialysis prescription, has a long use-life, and has a low rate of complications (eg, infection, stenosis, thrombosis, aneurysm, and limb ischemia). Of available accesses, the surgically created fistula comes closest to fulfilling these criteria. Studies over several decades consistently demonstrate that native fistula accesses have the best 4- to 5-year patency rates and require the fewest interventions compared with other access types.[3-5] However, in the United States between 1985 and 1995, the growth of the CKD Stage 5 HD program was accompanied by decreased use of native fistulae and increased use of grafts and cuffed central catheters for permanent HD access.[5,6] In 1995, the United States Renal Data System (USRDS) reported, for the 1990 incident cohort of patients, that insertion of polytetrafluoroethylene (PTFE) grafts occurred almost twice as often as construction of native accesses.[6] Significant geographic variation in the ratio of native fistula construction to graft placement also was noted.

The substitution of grafts for fistulae increased patient care costs, in part because of the increased number of procedures needed to maintain patency of grafts compared with native fistulae.[7] A review of Medicare billing showed that the first-year total yearly costs for patients initiating HD therapy using a fistula were lowest ($68,002) compared with grafts ($75,611) and catheters ($86,927).[8] Although the second-year total yearly costs were lower for all groups, catheters still resulted in the highest costs at $57,178 compared with $54,555 for grafts and $46,689 for fistulae. Similarly, in a single-center Canadian study, the cost of vascular access–related care was lower by more than 5-fold for patients who began the study period with a functioning fistula compared with those treated with a long-term catheter or graft.[9]

Before the first dissemination of the Dialysis Outcomes Quality Initiative (DOQI) recommendations on vascular access in 1997, many studies showed that practice patterns were contributing to patient morbidity and mortality, as well as costs. The failure of access was noted to be a major cause of morbidity for patients on HD therapy, with a number of reports indicating that a high percentage of hospitalizations for patients with CKD stage 5 were caused by vascular access complications.[6,7,10-12] The USRDS reported that HD access failure was the most frequent cause of hospitalization for patients with CKD stage 5,[6] and, in some centers, it accounted for the largest number of hospital days.[13] Reports also indicated a decreasing interval between placement of a vascular access and a surgical procedure needed to restore patency,[7,12] with significant costs to restore patency.[6,13] Since then, a study using data from the USRDS Morbidity and Mortality Study Wave 1 showed that patients receiving catheters and grafts have greater mortality risk than patients dialyzed with fistulae.[14] In patients with and without diabetes mellitus, cause-specific analyses found higher infection-related deaths for cuffed central catheters.

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In patients without diabetes, relative risks (RRs) were 1.83 ($P < 0.04$) with catheters and 1.27 ($P < 0.33$) with arteriovenous (AV) grafts (AVGs). In patients with diabetes, the RR was even higher than in those without diabetes: RR of 2.30 ($P < 0.06$) for catheters and RR of 2.47 ($P < 0.02$) for grafts compared with fistulae. Cardiac cause of death was highest in patients with central venous catheters (CVCs). A number of subsequent epidemiological studies, both in the United States[15,16] and abroad,[17] reaffirmed that greater use of fistulae was associated with reduced mortality and morbidity.

It was shown that an aggressive policy for monitoring hemodynamics within an AVG or AV fistula (AVF) to detect access dysfunction may reduce the rate of thrombosis (see Clinical Practice Guideline [CPG] 4). Thus, much access-related morbidity and associated costs might be avoided. The number of interventions required to maintain access patency may be decreased further by the use of fistulae rather than AVGs. Studies showed that the number of access events is 3- to 7-fold greater in prosthetic bridge grafts than in fistulae,[3,18] thereby contributing to the increased cost of grafts. Whether utilization of such interventions to reduce thrombosis rates ultimately prolongs the useable life of the access are unknown and should not be the sole outcome measure. Thrombosis is associated with additional risks to the patient that are not present with simple percutaneous angioplasty (PTA).[19]

The National Kidney Foundation (NKF) issued the Kidney Disease Outcomes Quality Initiative (KDOQI) CPGs for Vascular Access in an effort to improve patient survival and quality of life (QOL), reduce morbidity, and increase efficiency of care. Vascular access patency and adequate HD are essential to the optimal management of HD patients with CKD stage 5. The first is a necessary prerequisite for the second. To improve QOL and overall outcomes for HD patients, 2 primary goals were originally put forth in the vascular access guidelines[20]:

- Increase the placement of native fistulae
- Detect access dysfunction before access thrombosis.

We believe these goals still apply, with the emphasis on placement of the functioning fistula. The Centers for Medicare & Medicaid Services (CMS) has actively collected data on 3 Clinical Performance Measures (CPMs) derived from the original and revised KDOQI Guidelines for Vascular Access. The failure to "adequately" increase the number of fistulae among either incident or prevalent HD patients during the past 6 years[2] or to reduce the use of catheters led to a CMS mandate that the ESRD networks develop Quality Improvement Projects (QIPs) on Vascular Access. These have been distilled into 3 key points: avoid central catheterization, thus avoiding loss of central patency; maintain existing access by detecting impending failure, followed by prompt intervention; and maximize creation of fistulae as the best long-term access. Out of these concepts has grown the National Vascular Acce241ss Improvement Initiative (NVAII), emphasizing a fistula-first approach. Recently, the target for fistula creation was set as 65% by 2009 (www.cms.hhs.gov/ESRDQualityImproveInit/04_FistulaFirstBreakthrough.asp). The Work Group acknowledges the importance of increasing the number of fistulae in use, *but* believes that the emphasis should be shifted from the fistula construction rate to the

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rate of usable fistula accesses. This shift in emphasis is important to minimize wasted time and effort and reduce the primary failure rate and salvage procedures.

A number of barriers need to be overcome to achieve the goals set for vascular fistula construction; chief among these is the late referral of patients for permanent access placement, reflected in patient hospitalizations. In some regions, up to 73% of patients are hospitalized for initiation of HD therapy, almost invariably for dialysis catheter access placement.[21] Unexpectedly, the modest increases in fistula use rates have been accompanied by increases in the use of catheters.[2] Early referral of patients with CKD stage 5 to a nephrologist is absolutely essential to allow for access planning and thus increase the probability of fistula construction and maturation, thereby decreasing the need for catheter placement.

To achieve these objectives, the current Work Group has developed and revised the vascular access practice guidelines and strategies for implementation and has made a concerted effort to differentiate guidelines from recommendations. At the core of these guidelines is the goal of early identification of patients with progressive kidney disease and the identification and protection of potential fistula construction sites—particularly sites using the cephalic vein—by members of the health care team and patients.

After access has been constructed, dialysis centers need to use a multifaceted continuous quality improvement (CQI) program to detect vascular accesses at risk, track access complication rates, and implement procedures that maximize access longevity. Vascular access databases that are available to all members of the vascular access team (VAT) are crucial. The Work Group has developed explicit guidelines regarding which tests to use to evaluate a given access type and when and how to intervene to reduce thrombosis and underdialysis. The Work Group believes that the guidelines are reasonable, appropriate, and achievable. Attainment of these goals will require the concerted efforts of not only practicing nephrologists, but also nephrology nurses, access surgeons, vascular interventionalists, patients, and other members of the health care team.

In this update of the Vascular Access Guidelines, the Work Group did not perform a comprehensive review of all the guidelines. Seven topics underwent systematic review, and these are identified. The other guidelines were unified and consolidated. More recent references, including reviews, were included when appropriate.

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GUIDELINE 1. PATIENT PREPARATION FOR PERMANENT HEMODIALYSIS ACCESS

Appropriate planning allows for the initiation of dialysis therapy at the appropriate time with a permanent access in place at the start of dialysis therapy.

1.1 Patients with a glomerular filtration rate (GFR) less than 30 mL/min/1.73 m^2 (CKD stage 4) should be educated on all modalities of kidney replacement therapy (KRT) options, including transplantation, so that timely referral can be made for the appropriate modality and placement of a permanent dialysis access, if necessary. (A)

1.2 In patients with CKD stage 4 or 5, forearm and upper-arm veins suitable for placement of vascular access should not be used for venipuncture or for the placement of intravenous (IV) catheters, subclavian catheters, or peripherally inserted central catheter lines (PICCs). (B)

1.3 Patients should have a functional permanent access at the initiation of dialysis therapy.

1.3.1 A fistula should be placed at least 6 months before the anticipated start of HD treatments. This timing allows for access evaluation and additional time for revision to ensure a working fistula is available at initiation of dialysis therapy. (B)

1.3.2 A graft should, in most cases, be placed at least 3 to 6 weeks before the anticipated start of HD therapy. Some newer graft materials may be cannulated immediately after placement. (B)

1.3.3 A peritoneal dialysis (PD) catheter ideally should be placed at least 2 weeks before the anticipated start of dialysis treatments. A backup HD access does not need to be placed in most patients. A PD catheter may be used as a bridge for a fistula in "appropriate" patients. (B)

1.4 Evaluations that should be performed before placement of a permanent HD access include (Table 1):

1.4.1 History and physical examination, (B)

1.4.2 Duplex ultrasound of the upper-extremity arteries and veins, (B)

1.4.3 Central vein evaluation in the appropriate patient known to have a previous catheter or pacemaker. (A)

BACKGROUND

Since implementation of the NKF KDOQI Vascular Access Guidelines in 1997, which encouraged increased placement of fistulae, CMS has embraced this recommendation with the implementation of the Fistula First Breakthrough Initiative (FFBI). This initiative endorses the goals recommended by the NKF KDOQI: fistula rates of 50% or

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greater for incident—and at least 40% for prevalent—patients undergoing HD. The FFBI promotes the placement of fistulae in all suitable HD patients. Working through the ESRD Networks, the FFBI promotes the placement of fistulae using 11 "Change Concepts" that encourage the development of specific strategies; these 11 Change Concepts have been identified to help the kidney community improve the rate of fistula placement. Five of these strategies emphasize the same goals as CPG 1 and Clinical Practice Recommendation (CPR) 1: education of patients regarding fistulae, protection of vessels, vessel mapping, and sufficient lead-time for fistula maturation (NVAII; www.fistulafirst.org). The breakthrough initiative has reset the goal for fistula creation to 65% by 2009.

RATIONALE

Characteristics of a patient's arterial, venous, and cardiopulmonary systems will influence which access type and location are most desirable for each patient.[22-27] The patient's life expectancy and planned duration of CKD stage 5 therapy also can influence the type and location of the access. All patients should be evaluated as in Table 1.

Venipuncture complications may render veins potentially available for vascular access unsuitable for construction of a primary fistula. Patients and health care professionals should be educated about the need to preserve veins to avoid loss of potential access sites in the arms and maximize chances for successful fistula placement and maturation. Subclavian vein catheterization is associated with central venous stenosis.[28-30] Significant subclavian vein stenosis generally will preclude the use of the entire ipsilateral arm for vascular access. Thus, subclavian vein catheterization should be avoided for temporary access in patients with kidney disease.[31] The incidence of central vein stenosis and occlusion after upper-extremity placement of peripherally inserted long-term catheters (PICCs) and venous ports was 7% in 1 retrospective study of 150 patients.[32] PICCs also are associated with a high incidence of upper-extremity thrombosis. The incidence of upper-extremity venous thrombosis varies between 11% and 85%, which leads to loss of potential upper-extremity fistulae.[33-35] Because of the substantial risk for loss of useable upper-extremity veins and central venous stenosis with PICCs, the Work Group recommends strongly that PICCs not be used in patients with CKD.

Ideally, patients should have a functional permanent access at the time of dialysis therapy initiation. Function implies that the access not only delivers adequate blood flow for dialysis, but may be cannulated easily. In general, such an access has a flow of approximately 600 mL/min, is less than 0.6 cm below the surface of the skin, and has a minimal diameter of 0.6 cm (Rule of 6s) Both the size and anatomic qualities of venous and arterial components of primary fistulae can influence fistula maturation time. An aggressive policy of primary fistula creation may result in failures in patients with marginal anatomy. However, timely attempts to create a primary fistula before the anticipated need for dialysis therapy will allow adequate time for the fistula to mature and will allow sufficient time to perform another vascular access procedure if the first attempt fails, thus avoiding the need for temporary access. Early referral of a patient with CKD to a nephrologist is needed to facilitate CKD therapy with medications and diets that preserve kidney func-

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Table 1. Patient Evaluation Prior to Access Placement

Consideration	Relevance
Patient History	
History of previous CVC	Previous placement of a CVC is associated with central venous stenosis
Dominant arm	To maximize negative impact on quality of life, use of the nondominant arm is preferred.
History of pacemaker use	There is a correlation between pacemaker use and central venous stenosis.
History of severe CHF	Accesses may alter hemodynamics and cardiac output.
History of arterial or venous peripheral catheter	Previous placement of an arterial or venous peripheral catheter may have damaged target vasculature.
History of diabetes mellitus	Diabetes mellitus is associated with damage to vasculature necessary for internal accesses.
History of anticoagulant therapy or any coagulation disorder	Abnormal coagulation may cause clotting or problems with hemostasis of accesses.
Presence of comorbid conditions, such as malignancy or coronary artery disease, that limit patient's life expectancy	Morbidity associated with placement and maintenance of certain accesses may not justify their use in some patients.
History of vascular access	Previously failed vascular accesses will limit available sites for accesses; the cause of a previous failure may influence planned access if the cause is still present.
History of heart valve disease or prosthesis	Rate of infection associated with specific access types should be considered.
History of previous arm, neck, or chest surgery/trauma	Vascular damage associated with previous surgery or trauma may limit viable access sites.
Anticipated kidney transplant from living donor	Catheter access may be sufficient.
Physical Examination	
Physical Examination of Arterial System	
Character of peripheral pulses, supplemented by hand-held Doppler evaluation when indicated	An adequate arterial system is needed for access; the quality of the arterial system will influence the choice of access site.
Results of Allen test	Abnormal arterial flow pattern to the hand may contraindicate the creation of a radial-cephalic fistula.
Bilateral upper extremity blood pressures	Pressures determine suitability of arterial access in upper extremities.
Physical Examination of Venous System	
Evaluation for edema	Edema indicates venous outflow problems that may limit usefulness of the associated potential access site or extremity for access placement.
Assessment of arm size comparability	Differential arm size may indicate inadequate veins or venous obstruction which should influence choice of access site.
Examination for collateral veins	Collateral veins are indicative of venous obstruction.
Tourniquet venous palpation with vein mapping	Palpation and mapping allow selection of ideal veins for access.
Examination for evidence of previous central or peripheral venous catheterization	Use of CVCs is associated with central venous stenosis; previous placement of venous catheters may have damaged target vasculature necessary for access.
Examination for evidence of arm, chest, or neck surgery/trauma	Vascular damage associated with previous surgery or trauma may limit access sites.
Cardiovascular Evaluation	
Examination for evidence of heart failure	Accesses may alter cardiac output.

tion. In addition, counseling patients about CKD stage 5 treatment options is essential to plan for ideal access (ie, PD and HD access) (see CPG 2) (Table 1).

The Work Group's consensus is that maturation of an AVG access site—defined as reduction of surgically induced swelling and the graft's adherence to its tunnel tissue—usually requires about 3 weeks. Thus, ideally, AVGs should be placed 3 to 6 weeks before use.

Long-term catheters are the method of choice for temporary access of longer than 1 week duration. Catheters are suitable for immediate use. To maximize their use-life, they should not be inserted until needed. However, the Work Group recommends that a catheter be used for dialysis access for as brief a period as necessary (see CPG 2).

A vein must be mature, both physically and functionally, before use for vascular access. The time required for fistula maturation varies among patients. The Work Group does not advise use of the fistula within the first month after construction because

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premature cannulation of a fistula may result in a greater incidence of infiltration, with associated compression of the vessel by hematoma and permanent loss of the fistula. In general, allowing the fistula to mature for 6 to 8 weeks before investigating the reason for failure to mature is appropriate (see CPG 2). For a fistula to be considered successful, it must be usable. In general, a working fistula must have all the following characteristics: blood flow adequate to support dialysis, which usually equates to a blood flow greater than 600 mL/min; a diameter greater than 0.6 cm, with location accessible for cannulation and discernible margins to allow for repetitive cannulation; and a depth of approximately 0.6 cm (ideally, between 0.5 to 1.0 cm from the skin surface). This combination of characteristics can be remembered easily as the Rule of 6s.

Although there are no definitive data in the literature, any intervention that increases blood flow to the extremity may improve the chances of successful fistula development. Therefore, regular hand-arm exercises, with or without a lightly applied tourniquet, are recommended until the fistula matures. Failure of a fistula to mature occasionally is caused by venous side branches that drain critical flow from the primary vessel. Ligating these side branches may result in successful maturation (see CPG 6).

Studies relating to preoperative venous imaging/mapping for AVF construction underwent systematic review. Duplex ultrasound is the preferred method for preoperative vascular mapping. Vascular mapping in preparation for the creation of a vascular access refers to the evaluation of vessels, both arterial and venous, of patients with CKD who have selected HD therapy, and it should be performed in all patients before placement of an access. Preoperative vascular mapping was shown to substantially increase the total proportion of patients dialyzing with fistulae.[36-39] Several studies support the 2.0- to 2.5-mm vein diameter threshold for successful creation of a fistula.[39,40] Radiocephalic fistulae constructed in veins less than 2.0 mm in diameter had only a 16% primary patency at 3 months compared with 76% for those with veins greater than 2.0 mm.[40] In a pivotal study,[39] a threshold of 2.5-mm vein diameter, assessed by using duplex ultrasound, was used; this resulted in an increase in fistula creation to 63% compared with a retrospective 14% rate in the absence of vascular mapping.[22] A similar study using the same duplex ultrasound criteria showed a fistula increase from 34% in historical controls to 64%. Importantly, in this study, duplex ultrasound altered the surgical plan based entirely on the surgeon's clinical evaluation, resulting in increased placement of fistulae.[41]

There is no generally accepted "standard" for what constitutes vascular mapping. The arterial evaluation should include pulse examination, differential blood pressure measurement, assessment of the palmar arch for patency, arterial diameter assessed by using duplex ultrasound, and the presence of arterial calcification. A preoperative arterial diameter less than 1.6 mm has been associated with a high failure rate in radiocephalic fistulae.[42,43] Other studies suggested that a minimum diameter of 2.0 mm is required for successful fistula creation.[39] Venous evaluation should include a luminal diameter of 2.5 mm or greater, continuity with the proximal central veins, and absence of obstruction.[39] The central veins may be assessed indirectly by using duplex ultrasound.[44] Compared with invasive venography, duplex ultrasound had a specificity of 97% and sensitivity of 81% for detecting central vein occlusion.[45] Alternatively, venography or magnetic

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resonance angiography (MRA) may be used to evaluate central veins.[46] (See CPR 1.4 for suitable imaging studies for central veins).

LIMITATIONS

There has been no study comparing vascular access surgery based only on the clinical evaluation to preoperative vascular mapping outcomes. Such a study would be the equivalent of requiring a randomized prospective study comparing the efficacy of pulmonary clinical evaluation (tactile fremitus and auscultation, ie, physical examination only) with a chest radiograph (imaging) in identifying lung pathological states. Such a study is unlikely, based on current data showing that vascular mapping increases fistula creation. Although the level of evidence of a prospective randomized trial is not available, the Work Group consensus based on many studies supports vascular mapping as a guideline.

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A structured approach to the type and location of long-term HD accesses should help optimize access survival and minimize complications.

The access should be placed distally and in the upper extremities whenever possible. Options for fistula placement should be considered first, followed by prosthetic grafts if fistula placement is not possible. Catheters should be avoided for HD and used only when other options listed are not available.

2.1 The order of preference for placement of fistulae in patients with kidney failure who choose HD as their initial mode of KRT should be (in descending order of preference):

2.1.1 Preferred: Fistulae. (B)

2.1.1.1 A wrist (radiocephalic) primary fistula. (A)

2.1.1.2 An elbow (brachiocephalic) primary fistula. (A)

2.1.1.3 A transposed brachial basilic vein fistula: (B)

2.1.2 Acceptable: AVG of synthetic or biological material, such as: (B)

2.1.2.1 A forearm loop graft, preferable to a straight configuration.

2.1.2.2 Upper-arm graft.

2.1.2.3 Chest wall or "necklace" prosthetic graft or lower-extremity fistula or graft; all upper-arm sites should be exhausted.

2.1.3 Avoid if possible: Long-term catheters. (B)

2.1.3.1 Short-term catheters should be used for acute dialysis and for a limited duration in hospitalized patients. Noncuffed femoral catheters should be used in bed-bound patients only. (B)

2.1.3.2 Long-term catheters or dialysis port catheter systems should be used in conjunction with a plan for permanent access. Catheters capable of rapid flow rates are preferred. Catheter choice should be based on local experience, goals for use, and cost. (B)

2.1.3.3 Long-term catheters should not be placed on the same side as a maturing AV access, if possible. (B)

Special attention should be paid to consideration of avoiding femoral catheter access in HD patients who are current or future kidney transplant candidates. MRA imaging of both arteries and veins is the diagnostic procedure of choice for evaluating central vessels for possible chest wall construction.

2.1.4 Patients should be considered for construction of a primary fistula after failure of every dialysis AV access. (B)

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2.1.5 While this order of access preference is similar for pediatric patients, special considerations exist that should guide the choice of access for children receiving HD. Please refer to CPR 8 for specific recommendations.

2.1.6 In the patient receiving PD who is manifesting signs of modality failure, the decision to create a backup fistula should be individualized by periodically reassessing need. In individuals at high risk for failure (see the PD Adequacy Guidelines), evaluation and construction should follow the procedures in CPG 1 for patients with CKD stage 4.

2.2 Fistulae:

2.2.1 Enhanced maturation of fistulae can be accomplished by selective obliteration of major venous side branches in the absence of a downstream stenosis. (B)

2.3 Dialysis AVGs:

2.3.1 The choice of synthetic or biological material should be based on the surgeon's experience and preference. The choice of synthetic or biological conduits should consider local experience, technical details, and cost. (B)

2.3.2 There is no convincing evidence to support tapered versus uniform tubes, externally supported versus unsupported grafts, thick- versus thin-walled configurations, or elastic versus nonelastic material. (A)

2.3.3 While the majority of past experience with prosthetic grafts has been with the use of PTFE, other prosthetics (eg, polyurethane [PU]) and biological conduits (bovine) have been used recently with similar outcomes. (B)

2.3.4 Patients with swelling that does not respond to arm elevation or that persists beyond 2 weeks after dialysis AV access placement should receive an imaging study or other noncontrast study to evaluate central venous outflow (see CPG 1). (B)

2.4 Catheters and port catheter systems:

2.4.1 The preferred insertion site for tunneled cuffed venous dialysis catheters or port catheter systems is the right internal jugular vein. Other options include the right external jugular vein, left internal and external jugular veins, subclavian veins, femoral veins, and translumbar and transhepatic access to the IVC. Subclavian access should be used only when no other upper-extremity or chest-wall options are available. (A)

2.4.2 Ultrasound should be used in the placement of catheters. (B)

2.4.3 The position of the tip of any central catheter should be verified radiologically. (B)

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RATIONALE

Order of Placement (CPG 2.1)

There are no randomized controlled trials (RCTs) comparing the recommended anatomic order of distal-to-proximal access construction. However, good surgical practice makes it obvious that when planning permanent access placement, one should always consider the most distal site possible to permit the maximum number of future possibilities for access.[23] In general, a peripheral-to-central sequence of fistulae construction should be envisioned in the ideal case, beginning with the "snuff box" fistula at the base of the thumb, followed by the standard Brescia-Cimino wrist fistula, followed by a forearm cephalic fistula at dorsal branch and finally a midforearm cephalic fistula. If a forearm fistula is not feasible, an antecubital fistula,[47] cephalic fistula at elbow, and, finally, a transposed basilic fistula should be considered. In cases in which a fistula is not constructed initially, a graft can be used as a "planned bridge" to a fistula. Failing forearm grafts can be converted to upper-arm fistulae, and lower-level fistulae can be converted to higher-level fistulae. If a graft is constructed, preference is given to the following sequence: forearm loop; upper-arm, straight or curved; upper-arm loop. All upper-extremity options should be considered before using the thigh. At times, "exotic" grafts can be constructed on the anterior chest wall or to the internal jugular vein. Even in these situations, a systematic radiological evaluation of the venous systems should be conducted before placement.

Maintaining long-term functioning access can be difficult and frustrating for physicians and patients; starting distally and moving proximally provides for the possibility of preserving as many potential sites as possible for future access creation. It is a tragedy for patients and caretakers alike to exhaust anatomic sites prematurely by initially bypassing more distal sites. The decision to use a more proximal site initially should be documented by preoperative imaging studies or the likelihood for the development of arterial "steal."[23,48] (See CPGs 1, 5, and 6.) However, if upper-extremity options have been exhausted, the anatomic locations left for permanent access are the thigh (where grafts[49,50] and, less commonly, fistulae[51] can be constructed) and upper chest, where a variety of graft accesses can be constructed.[52] The possibilities in the chest usually are defined by preoperative evaluation of the central venous system and, at times, angiography[53] or MRA is required.[54] Because vascular access infection is intrinsically more likely in the thigh, access construction in this site usually is deferred to one of last resort. Graft patency in the thigh is minimally better than in the upper arm,[55] and the greater risk for infection mandates against its initial use. In extreme cases, the forgotten Thomas shunt can be constructed.[56]

The preference of fistulae over all other forms of access arises from their functional advantages because of a lower rate of complications.

- Fistulae have the lowest rate of thrombosis[57] and require the fewest interventions,[57,58] providing longer survival of the access.[3,4,57,58] The number of access events is 3- to 7-fold greater in prosthetic bridge grafts than in native fistulae.[4,57,58]
- As a result, costs of implantation and access maintenance are the lowest.[4,6,8]
- Fistulae have lower rates of infection than grafts, which, in turn, are less prone to infection than percutaneous catheters and subcutaneous port catheter systems.[59]

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Vascular access infections in HD patients are common, can be severe, and contribute to infection as the second leading cause of death in patients with CKD stage 5.[60]

- Fistulae are associated with increased survival and lower hospitalization.
  - Patients receiving catheters (RR = 2.3) and grafts (RR = 1.47) have a greater mortality risk than patients dialyzed with fistulae.[14]
  - Epidemiological evidence also indicates that greater use of fistulae reduces mortality and morbidity.[14-17]

Wrist (radiocephalic)[61] and elbow (brachiocephalic)[62] primary fistulae are the preferred types of access because of the following characteristics:

- Superior patency to other accesses after they are established and matured.[3,4,23,24,57,58,63-69]
- Lower complication rates compared with other access options,[3,23,24,63-69] including lower incidence of conduit stenosis, infection, and vascular steal phenomenon.
- In most cases, flow increases early (first week), with little additional increase as the fistula matures (see CPG 5).[70-72] Failure of fistula flow to increase is a sign of access dysfunction (see CPG 4).

The Work Group concluded that the 3 advantages of wrist and elbow primary fistulae, as listed, outweigh the following 4 potential disadvantages:

- The vein may fail to enlarge and/or increase blood flow to satisfactory levels (ie, fail to mature).[23,24,73]
- Comparatively long maturation times (1 to 4 months) must elapse after creation of these fistulae before they can be used. Thus, the access must be created several months in advance of the anticipated need for dialysis or an alternative temporary method of vascular access must be used while the fistula matures (see CPG 1).
- In some individuals, the vein may be more difficult to cannulate than an AVG. However, this can be addressed by mobilizing the vein superficially.[74]
- The enlarged vein may be visible in the forearm and be perceived as cosmetically unattractive by some individuals.

The wrist fistula is the first choice of access type because of the following advantages:

- It is relatively simple to create.[61,75]
- It preserves more proximal vessels for future access placement.[23,24,73]
- It has few complications. Specifically, the incidence of vascular steal is low, and in mature fistulae, thrombosis and infection rates are low.[3,4,24,57,58,65,66]

The only major disadvantage of the wrist (radiocephalic) fistula is a lower blood flow rate (BFR) compared with other fistula types. If adequate flow to support the HD prescription is not achieved with a radiocephalic fistula within 4 months after appropriate evaluation for correctable or modifiable factors (see CPG 4), another type of access should be established (see CPG 1). The major drawback of a radiocephalic fistula is the relatively high primary failure rate (15%) and only moderate secondary patency rate at 1 year (62%).[76]

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The elbow (brachiocephalic) primary fistula is the second choice for initial placement of an access. Its advantages include the following:[62,63,68,77-79]

- It has a higher blood flow compared with the wrist fistula.
- The cephalic vein in the upper arm usually is comparatively easier to cannulate and is easily covered, providing a potential cosmetic benefit.

The disadvantages of the elbow (brachiocephalic) primary fistula include the following:[26,66,77-80]

- It is slightly more difficult to create surgically than a radiocephalic fistula.
- It may result in more arm swelling than a radiocephalic fistula.
- It is associated with an increased incidence of steal compared with a radiocephalic fistula.
- It is associated with a greater incidence of cephalic arch stenosis than a forearm radiocephalic fistula.

If a wrist radiocephalic or elbow brachiocephalic fistula cannot be created, the patient should be considered for a transposed basilic vein fistula. In some cases, a forearm graft can be a viable alternative to mature the venous system for an elbow fistula as a secondary access. Transposed brachiobasilic fistulae have several disadvantages compared with other fistulae:[62,66,79,81-83]

- The transposition procedure may create significant arm swelling and patient pain.
- They have a greater incidence of steal and arm swelling than other fistula types.
- They are more technically challenging, especially in obese individuals.

The NVAII, now recognized as the FFBI, is a CMS-mandated 3-year CKD Stage 5 Network improvement project emphasizing a fistula-first approach.[84-88] The Work Group agrees with the "mission statement" to "increase the likelihood that every eligible patient will receive the most optimal form of vascular access for him/her, in the majority of cases an arterial venous fistula." For FFBI to optimally succeed, all its recommendations must be followed (NVAII, www.fistulafirst.org; last accessed 2/20/2006). However, the Work Group recognizes that in some cases, the "fistula first at all costs" approach may not be the most cost-effective or optimal for each individual. A functional fistula is the goal, not the insertion of a fistula with a poor chance at maturing. A graft can be used as a "planned bridge" to a fistula, and failing forearm grafts can be converted to upper-arm fistulae. Similarly, fistulae at a lower level can be converted to more proximal fistulae.

AVGs have the following advantages:

- A large surface area and vessel available for cannulation initially.[64,89-91]
- They are technically easy to cannulate.[64]
- The lag-time from insertion to maturation is short. For PTFE-derived grafts, it is recommended that not less than 14 days should elapse before cannulation to allow healing and incorporation of the graft into local tissues,[25,64,92] although ideally, 3 to 6 weeks are recommended.

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- Multiple insertion sites are available.[26,64,67,90-94]
- A variety of shapes and configurations is available to facilitate placement.[64,67,89-92,94]
- It is easy for the surgeon to handle, implant, and construct the vascular anastomosis.[25,26,64,91,92,94-104]
- The graft is comparatively easy to repair either surgically[65,94,101,105-107] or endovascularly.[108-112]

The sum of the available data, until recently, supported PTFE grafts over other biological and other synthetic materials, based on lower risk for disintegration with infection, longer patency, better availability, and improved surgical handling. Biological grafts (bovine heterografts) have greater reported rates of complications compared with synthetic grafts.[91-93,100]

For nearly 2 decades, PTFE has been the material of choice for bridge grafts. However, during the past decade, modifications[113] and the use of other materials, such as PU,[114,115] cryopreserved femoral vein,[116,117] bovine mesenteric vein, and hybrids[118] with self-sealing composite material, have been developed and used.[119] None of these has shown any "survival" patency over plain PTFE, except for the composite/PU graft. The latter has an advantage because of its self-sealing property to be cannulated within hours, *if needed,* for dialysis. As a result, it can be placed without having to use a catheter for initiation of dialysis therapy, in some cases. Direct comparisons between PTFE and human umbilical cord vein grafts and other synthetic polymers have not been made.

The lure to construct AVGs using larger more proximal vessels should be resisted. Although these have higher flow and better initial function and/or patency, they limit potential sites for future placement.[23,25,73] A synthetic dialysis AVG is expected to last 3 to 5 years.[73] Grafts using smaller more peripheral vessels can experience more frequent thromboses that require treatment. However, these grafts have the advantage of preserving more proximal sites for new access creation should this become necessary in the future.[4,23-25] The 2 preferred graft site types are the antecubital loop graft and upper-arm curved graft. Femoral placement of access has been associated with proximal venous stenosis, which may be problematic later in patients receiving kidney transplantation.

Potential sites for arterial inflow include radial artery at the wrist, brachial artery in the antecubital fossa, brachial artery in the lower portion of the arm, brachial artery just below the axilla, axillary artery, and femoral artery. Potential sites for venous outflow include median antecubital vein, proximal and distal cephalic vein, basilic vein at the level of the elbow, basilic vein at the level of the upper arm, axillary vein, jugular vein, and femoral vein.

Fistulae (CPG 2.2)

A 70% AV "working" fistula access rate can be achieved, even in patients who have diabetes[85-88] and women.[84] Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS) indicate that the fistula can be cannulated as early as 1 month after construction.[120] Thus, an access that shows evidence of maturation failure on physical examina-

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tion or by using duplex ultrasound[72] should undergo investigation. A study found that combining venous diameter (>0.4 cm) and flow volume (>500 mL/min) increased the predictive power of adequate fistula maturation to 95% (19 of 20) versus neither criterion met (33%; 5 of 15).[72] Women were less likely to have an adequate outcome vein diameter of 0.4 cm or greater: 40% (12 of 30) compared with 69% in men (27 of 39). However, of note, the accuracy of experienced dialysis nurses in predicting eventual fistula maturity was excellent at 80% (24 of 30).

Many accesses with multiple outflow veins can be salvaged by ligation of side branches.[121,122] As more older patients have fistula constructions, the possibility of the access failing to mature is likely to increase.[123] Failure to mature should be evaluated by 6 weeks after construction by physical examination and, if needed, ultrasound.[72,124] Prompt correction should be undertaken.[125,126]

Exercises to Mature the Fistula (B−)

Isometric exercise has been shown to increase the diameter of forearm veins,[127] and exercise should be prescribed if there is sufficient lead time before surgery.

Dialysis AVGs (CPG 2.3)

Graft patency is independent of manufacturer,[128–130] unaffected by an external wrap around the graft,[131] and is not affected by wall thickness.[131,132] The provision of a cuff or hood at the venous outflow to enlarge the outflow and reduce shear stress has produced only a marginal increase in graft patency.[133–136] To control inflow or shear stresses, a variety of tapers have been examined at both arterial and venous anastomoses. There seems to be little effect from using a 6- to 8-mm graft compared with the standard straight 6 mm.[137] A straight 8 mm also can be used and gives the highest flows.[138] Arterial tapers are used to restrict inflow and reduce the risk for steal syndrome. Their effectiveness is questionable, and they may negatively affect patency and survival.[139]

As previously discussed in CPG 2.1, a variety of modifications to the graft or other materials is available to the surgeon.[113–119] Several studies are available to guide the interested reader.[140–142] Predictors for successful placement of AVGs have been analyzed.[143]

The neointimal hyperplasia that produces stenosis has been considered to be, in part, a reaction to injury. No improvement in patency was noted in an RCT that compared staples with standard sutures at the vascular anastamoses.[144] Use of nitinol surgical clips produces less intimal damage than conventional sutures,[145] but RCTs showing a resulting change in outcome are lacking.

It should be remembered that a short segment of graft material can be used to develop a predominant fistula at the elbow.[146]

Catheters and Port Catheter Systems (CPG 2.4)

Basic Principles

1. Long-term catheter systems—tunneled cuffed catheters (TCCs) and tunneled port catheter systems—should have their tips within the right atrium confirmed by fluoroscopy for optimal flow.

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2. Short-term catheter tips should be in the superior vena cava (SVC) and confirmed by using chest radiograph or fluoroscopically at the time of placement before initiating dialysis therapy.
3. Uncuffed HD catheters should only be used in hospitalized patients and for less than 1 week. Uncuffed femoral catheters should only be used in bed-bound patients.
4. There should be a plan to: i) discontinue, or ii) convert any short-term catheter to a long-term catheter within 1 week.
5. Long-term catheters and port catheter systems, if possible, should not be placed on the same side as a maturing AV access.
6. Femoral catheters should be a suitable length to deliver high-volume flow and be positioned to minimize recirculation. One that does not reach the IVC frequently cannot deliver 300 mL/min. Longer catheters (24 to 31 cm) are more likely to reach the desired position, although there is more resistance from the catheter length.
7. There currently is no proven advantage of 1 long-term catheter design over another, although this area is undergoing a great deal of study. Catheters capable of a rapid BFR (>350 mL/min at prepump pressures not more negative than 250 mm Hg) are preferred. Catheter choice should be based on local experience, goals for use, and cost.
8. ***Pediatric exception:*** Some pediatric data exist suggesting that the twin-catheter system may provide better performance than the standard dual-lumen catheter configuration. Please refer to the Pediatric Guidelines.
9. Dialysis port catheter systems may be used in lieu of long-term catheters for a bridge access or as a permanent access for patients.

Catheter devices can be defined according to design, intent, and duration of use. For the entirety of the discussion, catheters will be referred to as acute short-term noncuffed catheters (NCCs) or long-term TCCs intended as access for dialysis over weeks to months. The term right arterial catheter should be avoided. They are either NCCs and placed predominantly for acute use (3 to 5 dialyses within 1 week) or TCCs and placed when the need for dialysis therapy is believed to be longer than 1 week. Long-term catheters usually are tunneled. The catheters themselves usually are dual lumen and can be coaxial (now unusual) or "double D" (most common) and are either stepped (ie, the arterial and venous tips are staggered by 1 to 2 cm) or split so that the tips are not next to each other. Newer designs incorporate a spiral separator allowing either lumen to be used as the arterial port catheter system.

Port catheter systems are a distinct kind of catheter-based device system in which the catheter tubing is connected to a subcutaneously placed device. In the only port device currently in use for HD, access to the catheter lumen occurs percutaneously by using a buttonhole technique. These port catheter systems have a pinch valve mechanism that requires special cannulation needles to open the valves accessing the circulation.

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Tunneled Cuffed Venous Catheters

Tunneled cuffed venous catheters have been shown to have the following advantages, relative to other access types:

1. They are universally applicable.
2. They can be inserted into multiple sites relatively easily.
3. No maturation time is needed, ie, they can be used immediately.
4. Skin puncture not required for repeated vascular access for HD.
5. They do not have short-term hemodynamic consequences, eg, changes in cardiac output or myocardial load.
6. They have lower initial costs and replacement costs.
7. They possess the ability to provide access during a period of months, permitting fistula maturation in patients who require immediate HD.[73,147-155]
8. They facilitate correcting thrombotic complications.[147,156-158]

Tunneled cuffed venous catheters possess the following disadvantages relative to other access types:

1. High morbidity caused by:
   - Thrombosis[148,156-158] and
   - Infection.[30,148,159]
2. Risk for permanent central venous stenosis or occlusion.[30,148,160,161]
3. Discomfort and cosmetic disadvantage of an external appliance.
4. Shorter expected use-life than other access types.[64,69,156,162]
5. Overall lower BFRs, requiring longer dialysis times.[163]

Tunneled cuffed venous catheters should be placed in an area where ultrasound guidance and fluoroscopy are available. The preferred site is the right internal jugular vein because this site offers a more direct route to the right atrium than the left-sided great veins. Catheter insertion and maintenance in the right internal jugular vein are associated with a lower risk for complications compared with other potential catheter insertion sites.[164-166] Catheter placement in the left internal jugular vein potentially puts the left arm's vasculature in jeopardy for a permanent access on the ipsilateral side. Catheter placement in the left internal jugular vein may be associated with poorer BFRs and greater rates of stenosis and thrombosis.[150,166] Femoral and translumbar vein placement are associated with the greatest infection rates compared with other sites.[167] Catheters should not be placed in the subclavian vessels on either side because of the risk for stenosis,[30,168] which can permanently exclude the possibility of upper-extremity permanent fistula or graft. Catheters should not be placed on the same side as a slowly maturing permanent access. Catheter-induced central vein stenosis is related to the site of insertion,[169,170] number and duration of catheter uses, and occurrence of infection.[170,171]

Ultrasound insertion has been shown to limit insertion complications.[172-174] Evidence is sufficient to recommend that ultrasound guidance be used for all insertions because it minimizes inadvertent arterial cannulation.[175,176] Fluoroscopy allows ideal catheter tip placement[177,178] to maximize blood flow.[179] At the time of placement, the

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tip(s) of the catheter should be in the midatrium, with the arterial lumen facing the mediastinum.

Use of catheters presents a conundrum because of the need for immediate vascular access versus the risk for complications from prolonged catheter use.[180] Blood flow for dialysis obtained from catheters typically is less than that obtained from fistulae or grafts.[2] Catheter length becomes crucial when TCCs are placed in the femoral area or through the translumbar or transhepatic routes.[181] Correlations between arterial prepump or venous return pressures and dialyzer blood flows are not linear.[182,183] It is possible to develop an optimal relationship between catheter length and diameter to achieve standardized (average, low, and high) blood flows regardless of the lengths of the catheters by incorporating the pressure-flow relationships, as well as Poiseuille's equation.[183]

Use of catheters as first choice for long-term vascular access is discouraged because of infection, susceptibility to thrombosis, and inconsistent delivery of blood flow. In patients with documented inadequate vascular access anatomy, use of catheters is feasible with both double-lumen[184-188]and twin-catheter systems.[189-191] However, exceptions may occur in children.

In the United States, the demand for greater blood flows to reduce treatment times has resulted in catheters with larger lumens being placed. A variety of catheters can consistently deliver a flow greater than 350 mL/min to the dialyzer at prepump pressure of −200 to −250 mm Hg. The decision to use a step or a split design should be decided by local preferences. In general, all catheters will develop recirculation at some point,[182,192] particularly if the arterial and venous blood tubing are reversed for any reason.[193] This is minimized by using a split-tip catheter,[194,195] but other designs are likely to produce the same effect.

The decision to use the femoral vein for long-term access (catheter or graft) as reported by some[196,197] should be undertaken with great care. Any patient who has the option of undergoing a kidney transplantation should not have a femoral catheter placed to avoid stenosis of the iliac vein, to which the transplanted kidney's vein is anastomosed. The Work Group recommends the concept of shared governance in this type of decision,[198] with both dialysis staff and transplant team planning long-term access for such patients. There are no data on the effect of catheter length from the femoral vein site. Although length increases resistance, it also reaches anatomic sites with greater IVC flow. If dialysis blood flow is less than 300 mL/min from a properly placed femoral catheter, guidewire exchange to a longer catheter should be considered.

Noncuffed Double-Lumen Catheters

These catheters are suitable for percutaneous bedside insertion and provide acceptable BFRs (300 mL/min) for temporary HD.[64,147,161,199,200] These catheters are suitable for immediate use, but have a finite use-life and therefore should not be inserted until they are needed.[64,147,161] The rate of infection for internal jugular catheters suggests they should be used for no more than 1 week.[60,64,147,161,201,202] Infection and dislodgment rates for femoral catheters require that they be left in place for no more than 5 days and only in bed-bound patients with good exit-site care. To minimize recirculation, femoral catheters

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should be at least 19 cm long to reach the IVC.[203] The Work Group believes that TCCs are preferred for longer durations of HD therapy over NCCs because they are associated with lower infection rates and greater BFRs.[60,64,147,149,151-153,155,161,184,201-204] Short-term catheters may be used for up to 1 week. Beyond 1 week, the infection rate increases exponentially. Actuarial analysis of 272 catheters (37 TCCs versus 235 NCCs) showed a difference in infection rates by 2 weeks.[205] Infection rates per 1,000 days at risk for NCCs were more than 5 times as great as with internal jugular TCCs and almost 7 times greater with femoral NCCs.[205]

Ultrasound-directed cannulation of NCCs minimizes insertion complications, as it does with TCCs, and should be used when available.[206,207] Because most NCCs are placed at the bedside, the need for a postinsertion chest radiograph after internal jugular or subclavian insertion is mandatory to confirm the position of the catheter tip in the SVC and exclude such complications as pneumothorax and hemothorax.[28,64,147,151,208-212] Although there are no studies reporting on the safety of patients with NCCs going home while awaiting placement at a dialysis center, the Work Group believes that the risk for infection, inadvertent removal, hemorrhage, air embolism, and patient comfort mandates that patient safety come first. Therefore, a patient with an NCC should not be discharged. A short-term catheter can be converted to a TCC if there is no evidence of active infection.[213]

Port Catheter Systems

In an effort to surmount many of the infection problems associated with long-term catheters, totally implantable access systems have been designed.[214,215] Clinical data support the use of subcutaneous HD access systems as a bridge device[216-218] in patient populations at greater risk for fistula maturation failure or needing longer periods to mature fistulae (>1 operation or multiple attempts need to be made). Studies also documented the utility of subcutaneous HD access systems in catheter-dependent patients who have exhausted other access options[219] and in children.[220] The most significant limitation of these devices has been infection, particularly of the implantation pocket. Although these can be treated successfully,[221] prevention is key. Recommended procedures for accessing and maintaining these devices are mandatory to achieve optimal device performance.

Complications of catheter access are detailed more fully in CPG 7, and accessing the patient's circulation is discussed in CPG 3.

LIMITATIONS

The recommendations made in this section are based on the best currently available information and basic principles of surgery. No RCTs will ever be performed comparing the 3 access types available, nor should they be in view of the known risks of catheters. However, developments in the future of synthetic materials or the prevention of neointimal hyperplasia may permit such trials.

SUMMARY

Management of the patient who requires HD access for KRT demands continuous attention from the VAT. With the increase in incidence of HD-dependent patients with CKD

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within our population, the multidisciplinary KDOQI CPGs and CPRs presented provide a pathway and strategy for HD access insertion and/or creation. The most appropriate initial access depends on immediate need for HD, history and physical examination findings, and suitability of available veins in the extremity. Percutaneous catheter-based access affords the luxury of immediate access and absence of requirement for cannulation; however, these devices are plagued by their propensity for infection, thrombosis, inadequate blood flow, and—most importantly—damage to large central veins, leading to stenosis and jeopardizing long-term permanent access. The fistula access, while at times less successful in the immediate short term, is always the preferred long-term access type because of its greater longevity, fewer interventions for maintenance, and lower infection rates. The surgeon should focus on sites distally on the extremity, reserving proximal sites for potential future access insertions should the initial access site fail. In the absence of a suitable vein for a fistula, prosthetic access can be considered. When all sites in the upper extremities have been exhausted, the lower extremity or chest should be considered for access creation. Long-term catheters and port catheter systems should be reserved for last except in those with severe comorbidities, such as congestive heart failure (CHF) and severe peripheral vascular disease (PVD), the very elderly, those with inadequate vascular anatomy, or those with limited life expectancy.

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GUIDELINE 3. CANNULATION OF FISTULAE AND GRAFTS AND ACCESSION OF HEMODIALYSIS CATHETERS AND PORT CATHETER SYSTEMS

The use of aseptic technique and appropriate cannulation methods, the timing of fistula and graft cannulation, and early evaluation of immature fistulae are all factors that may prevent morbidity and may prolong the survival of permanent dialysis accesses.

3.1 Aseptic techniques:

3.1.1 For all vascular accesses, aseptic technique should be used for all cannulation and catheter accession procedures. (See Table 2.) (A)

3.2 Maturation and cannulation of fistulae:

3.2.1 A primary fistula should be mature, ready for cannulation with minimal risk for infiltration, and able to deliver the prescribed blood flow throughout the dialysis procedure. (See Table 3.) (B)

3.2.2 Fistulae are more likely to be useable when they meet the Rule of 6s characteristics: flow greater than 600 mL/min, diameter at least 0.6 cm, no more than 0.6 cm deep, and discernible margins. (B)

3.2.3 Fistula hand-arm exercise should be performed. (B)

3.2.4 If a fistula fails to mature by 6 weeks, a fistulogram or other imaging study should be obtained to determine the cause of the problem. (B)

3.3 Cannulation of AVGs:

Grafts generally should not be cannulated for at least 2 weeks after placement and not until swelling has subsided so that palpation of the course of the graft can be performed. The composite PU graft should not be cannulated for at least 24 hours after placement and not until swelling has subsided so that palpation of the course of the graft can be performed. Rotation of cannulation sites is needed to avoid pseudoaneurysm formation. (See Table 4.) (B)

3.4 Dialysis catheters and port catheter systems:

Infection-control measures that should be used for all HD catheters and port catheter systems include the following:

3.4.1 The catheter exit site or port cannulation site should be examined for proper position of the catheter/port catheter system and absence of infection by experienced personnel at each HD session before opening and accessing the catheter/port catheter system. (B)

3.4.2 Changing the catheter exit-site dressing at each HD treatment, using either a transparent dressing or gauze and tape. (A)

3.4.3 Using aseptic technique to prevent contamination of the catheter or port catheter system, including the use of a surgical mask for staff and patient and clean gloves for all catheter or port catheter system connect, disconnect, and dressing procedures. (A)

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Table 2. Skin Preparation Technique for Subcutaneous AV Accesses

- Locate, inspect and palpate the needle cannulation sites prior to skin preparation. Repeat prep if the skin is touched by the patient or staff once the skin prep has been applied, but the cannulation not completed.
- Wash access site using an antibacterial soap or scrub and water.
- Cleanse the skin by applying 2% chlorhexidine gluconate/70% isopropyl alcohol or 70% alcohol and/or 10% povidone iodine as per manufacturer's instructions for use.

Notes:

- 2% chlorhexidine gluconate/70% isopropyl alcohol antiseptic has a rapid (30 s) and persistent (up to 48 hr) antimicrobial activity on the skin. Apply solution using back and forth friction scrub for 30 seconds. Allow area to dry. Do not blot the solution.
- Alcohol has a short bacteriostatic action time and should be applied in a rubbing motion for 1 minute immediately prior to needle cannulation.
- Povidone iodine needs to be applied for 2-3 minutes for its full bacteriostatic action to take effect and must be allowed to dry prior to needle cannulation.
- Clean gloves should be worn by the dialysis staff for cannulation. Gloves should be changed if contaminated at any time during the cannulation procedure.
- New, clean gloves should be worn by the dialysis staff for each patient with proper infection control measures followed between each patient.

RATIONALE

There is considerable evidence that the use of maximal sterile precautions, as opposed to clean aseptic technique, for cannulation of AV accesses and catheter accession is both impractical and unnecessary.[222-225] However, the importance of strict dialysis precautions[226] and aseptic technique[222] cannot be overemphasized in the prevention and minimization of all access infection.[227] Despite the general acceptance of the importance of standard precautions for hand washing and glove changes, these simple acts to minimize transmission of disease frequently are skipped. An audit in a selection of Spanish HD units examined opportunities to wear gloves and wash hands per the standard preventive guidelines (high-risk activities of connection, disconnection, and contact between patients during dialysis). Gloves were worn by only 19% and hands were washed after

Table 3. Technique for Mature AVF Cannulation

Technique	Rationale
After skin preparation, apply a tourniquet to increase the venous pressure, and pull skin taut in opposite direction of needle insertion. Avoid excessive pressure to the cannulation site to prevent flattening of the vessel. Stabilize but do not obliterate the vessel.	Compresses peripheral nerve endings between epidermis and dermis. Increases surface tension thereby facilitating smoother incision of skin with less surface area contacting cutting edge of needle. Enables better stabilization of graft or vessel to be cannulated.
For easily palpated vessel, use approximately 25° angle with the bevel up. Arterial needle placement can be in anterograde (up or in the direction of the blood flow) or retrograde (down or against the direction of blood flow). The venous needle should always be in the same direction as the blood flow.	Less steep angles increase risk of dragging cutting edge of needle along surface of vessel. Steeper angles increase risk of perforating underside (backwall) of vessel. Needle direction of the venous needle in the same direction as the blood flow will prevent excessive pressure at the needle site. The arterial needle in either direction will not increase the risk of recirculation as long as the access blood flow is greater to the blood pump setting.
Once the vessel has been penetrated: • Advance the needle slowly with cutting edge facing top of vessel and do not rotate axis.	Any manipulation may traumatize the intima of the vessel. The use of a backeye needle will eliminate the need to rotate the needle due to poor flows.
• Tape the needle at the same angle or one similar to the angle of insertion.	Pressing the needle shaft flat against the skin moves the needle tip from the desired position within the vessel lumen.
• Remove needle at same or angle similar to angle of insertion, and NEVER APPLY PRESSURE BEFORE NEEDLE IS COMPLETELY OUT.	Avoid trauma to any intima by dragging cutting edge along it. Avoid pressing cutting edge into intima when applying pressure for HD.

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Table 4. Technique for AVG Cannulation

Technique	Rationale
After skin preparation, pull skin taut in opposite direction of needle insertion. Avoid excessive pressure to the cannulation site to stabilize and prevent flattening of the graft material.	Compresses peripheral nerve endings between epidermis and dermis. Facilitates smoother incision of skin with less surface area contacting cutting edge of needle. Enables better stabilization of graft or vessel to be cannulated.
Use approximately 45° angle of insertion.	Less steep angles increase risk of dragging cutting edge of needle along surface of vessel. Steeper angles increase risk of perforating underside of vessel.
Once the vessel has been penetrated, there are basically 2 methods employed in current practice:	
a) Advance the needle slowly with cutting edge facing top of vessel and do not rotate axis.	a) Any manipulation may traumatize the intima of the vessel. This is the preferred method for routine AVG cannulation technique.
b) For a deep, hard to palpate AVG immediately rotate the axis of the needle 180° and advance slowly with bevel cutting edge facing bottom of the vessel.	b) Rotating the axis avoids traumatizing the top of intima and prevents the tip of the needle from entering the backside of the graft material. This should only be utilized when the graft backwall location is difficult to determine and the risk of continuing the needle advancement into the backwall is high.
Tape the needle at the same angle or one similar to the angle of insertion.	Pressing the needle shaft flat against the skin moves the needle tip from the desired position within the vessel lumen.
Remove needle at same or angle similar to angle of insertion, and NEVER APPLY PRESSURE BEFORE NEEDLE IS COMPLETELY OUT.	Avoid trauma to any intima by dragging cutting edge along it. Avoid pressing cutting edge into intima when applying pressure for HD.

patient contact on only 32% of all occasions.[228] Mandatory hand washing before patient contact occurred only 3% of the time. A decade later, wearing of gloves improved to 92%, but the practice of hand washing before or after these patient-oriented procedures remained low at 36% after and 14% before such activities.[229] Greater adherence was found in acute than in long-term HD units. A greater patient-nurse ratio independently influenced hand-washing rates. With the increasing microbial resistance to mainstream antibiotics,[230] infection prevention must be considered the first rule of vascular access maintenance.[231] Data from prospective studies in both Canada and the United States clearly show that great variability exists between centers in infection rates, indicating the need to have not only a national registry, but also a local (ie, in-center) infection surveillance program.[232-234] Increased awareness at the individual center level is key to stemming access infection and its extreme consequences, such as endocarditis and metastatic infections (eg, spinal abscesses), conditions that are disabling at best, sometimes fatal, and prohibitively costly to treat.[235,236]

In the effort to prevent infection, it is not only staff that must be vigilant to potential breaks in technique and the need for the appropriate use of masks. Patients also must be taught that lapses in their use of masks and poor personal hygiene are known to increase their risk for infection. *Patients with type 2 diabetes are at increased risk for nasal staphylococcal carriage and catheter-related bacteremia (CRB) as a result.*[237,238]

Maturation and Cannulation of Fistulae (CPG 3.2)

If the fistula is created with both adequate inflow artery and outflow vein, the increased flow in the vein should be immediately apparent postoperatively, evidenced by larger appearance and the presence of a continuous audible and palpable thrill along the vein, as well as actual flow measurements.[126] Experienced staff should examine the fistula and the outflow vein each time the patient comes to dialysis to monitor the maturation progress. Aspects of the physical examination are summarized in Table 5. The ability of

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Table 5. Access Physical Examination

Exam Steps	Fistula (Normal)	AVG (Normal)	Stenosis or Poor Maturation (Abnormal)	Infection or Steal Syndrome (Abnormal)
Look	Well developed main venous outflow, no irregularitiesor areas or aneurysm formations, areas of straight vein that can be used for cannulation. Vessel partially collapses when arm is elevated above head.	Uniform sized graft in a loop or straight configuration. No irregular areas or aneurysm formations with organized site rotation used for cannulation sites.	Fistula with poor maturation—multiple venous outflow veins (accessory veins), poorly defined cannulation areas. Fistula: Stenosis can occur in artery or any of the venous outflow veins. Look for a narrowing of the outflow vein or aneurysm formations. Fistula or Graft: Dilated neck veins or small surface collateral veins in the arm or neck above the area of access.	*Infection:* Redness, swelling, broken skin, drainage, induration. *Steal Syndrome:* Hand of the access limb may appear discolored due to poor arterial blood flow to the hand. Check nail beds, fingers and hand for skin color changes.
Listen with a stethoscope	Low pitch continuous diastolic and systolic	Low pitch continuous diastolic and systolic	High pitch discontinuous systolic only	*Steal Syndrome:* Fistula may have a very strong bruit
Feel with your finger tips	Thrill at the arterial anastomosis and throughout the entire outflow vein that is easy to compress	Thrill strongest at the arterial anastomosis, but should be felt over entire graft and easy to compress	Fistula: Pulse at the site of a stenotic lesion Pulse has a water-hammer feel. Graft: Thrill and/or pulse strong at the site of a stenotic lesion pulse has a water-hammer feel. A graft with a low intra-access blood flow feels mushy. Local area of the graft that feels mushy or irregular in shape can be a site of aneurysm formation.	*Infection:* Warm to touch, swelling *Steal Syndrome:* Feel bilateral limbs (hands and fingers) and compare for the access limb to be the same as the nonaccess limb. Compare temperature, grip strength and range of motion, and any complaints of pain. If the access limb has any major differences than the nonaccess limb, consider steal syndrome.

"trained, experienced dialysis nurses" to accurately predict eventual fistula maturity is excellent.[72] This is even more reason to have a protocol for regular clinical examination in place in dialysis centers to teach the skills of physical examination (see CPG 4 and CPG 5) to all staff members and assess the developing fistula and not focus on the access in current use only. The optimal time to do this examination is before fluid removal because hypotension can confound the findings. Patients who are not yet on dialysis therapy should be taught how to perform self-examination and be given appropriate contact information for questions and concerns. Poor prognostic signs, such as significant decrease in the thrill, should be referred immediately back to the surgeon or the interventionalist for prompt evaluation and intervention. At a minimum, all newly created fistulae must be physically examined by using a thorough systematic approach by a knowledgeable professional 4 to 6 weeks postoperatively to ensure appropriate maturation for cannulation.[239] The steps for cannulation are summarized in Table 3.

Protocol for Initial Cannulation of AVFs

If the physical assessment has shown that the fistula is adequately matured, ideally, the next step is to perform a trial cannulation. In general, the earliest that this situation occurs is when the vein diameter is greater than 0.4 cm, has a flow greater than 500 mL/min,[59] and at least 1 month has elapsed since fistula creation[60] (Table 3). If possible, the trial cannulation of the fistula should be done on a nondialysis day. This serves to eliminate any potential complications associated with the administration of heparin.

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If a trial cannulation is not possible, it is best to perform the initial cannulation of the new access at the patient's midweek HD treatment. Performing the initial cannulation midweek helps avoid such complications as fluid overload and elevated chemistry test results associated with the weekends.

To ensure that the needle is placed properly, needle placement should be confirmed with a normal saline flush before connecting the needles to the blood pump and starting the pump. Blood return alone is not enough to show good needle placement. One option to easily check for proper needle placement is the use of "wet" needles. The needle is purged of air and the saline in the attached syringe is used to flush the needle. If an infiltration has occurred, the normal saline is less harmful to the surrounding AVF tissue. The wet needle also prevents the risk for a blood spray or spill if dry needles are used for cannulation and the caps are opened to "bleed out" the needle from the air. The opening of the needle is a risk for blood exposure to the dialysis team member, patient, and nearby patients. For these reasons, use of a wet needle is a safer technique for the AVF, patient, and dialysis team members, especially for the initial AVF cannulation. This option should be considered as part of the dialysis unit's cannulation policy and procedures. The recommended procedure is described next.

1. Attach a 10-mL syringe filled with 8 mL of normal saline solution to the AVF needle, but do not prime the needle until immediately before the cannulation.
2. Grasp the fistula needle by the butterfly wings and prime the needle with normal saline until all the air is purged. Clamp the needle closed. Remove the protective cap and immediately proceed with the cannulation technique.
3. When the needle has advanced into the vessel, blood flashback will be visible (the needle may need to be unclamped to see the blood flashback) and, if visible, aspirate back 1 to 5 mL with the 10-mL syringe. Flush the needle with the normal saline solution and clamp. The syringe must aspirate and flush with ease. Monitor for signs or symptoms of infiltration. Patients usually experience immediate sharp pain upon infiltration of saline or blood into the tissues.

Needle selection for the initial cannulation is critical. One method used to select the appropriate needle size is a visual and tactile examination. This examination allows the cannulator to determine which needle gauge would be most appropriate, based on the size of the vessels in the fistula. Alternately, place 17 G and 16 G needles with the protective cap in place (prevents a needle stick) over the cannulation site. Compare the vein size with the needle size with and without the tourniquet applied. If the needle is larger than the vein with the tourniquet, it is too large and may infiltrate with cannulation. Use the needle size that is equal to or smaller than the vein (without the tourniquet) for the cannulation.

The smallest needle available, usually a 17 G, typically is used for initial cannulation attempts. It is important to keep in mind that blood flow delivered by a 17 G needle is limited. Prepump arterial monitoring is recommended to ensure that blood pump speed does not exceed that which the needle can provide. Prepump arterial pressure should not exceed −250 mm Hg. Based on performance of the fistula using a 17 G needle, the decision to increase the needle size for subsequent cannulation can be made.

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A needle with a back eye should always be used for the arterial needle to maximize the flow from the access and reduce the need for flipping the needle.

1. Apply a tourniquet to the access arm.
2. After disinfecting the access site per unit protocol, carefully cannulate the fistula, using a 25° insertion angle.
3. When blood flash is observed, flatten the angle of the needle, parallel to the skin, and advance slowly. When the needle is in the vessel, remove the tourniquet and tape the needle securely per unit protocol.
4. Assess for adequate blood flow by alternately aspirating and flushing the needle with a syringe.
5. Assess carefully for signs of infiltration, ie, pain, swelling, or discoloration.
6. Repeat steps 1 to 5 for the second needle.

Cannulation Tips

1. A fistula that only works with a tourniquet in place is still underdeveloped, usually because of inflow stenosis, and needs more time or reevaluation by the VAT before use.
2. The combined use of the new fistula and bridge vascular access (ie, TCC as a return for blood) may be necessary until the fistula is well developed.
3. Cannulation performed at a nonturnover time may provide more time for the cannulation procedure.

Infiltrations, Problems, and Tips

1. Infiltrations with the cannulation can occur before dialysis, during dialysis with the blood pump running, or after dialysis with the needle removal.
2. Monitor closely for signs and symptoms of infiltration. A quick response to a needle infiltration can help minimize damage to the access.
3. If the infiltration occurs after the administration of heparin, care must be taken to properly clot the needle tract and not the fistula. In some cases, the decision to leave the needle in place and cannulate another site may be appropriate. The immediate application of ice can help decrease the pain and size of the infiltration and may decrease bleeding time.
4. Use caution when taping needles. Avoid lifting up on the needle after it is in the vein. An improper needle flip or taping procedure can cause an infiltration.
5. If the fistula is infiltrated, it is best to rest the fistula for at least 1 treatment. If this is not possible, the next cannulation should be above the site of the infiltration. If the patient still has a catheter in place, restart use of the fistula with 1 needle and advance to 2 needles, larger needle size, and greater BFRs as the access allows.
6. Proper needle removal prevents postdialysis infiltrations. Apply the gauze dressing over the needle site, but do not apply pressure. Carefully remove the needle at approximately the same angle as it was inserted. This prevents dragging the needle across the patient's skin. Using too steep of an angle during needle removal may cause the needle's cutting edge to puncture the vein wall.
7. Do not apply pressure to the puncture site until the needle has been completely removed.

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Fistula Hand-Arm Exercise (CPG 3.2.3)

Strengthening the forearm by using isometric exercises to increase handgrip strength (eg, squeezing a rubber ball with or without a lightly applied tourniquet) may increase blood flow, thereby enhancing vein maturation,[240] and has been shown to significantly increase forearm vessel size,[127,241] thereby potentially increasing flow through a fistula created using these vessels. The resulting muscle mass increase also may enhance vein prominence. Exercise also may decrease superficial fat. Correction of anemia also could increase cardiac output and decrease peripheral resistance, potentially resulting in increased flow through the fistula.

Access Flow for Dialysis in Fistulae (CPG 3.3)

After appropriate physical examination, a fistulogram is the gold standard for evaluating poor maturation of the fistula if the patient is already on dialysis therapy. Use of a nonnephrotoxic contrast material, carbon dioxide, or ultrasound should be used for patients not yet on dialysis therapy. Although a fistula can maintain patency at lower blood flows than grafts, thrombosis still occurs and, if not treated promptly, can lead to permanent loss of the access. Thrombosis rates can be reduced by prospective correction of problems.[242] Delivery of dialysis is flow dependent: access flow less than 350 mL/min is likely to produce recirculation and inadequate delivery of dialysis. (See the HD Adequacy Guidelines.) Some centers have used diluted contrast (25%), and there are now published data that suggest this diluted contrast does not adversely impact residual kidney function.[639] The images are of acceptable quality. The appropriate intervention for poor maturation is based on the cause of the dysfunction and may involve PTA of stenotic lesions, ligation or occlusion of vein branches (if the problem is simply > 1 major outflow vein),[122,243] and/or surgical intervention, including revision of the anastomosis.[75,125,126]

Cannulation of AVGs (CPG 3.4)

Manufacturers' guidelines are based on the time needed for tissue-to-graft incorporation, thereby preventing the possibility of a hematoma dissecting along the perigraft space. However, most patients experience significant tissue swelling as a result of the tunneling, and palpation of the graft is difficult for the cannulator and painful for the patient.

Placement of a graft that allows for early cannulation may be advantageous in the patient who needs to begin dialysis therapy, has no other access, and does not have veins suitable for a fistula. Such an access would preclude the necessity to place a catheter while a conventional graft matures. This type of graft confers no additional benefit beyond early cannulation.[114,119,128]

Biografts are more likely to become aneurysmal than PTFE grafts,[116] and cannulation techniques should be a hybrid of the techniques for a graft regarding depth of the access and the texture of an autogenous vein. Rotation of cannulation sites should be observed in these grafts; however, constant cannulation (buttonhole) has not been studied.[244]

Dialysis Catheters and Port Catheter Systems (CPG 3.5)

A dislodged (cuff exposed) or potentially infected catheter or exit site requires further assessment and possibly an intervention before being deemed safe to access for dialysis.

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Table 6. Considerations for Accessing Catheters and Cleansing Catheter Exit Sites

Prepare procedure site using dialysis precautions
Conduct procedures using aseptic technique (correct hand-washing, masks for patient and staff, "no-touch" technique, and disposable clean gloves).
Chlorhexidine 2% with 70% alcohol is the preferred solution for cleansing of long-term catheter sites.[a] For patients with sensitivities to chlorhexidine 2% with 70% alcohol, chlorhexidine aqueous[a] may be used instead. For patients with sensitivities to chlorhexidine aqueous, povidone solution[b] may be used.
Skin cleansing should include the following steps: • Apply solution/swab in a circular motion working from catheter exit site outwards. • Cover an area 10 cm in diameter. • Repeat this step twice. Do *not* rinse off or blot excess solution from skin. • Allow solution to dry completely before applying dressing.
To cleanse the connection between any CVC hub and cap use 2 swabs: • Grasp connection with 1 swab. • Use second swab to clean from catheter connection up catheter for 10 cm. • Cleanse hub connection site and cap vigorously with the first swab. Discard swab. • Do not drop a connection site once it is cleaned.
To cleanse the section of the catheter that lies adjacent to the skin, gently swab the top and underside of the catheter starting at the exit site and working outwards.

a. Check catheter manufacturer's warnings about effect of disinfectants on catheter material
b. Use according to manufacturer's directions.

The Centers for Disease Control and Prevention (CDC) has no preference between transparent dressing and gauze, except in the case in which the exit site is oozing, which requires gauze.[222] Standard practice is to clean the exit site and redress at each dialysis treatment (see Table 6).

Airborne contaminants from both patients and staff are prevented best by the use of surgical masks when the catheter lumens or exit site are exposed. Wearing clean gloves and avoiding touching exposed surfaces further decreases the risk for infection. Aseptic technique includes minimizing the time that the catheter lumens or exit site are exposed.[222,226] Manufacturers' directions should be adhered to for the types of disinfectants recommended for safe cleaning of the skin and device. If not contraindicated, the CDC recommends use of 2% chlorhexidine,[222] shown to be superior to povidone-iodine.[245,246] Careful attention to hub care can decrease the CRB rate almost 4-fold to a rate approaching 1 episode/1,000 days.[247]

LIMITATIONS

Many of the guidelines are based on good standards of clinical practice. Those relating to the use of "aseptic" technique follow the recommendations of the CDC. It is unlikely that randomized trials will ever be done in this area.

AUXILLARY MATERIALS

Establishing Constant-sites in Native Fistulae by Using Standard Sharp Fistula Needles

1. Perform a complete physical assessment of the fistula and document the findings.
2. Select the cannulation sites carefully. Consider straight areas, needle orientation, and ability of the patient to self-cannulate. Sites should be selected in an area without aneurysms and with a minimum of 2 inches between the tips of the needles.

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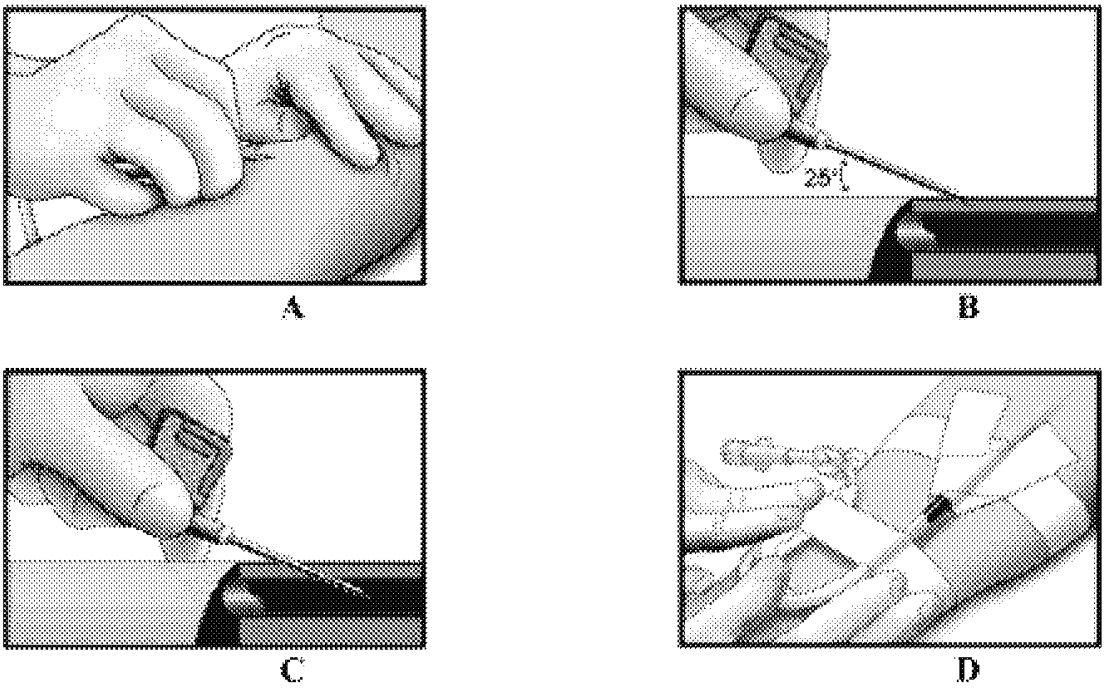
Figure 1. Starting a buttonhole. Reproduced with permission from Medisystems Inc.



3. Remove any scabs over the cannulation sites.
4. Disinfect the cannulation sites per facility protocol.
5. Using a sharp fistula needle, grasp the needle wings and remove the tip protector. Align the needle cannula, with the bevel facing up, over the cannulation site and pull the skin taut (Fig 1A).

- Cannulate the site at a 25° angle; self-cannulators may require a steeper angle (Fig 1B). It is important to cannulate the developing constant-site access in exactly the same place, using the same insertion angle and depth of penetration each time.* This requires that a single cannulator perform all cannulations until the sites are well established.
- A flashback of blood indicates the needle is in the access. Lower the angle of insertion. Continue to advance the needle into the fistula until it is appropriately positioned within the vessel (Fig 1C).
- Securely tape the fistula needle (Fig 1D) and proceed with dialysis treatment per facility protocol.

*Note: It takes approximately 6–10 cannulations using a sharp needle to create a scar tissue tunnel track. Arterial and venous sites may not develop at the same rate. Once a scar tissue tunnel track is well formed, the antistick dull bevel needles should be used. If standard sharp needles are used beyond the creation of the buttonhole sites, the scar tissue tunnel can be cut. More pressure and more needle manipulation will be required to advance the antistick needle down the tunnel track. This can lead to bleeding or oozing from the needle site during use on HD. The sharp needle can also puncture the vessel at a new site or cause an infiltration. The quick transition to the antistick needle will preserve the integrity of the buttonhole site and prevent complications.

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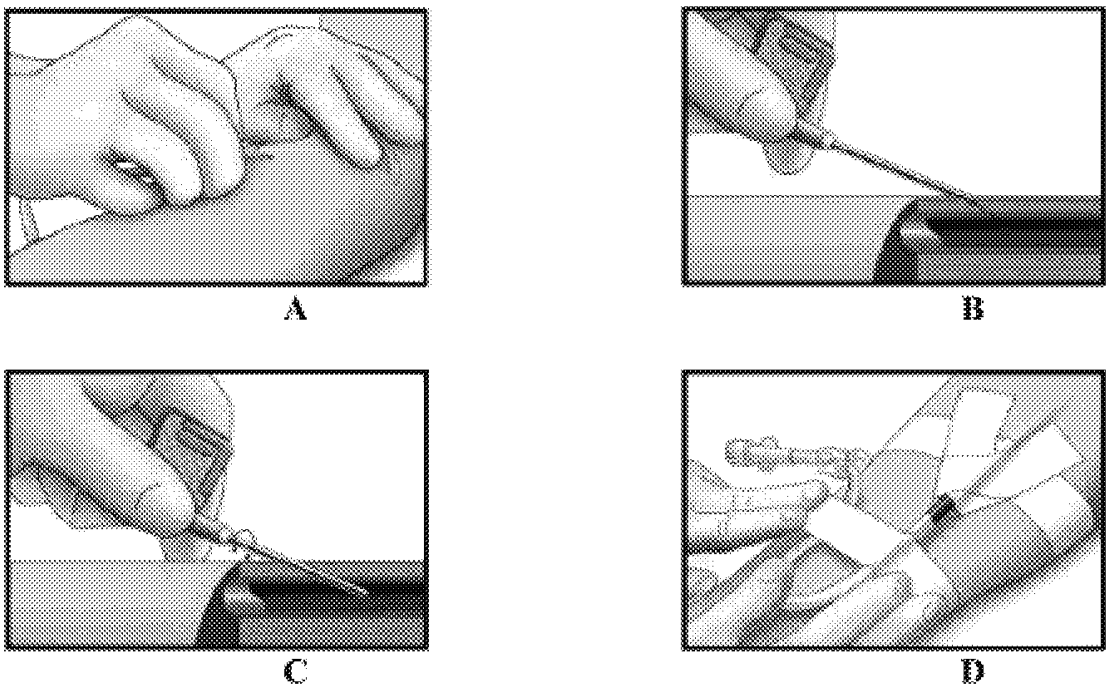
Figure 2. Cannulating a buttonhole. Reproduced with permission from Medisystems Inc.



Cannulating Mature Constant Sites in Native Fistulae Using an Antistick Dull Bevel

1. Perform a complete physical assessment of the fistula and document the findings.
2. Remove any scabs over the cannulation sites.
3. Disinfect the cannulation sites per facility protocol.
4. Using an antistick dull bevel, grasp the needle wings and remove the tip protector. Align the needle cannula, with the bevel facing up, over the cannulation site and pull the skin taut (Fig 2A).*

- Carefully insert the needle into the established cannulation site (Fig 2B). Advance the needle along the scar tissue tunnel track. If mild to moderate resistance is met while attempting to insert the needle, rotate the needle as you advance it, using gentle pressure (Fig 2C).
- A flashback of blood indicates when the needle is in the access. Lower the angle of insertion. Continue to advance the needle into the fistula until it is appropriately positioned within the vessel.
- Securely tape the needle set (Fig 2D) and proceed with the dialysis treatment per facility protocol.

*Note: Ensure that the same needle insertion angle and depth of penetration are used consistently for each cannulation of a constant site.

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GUIDELINE 4. DETECTION OF ACCESS DYSFUNCTION: MONITORING, SURVEILLANCE, AND DIAGNOSTIC TESTING

Prospective surveillance of fistulae and grafts for hemodynamically significant stenosis, when combined with correction of the anatomic stenosis, may improve patency rates and may decrease the incidence of thrombosis.

The Work Group recommends an organized monitoring/surveillance approach with regular assessment of clinical parameters of the AV access and HD adequacy. Data from the clinical assessment and HD adequacy measurements should be collected and maintained for each patient's access and made available to all staff. The data should be tabulated and tracked within each HD center as part of a Quality Assurance (QA)/CQI program.

4.1 Physical examination (monitoring):

Physical examination should be used to detect dysfunction in fistulae and grafts at least monthly by a qualified individual. (B)

4.2 Surveillance of grafts:

Techniques, not mutually exclusive, that may be used in surveillance for stenosis in grafts include:

4.2.1 Preferred:

4.2.1.1 Intra-access flow by using 1 of several methods that are outlined in Table 7 using sequential measurements with trend analysis. (A)

4.2.1.2 Directly measured or derived static venous dialysis pressure by 1 of several methods. (A) (Protocol provided in Table 8 for using transducers on HD machines to measure directly; criteria in Table 9 for derived methods.)

4.2.1.3 Duplex ultrasound. (A)

4.2.2 Acceptable:

4.2.2.1 Physical findings of persistent swelling of the arm, presence of collateral veins, prolonged bleeding after needle withdrawal, or altered characteristics of pulse or thrill in a graft. (B)

4.2.3 Unacceptable:

4.2.3.1 Unstandardized dynamic venous pressures (DVPs) should not be used. (A)

4.3 Surveillance in fistulae:

Techniques, not mutually exclusive, that may be used in surveillance for stenosis in AVFs include:

4.3.1 Preferred:

4.3.1.1 Direct flow measurements. (A)

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4.3.1.2 Physical findings of persistent swelling of the arm, presence of collateral veins, prolonged bleeding after needle withdrawal, or altered characteristics of pulse or thrill in the outflow vein. (B)

4.3.1.3 Duplex ultrasound. (A)

4.3.2 Acceptable:

4.3.2.1 Recirculation using a non–urea-based dilutional method. (B)

4.3.2.2 Static pressures (B), direct or derived. (B)

4.4 When to refer for evaluation (diagnosis) and treatment:

4.4.1 One should not respond to a single isolated abnormal value. With all techniques, prospective trend analysis of the test parameter has greater power to detect dysfunction than isolated values alone. (A)

4.4.2 Persistent abnormalities in any of the monitoring or surveillance parameters should prompt referral for access imaging. (A)

4.4.3 An access flow rate less than 600 mL/min in grafts and less than 400 to 500 mL/min in fistulae. (A)

4.4.4 A venous segment static pressure (mean pressures) ratio greater than 0.5 in grafts or fistulae. (A)

4.4.5 An arterial segment static pressure ratio greater than 0.75 in grafts. (A)

Table 7. Flow Methods in Dialysis Access

Duplex Doppler Ultrasound (Quantitative color velocity imaging: [**DDU**]
Magnetic Resonance Angiography: [**MRA**]
Variable Flow Doppler Ultrasound (Specs USA):[**VFDU**]
Ultrasound dilution (Transonics):[**UDT**]
Crit-Line III (optodilution by ultrafiltration;HemaMetrics): [**OABF**]
CritLine III direct transcutaneous (HemaMetrics): [**TQA**]
Glucose pump infusion technique [**GPT**]
Urea dilution [**UreaD**]
Differential Conductivity (GAMBRO): [**HDM**]
In Line Dialysance (Fresenius):[**DD**]

RATIONALE

Definitions

The following terms will apply to HD vascular access

Monitoring—the examination and evaluation of the vascular access by means of physical examination to detect physical signs that suggest the presence of dysfunction.

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Surveillance—the periodic evaluation of the vascular access by using tests that may involve special instrumentation and for which an abnormal test result suggests the presence of dysfunction.

Diagnostic testing—specialized testing that is prompted by some abnormality or other medical indication and that is undertaken to diagnose the cause of the vascular access dysfunction.

Purpose of Access Surveillance

Vascular access function and patency are essential for optimal management of HD patients. Low BFRs and loss of patency limit HD delivery, extend treatment times, and, in too many cases, result in underdialysis that leads to increased morbidity and mortality.[248] Between 1991 and 2001, the incidence of vascular access events in patients undergoing HD increased by 22%.[249] In long-term AV accesses, especially grafts, thrombosis is the leading cause of loss of vascular access patency. Thrombosis increases health care spending[7,250] and adversely affects QOL,[162,250–253] and vascular access–related complications account for 15% to 20% of hospitalizations among patients with CKD stage 5 undergoing HD.[7,12,252] Prevention of access dysfunction by maintaining adequate flow and preventing thrombosis translates into a policy of "Dialysis Dose Protection." (See the KDOQI HD Adequacy Guidelines.) It is not feasible for any one individual to manage all aspects of access care. Multidisciplinary teams should be formed at each HD center,[254–256] with a VAT coordinator, if possible. Whatever the team's size and composition, its most important function is to work proactively to ensure the patient is receiving an adequate dialysis dose by maintaining access function and patency.

The basic tenet for vascular access monitoring and surveillance is that stenoses develop over variable intervals in the great majority of vascular accesses and, if detected and corrected, underdialysis can be minimized or avoided (dialysis dose protection) and the rate of thrombosis can be reduced. Whether prospective monitoring and surveillance can prolong access survival currently is unproven. However, it fosters the ability to salvage vascular access sites through planning, coordination of effort, and elective corrective intervention, rather than urgent procedures or replacement.[257] A number of monitoring and surveillance methods are available: sequential access flow, sequential dynamic or static pressures, recirculation measurements, and physical examination.

Failure to detect access dysfunction has consequences on morbidity and mortality.[248,249] In a recent study of 721 randomly selected patients from all 22 long-term HD units in northeast Ohio, barriers found to significantly ($P < 0.001$) and independently relate to inadequate dialysis dose delivery were patient noncompliance, low dialysis prescription, catheter use, and access thrombosis.[253] Every 0.1 decrease in Kt/V was independently and significantly ($P < 0.05$) associated with 11% more hospitalizations, 12% more hospital days, and a $940 increase in Medicare inpatient expenditures. Vascular access–related complications accounted for 24% of all hospital admissions.[258] The reader is referred to the KDOQI HD Adequacy Guidelines for additional information on the importance of achieving the prescribed dialysis dose with regard to mortality.

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Table 8. Static Intra-Access Pressure (IAP) Surveillance

a) Establish a baseline when the access has matured and shortly after the access is first used. Trend analysis is more useful than any single measurement.
b) Assure that the zero setting on the pressure transducers of the dialysis delivery system being used has been calibrated to be accurate within ±5 mm Hg.
c) Measure the mean arterial blood pressure (MAP) in the arm contralateral to the access.
d) Enter the appropriate output or display screen where venous and arterial pressures can be visualized (this varies for each dialysis delivery system). If a gauge is used to display pressures, the pressure can be read from the gauge.
e) Stop the blood pump and cross clamp the venous line just proximal to the venous drip chamber with a hemostat (this avoids having to stop ultrafiltration for the brief period needed for the measurement). On the arterial line, no hemostat is needed since the occlusive roller pump serves as a clamp.
f) Wait 30 seconds until the venous pressure is stable, then record the arterial and venous intra-access pressure (IAP) values. The arterial segment pressure can only be obtained if a pre-pump drip chamber is available and the dialysis system is capable of measuring absolute pressures greater than 40 mm Hg.
g) Unclamp the venous return line and restore the blood pump to its previous value.
h) Determine the height correction, Δh between the access and the drip chamber(s) either by direct measurement (A) or using a formula (B) based on the difference in height between the top of the drip chamber and the top of the arm rest of the dialysis chair (Δ). Both measurements need to be in cm. Height corrections are not needed if the measurements in step 6 are done with access level with the drip chamber
   - Measure the height from the venous or arterial needle to the top of the blood in the venous drip chamber. The offset in Hg = height (cm) x 0.76
   - Use the formula, offset in mm Hg = 3.6 + 0.35 x Δ.
i) The same correction values can be used for both if the 2 drip chambers are at the same height. If the drip chambers are not at equal heights, the arterial and venous height offsets must be determined individually. In a given patient with a given access the height offsets need to be measured only once and then used until the access location is altered by construction of a new access.
j) Calculate the normalized arterial and venous segment static IAP ratio(s), P_{IA}/MAP

Arterial ratio = (arterial IAP + arterial height correction)/MAP

Venous ratio = (venous IAP + venous height correction)/MAP

Table 9. Criteria for Intervention

	Access Pressure Ratio					
Degree of Stenosis	Graft			Fistula		
	Arterial Segment		Venous Segment	Arterial Segment		Venous Segment
<50% of diameter	0.35-0.74		0.18-0.49	0.13-0.43		0.08-0.34
>50% of diameter						
Venous outlet	>0.75	or	>0.5	>0.43	or	>0.35
Intra-access	>0.65	and	<0.5	>0.43	and	<0.35
Arterial inflow	<0.3		Clinical findings	<0.13 + clinical findings		Clinical findings

Asymptomatic, but hemodynamically significant, stenoses usually are detected through a systematic monitoring and surveillance program. Detection of such stenoses is important to prevent progression to a functionally significant stenosis, currently defined as a decrease of greater than 50% of normal vessel diameter, accompanied by hemodynamic or clinical abnormality, such as abnormal recirculation values, elevated

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venous pressures, decreased blood flow, swollen extremity, unexplained reduction in Kt/V, or elevated negative arterial prepump pressures, that prevent increasing to acceptable blood flow.[259] This definition evolves from an analysis of hemodynamics and clinical correlation.

Normal Hemodynamics

Access flow and pressure are related in a permanent AV access through the relationship:

$$Q_A = \Delta P/R$$

The driving force for access flow, Q_A, is the pressure gradient, ΔP, between the artery and central veins. This driving force tends to be the same for both fistulae and grafts. Within the constraints imposed by the arterial anastomotic site, the ultimate access flow in mature accesses tends to be similar in fistulae and grafts.[260,261] What differs is the rate of maturation. Grafts reach their maximum flow rate in a matter of days to weeks, as opposed to fistulae, which may require weeks to months to mature.[71,138,262-264] This difference in achieving maximum flow may explain the difference in the incidence of immediate steal between the 2 access types, with the fistulae permitting more time for adaptation to occur.

Figure 3. Pressure profiles in grafts (top) and fistulae (bottom). Symbols: P, pressure; ΔP, change in pressure; R, resistance; Q_{AC}, access flow; A, arterial; V, venous. Figure adapted from Sullivan K, Besarab A: Strategies for maintaining dialysis access patency. Chapter 11. In Cope C (ed): Current Techniques in Interventional Radiology (ed 2). Philadelphia, PA, Current Medicine, 1995, pp 125–131.

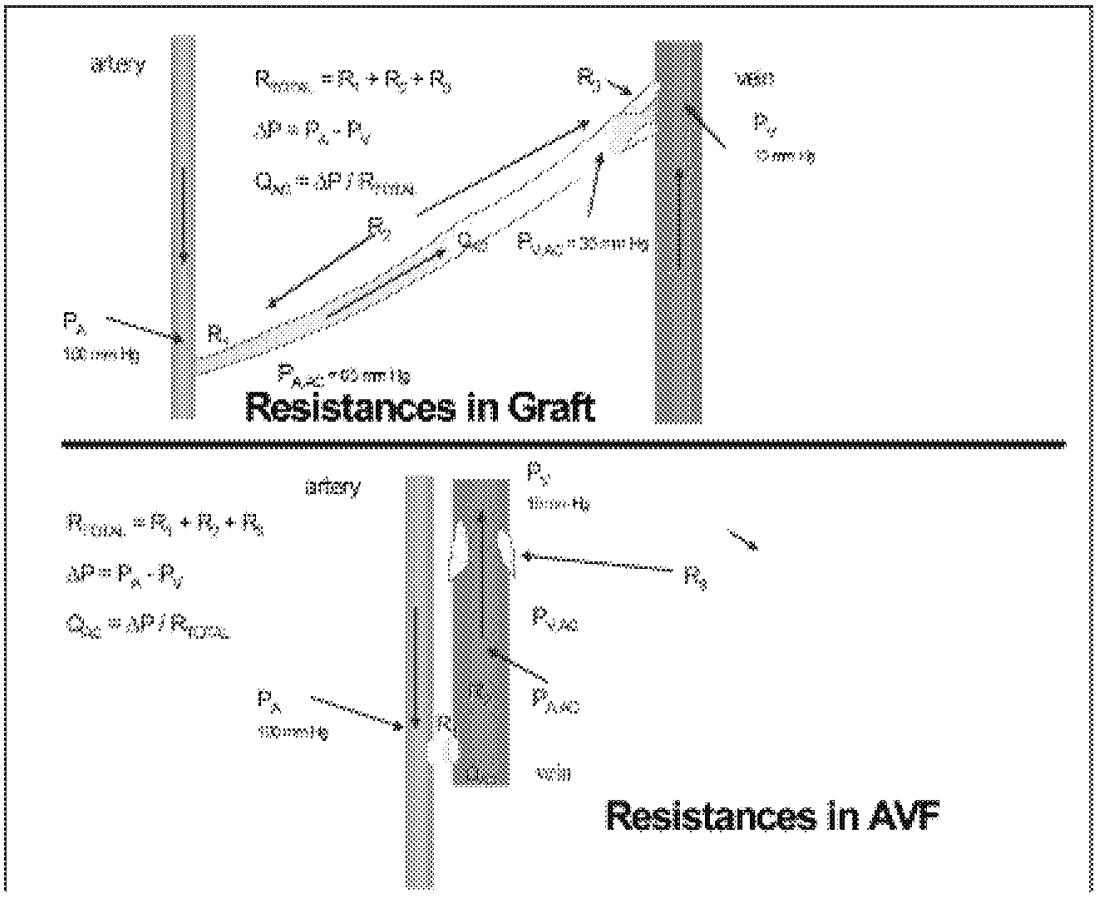

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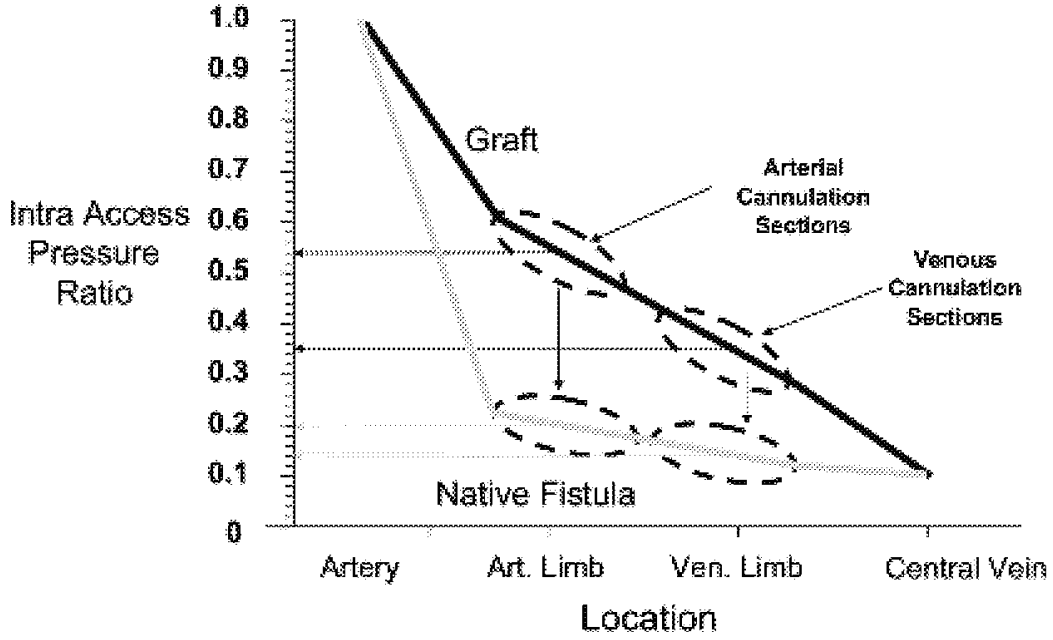
Figure 4. IAPs within normal grafts and fistulae. Reprinted with permission: Besarab A, Frinak S, Aslam M: Pressure measurements in the surveillance of vascular accesses. In Gray R (ed): A Multidisciplinary Approach for Hemodialysis Access. Philadelphia, PA, Lippincott Williams & Wilkins, 2002, Chapter 21, pp 137–150.



The pressure profile differs in the 2 access types. As shown in Fig 3, the pressure decrease profile in a graft progressively decreases along the length of the graft. At both anastomoses, there are pressure gradients, even in the absence of stenosis (illustrated as the luminal incursions). Within the body of the graft, there is a 20- to 30-mm ΔP that is the effective driving force.[265–267]

Conversely, in a fistula, the preponderance of the arterial pressure is dissipated within the first few centimeters of the access; pressures in the "arterial segment" are only approximately 20% of those in the feeding artery.[265–267] Fig 4 shows the difference in profiles.

The IAP ratio refers to the actual pressure at the site of measurement divided by the mean arterial blood pressure (MAP). The effective ΔP in the fistula generally is only 8 to 10 mm Hg, frequently 25%, and seldom more than half those noted in grafts. Despite these differences in pressure profiles, access flow in grafts and fistulae are approximately equal at 6 months[267] because the overall ΔP is the same. However, fistulae—unlike grafts—have an intact endothelial lining that allows them to actively dilate and remodel over extended periods. As a result, progressive flow increases are limited only by cardiac factors. Fistulae also differ from grafts in having side branches that reduce resistance to flow (parallel circuits). However, multiple accessory veins can limit the development of the major superficial vein needed for cannulation (see CPGs 1 and 2). Ligation of accessories or spontaneous occlusion of side branches within a fistula results in an access that hemodynamically mimics the profile of a graft.

It is immediately apparent that 2 anatomic factors determine access function: (1) quality and (2) physical dimensions of the artery and vein. The major determinant of

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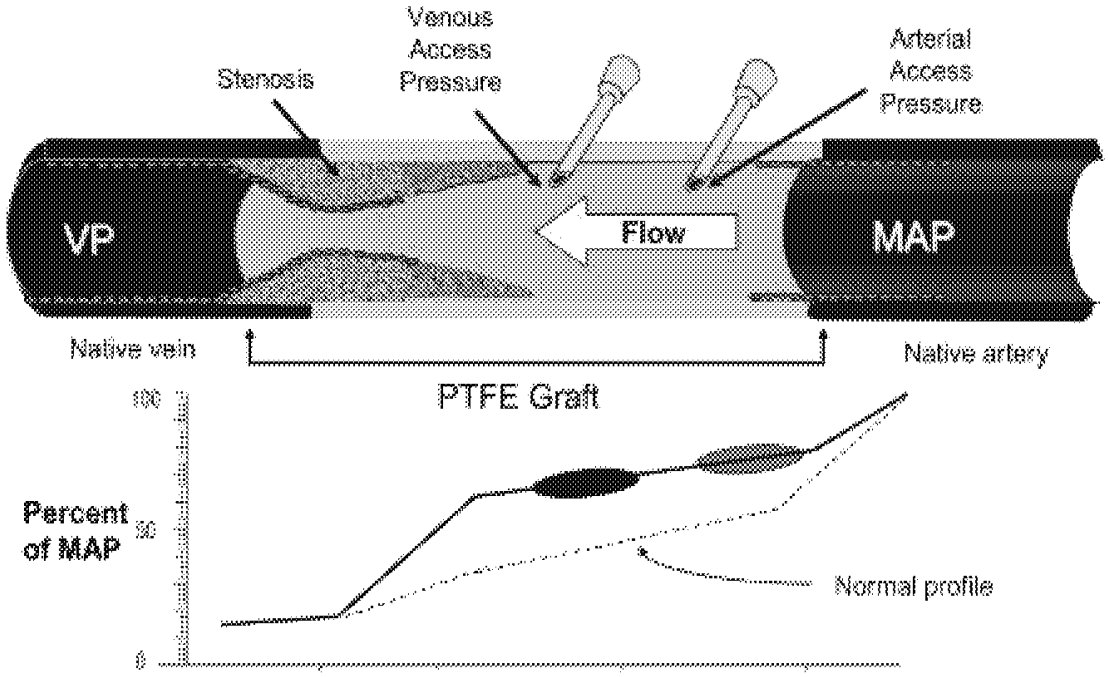
Q_A in a given patient will be determined by the capacity of the artery to dilate and its general "health." In general, arteries at more distal sites have less capacity to deliver flow than more proximal sites, ie, radial < brachial < axillary < femoral. Arteries that are calcified or affected by atherosclerosis will result in lower flow accesses whether supplying a fistula or a graft. If the artery is healthy, flow capacity will be determined by the characteristics of the vein used in access construction. Too small a vein will limit the flow in both a fistula and graft. Unfortunately, arterial disease is not uncommon; access inflow stenosis occurs in one third of the patients referred to interventional facilities with clinical evidence of venous stenosis or thrombosis.[268] This is much greater than has been traditionally reported.[10,24,105,108,269] Thus, it is very important to assess the access by using physical examination early after its construction. Because flow and pressure measurements are not performed routinely until the access is cannulated, initial assessment of the access depends on the physical examination, which can detect many problems in a fistula.

Effect of Stenosis on Hemodynamics: Access Flow, IAP, Access Recirculation, and Physical Examination

In grafts, the majority of stenoses develop in the venous outflow, frequently right at or within several centimeters of the venous anastomosis.[10,24,105,108] Lesions within the graft also occur, and most accesses have more than 1 lesion at any 1 time.[10,266,267,269] The pathophysiological state of graft failure arises from neointimal hyperplasia. In a fistula, there may be ischemic effects, as well as injury resulting from recurrent cannulation and subsequent fibrosis. Stenoses in a fistula tend to occur at the surgical swing sites (including the arterial anastomosis) or the puncture zone of the vein. The outcome is the same in both fistulae and grafts: a reduction in access flow rate. However, the effect on

Figure 5. Effect of venous outlet stenosis on pressure profile. Reproduced with permission from Medisystems Inc.



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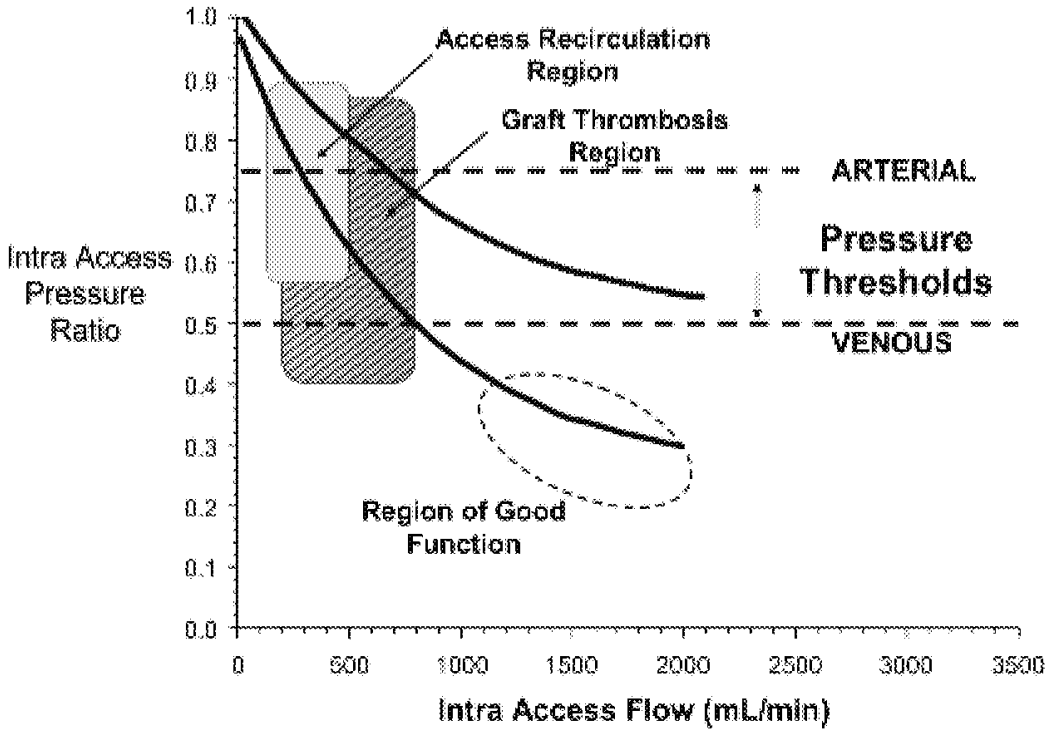
IAP differs according to access type and site of stenosis. As illustrated in Fig 5, an outlet stenosis in a graft will increase the pressure at all locations upstream from the stenosis. Conversely, an inflow lesion will decrease all pressures downstream of the stenosis. An intragraft stenosis between the needles will decrease flow while increasing pressure upstream and decreasing pressure downstream of the lesion.

In a fistula, pressure profiles depend on the location of the lesion and the presence or absence of collateral or accessory veins. Arterial inflow lesions that develop after acceptable maturation are detected more easily by using Q_A, the inability to deliver blood flow to the dialyzer, reductions in adequacy, and recirculation measurements[270,271] than by IAP measurements. Intra-access pressure (P_{IA}) with inflow lesions tends to remain unchanged or decrease as Q_A decreases over time.[272] An outflow lesion will produce a pressure profile similar to that seen in grafts; the magnitude of the pressure elevation is dictated by the number of venous tributaries. Not uncommonly, in upper-arm fistulae, there is spontaneous or deliberate occlusion of side branches (as with transposition); an outflow lesion then produces a pressure profile very similar to that of grafts.

For a given graft access, the access flow pressure profile resulting from venous outflow stenosis is illustrated in Fig 6.

An initially well-functioning graft with an access flow approaching 2 L/min (usually in the upper arm) will manifest decreasing flow as both the arterial and venous pressure slowly increase with the development of outflow tract stenosis. Hemodynamic simulations indicate that flow decreases by less than 20% until the stenosis process produces a 40% to 50% decrease in luminal diameter. Thereafter, flow decreases rapidly as

Figure 6. Effect of graft venous outlet stenosis. Reprinted with permission: Besarab A: Blood Purif 2006;24:77–89 (DOI: 10.1159/000089442). S. Karger AG, Basel.



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the degree of stenosis increases to 80%.[273] Because the intimal hyperplasia process progresses with time, its detection requires sequential measurements of flow or pressure or both to detect a threshold at which action should be taken. Note that the graft thrombosis region by flow shown in the hatched area is reached long before a graft would show recirculation and therefore affect the delivered dose of dialysis. Access recirculation in grafts is a late manifestation of stenosis and a poor predictor of imminent thrombosis; it occurs in less than 20% of cases.[271] For this reason, the Work Group no longer recommends recirculation measurements in grafts. Conversely, because fistulae typically can maintain patency at much lower flows than grafts, recirculation occurs much more frequently; 1 study reported that about one third of fistulae had a significant recirculation fraction by using an ultrasound dilution technique.[271] When recirculation was measured by using the Fresenius Body Thermal Monitor (BTM), the device was able to detect fistulae requiring revision with a sensitivity of 81.8% and specificity of 98.6%, although the BTM method does not differentiate between access and cardiopulmonary recirculation.[274]

The main issue for most HD clinics is which surveillance test best meets their needs. The following discussion summarizes the methods available and the reason for the ordering of the test by the Work Group in CPGs 4.2 and 4.3.

Physical Examination (Look, Touch, Listen)

Physical examination can be used as a monitoring tool to exclude low flows associated with impending graft failures.[275,276] There are 3 components to the access examination: inspection (look), palpation (touch), and auscultation (listen).[276] The Work Group is convinced that the basic skills have been largely abandoned in favor of technology and need to be taught to all individuals who perform HD procedures.[277] Simple inspection can reveal the presence of aneurysms. A fistula that does not at least partially collapse with arm elevation is likely to have an outflow stenosis. This logic applies to the case in which a tourniquet does not appear necessary for optimal cannulation. Strictures can be palpated and the intensity and character of the bruits can suggest the location of stenosis. Downstream stenosis also produces an overall dilation of the vein, giving it "aneurysmal" proportions.

In grafts, one can determine the direction of flow in a loop configuration and avoid inadvertent recirculation by erroneous needle insertion. In a patent graft in which blood flow is less than the blood pump flow setting, the presence of recirculation can be detected easily by occluding the graft between the needles and looking at the arterial and venous pressures. A strong pulse too often is misinterpreted as being evidence of good flow, rather than the opposite. A pulse suggests lower flows.[278] In a newly thrombosed graft, the arterial pulse often is transmitted into the proximal end of the graft, leading to erroneous cannulation, which could be avoided easily by simply using a stethoscope to confirm absence of flow. A bruit over an access system and its draining veins that is only systolic is always abnormal; it should be continuous. An intensification of bruit suggests a stricture or stenosis.[278] Palpable thrill at the arterial, middle, and venous segments of the graft predicts flows greater than 450 mL/min.[278] A palpable thrill in the axilla correlates with a flow of at least 500 mL/min.[279] The character of pulse and thrill correlates

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with postintervention outcome for stenosis.[280] The interested reader is referred to additional literature for further enjoyment and enlightenment.[271]

Of note, a preliminary study has shown that sounds acquired by using electronic stethoscopes that were then digitized and analyzed on a personal computer could be used to characterize stenoses.[281] Stenotic vessel changes were found to be associated with changes in acoustic amplitude and/or spectral energy distribution. Acoustic parameters correlated well ($r = 0.98$; $P < 0.0001$) with change in degree of stenosis, suggesting that stenosis severity may be predicted from these parameters. Furthermore, acoustic parameters appeared to be sensitive to modest diameter changes of 20%. These results suggest that, in the future, readily available computerized analysis of vascular sounds may be useful in vessel patency surveillance.

Access Flow

Access flow can be measured by using a number of techniques, as summarized in Table 7. Doppler ultrasound (DU)[282-287] and MRA[46,54,288-290] are direct techniques for assessing flow in vascular accesses. Duplex Doppler ultrasound (DDU) requires an accurate measurement of the cross-sectional diameter of the access. The method is operator dependent and subject to error caused by variation in cross-sectional area and the angle of insonation.[291,292] Because turbulence in the access can limit the accuracy of the measurements, flow measurements can be made in the feeding artery (usually the brachial) or distal part of the access.[272] The difference between the flow in the artery and the access usually is less than 10%. Despite these operator-related and equipment-related limitations, *sequential* measurements have been used extensively to detect and refer patients for interventions or predict the risk for thrombosis. In addition to flow measurements, both DDU and MRA provide anatomic assessment and direct evidence for the presence, location, and severity of access stenosis. However, the current cost of these methods, as well as the inability to make measurements during HD, limits their use. Research and development are needed to simplify procedures and reduce costs.

Indirect methods use an indicator dilution technique; the major techniques include ultrasound dilution (UDT),[272,293] a timed ultrafiltration method[294]; transcutaneous access flow rate (TQA), a method that can be performed during or independently of HD[295,296]; glucose infusion[297,298]; differential conductivity[299,300]; and, finally, ionic dialysance.[301,302] All the methods described, except for TQA, variable flow DU, and glucose infusion, require measurements with the blood tubing initially in the normal position and then reversed to induce access recirculation.

With UDT, access flow is measured from the induced recirculation when the needles are reversed. The software calculates the area under the curves (AUC) as a measure of recirculation.

$$Q_A = Q_{BP}\,(1/R - 1)$$

where Q_{BP} is blood pump flow and R is degree of recirculation induced. The UDT method is the only one that independently measures actual flow in the tubings, rather than accepting the readings on the HD system for the roller pump.

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Pitfalls in measurement have been identified and recently reviewed.[303] Accurate calibration of the blood pump is essential with most methods, but frequently is not performed regularly. The indicator injection also must not affect flow in the access itself. The technique must separate access recirculation from cardiopulmonary recirculation that is unavailable with high-efficiency dialysis. Finally, access flow is a function of the ratio of systemic to access resistance, and measurements should be conducted within the first 90 minutes of dialysis to minimize effects of hypotension. Table 10 summarizes the recommendations for access flow surveillance. All methods require some modification/interruption of the dialysis treatment, except perhaps ionic dialysance.

With ionic dialysance, alteration of the proportioning ratio of dialysate to water alters the dialysis sodium concentration, as well as blood sodium level. The resulting change in blood sodium level, as well as the change in dialysate conductivity, serves as the indicator for calculating Q_A.

$$Q_A = [(D \cdot Dr)/(D - Dr)] \cdot [1/\text{blood water fraction})]$$

where *D* is the dialysance in the normal blood tubing position and *Dr* is the value with the tubing reversed. As with UDT, ultrafiltration should be minimized and recirculation must be absent in the normal blood tubing configuration. At flow rates less than 1,000 mL/min, the method consistently underestimates access flow compared with UDT.[301,302]

With the timed ultrafiltration method, a difference in hematocrit (Hct) is the indicator

$$Q_A = Qf\ H_0(\Delta H_r - \Delta H_n)$$

where *Qf* is ultrafiltration rate, H_0 is initial Hct, and ΔH is change in Hct induced by ultrafiltration with the tubing in reversed (*r*) and normal (*n*) positions. The method correlates well with UDT.

The TQA method has not been extensively used.

The variable-flow DU method[304-306] measures velocity between the 2 dialysis needles at varying dialyzer blood flows. Using a conservation of volume approach, a computer

Table 10. Access Flow Protocol Surveillance

Access flow measured by ultrasound dilution, conductance dilution, thermal dilution, Doppler or other technique should be performed monthly. The assessment of flow should be performed during the first 1.5 hr of the treatment to eliminate error caused by decreases in cardiac output or blood pressure related to ultrafiltration/hypotension. The mean value of 2 separate determinations (within 10% of each other) performed at a single treatment should be considered the access flow.
Graft
If access flow is <600 mL/min in a graft, the patient should be referred for fistulogram.
If access flow 1,000 mL/min that has decreased by more than 25% over 4 mo, the patient should be referred for fistulogram.

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algorithm solves for access flow without the need to measure the cross-sectional diameter of the access.[306] The method's accuracy is best at flows less than 1,000 mL/min.

The easy availability of urea as a marker has led some to use it as an indicator substance to calculate recirculation and therefore derive flow. Such measurements underestimate flow compared with conductivity.[307] Although Q_A can be estimated by using the urea method, the sensitivity and specificity of a low value is a poor predictor of access outcome and may lead to cost-ineffective investigations.[307]

Variation in access flow during dialysis[308] can result from changes with cardiac output,[309-311] MAP,[309,310] and changes in blood volume.[311] Access flow can increase by up to 11% or decrease by up to 30% from initial values by the end of dialysis, potentially impairing the ability of Q_A to predict impending vascular access failure.[312] Access resistance remains stable during treatments and could be a more useful measure of vascular access performance as part of an access surveillance program. For all these reasons, it is recommended that measurements be made early in the HD treatment.

Access Pressure

Measurements of pressure from the HD circuit were not originally designed to assess access (dys)function, either directly or indirectly. Rather, they were used to calculate the mean transmembrane pressure so that the appropriate ultrafiltration rate could be achieved. Volumetric control systems made these measurements unnecessary. Pressure measurements were retained to provide safety. During HD, blood is drawn out of the vascular access through the arterial needle by the blood pump on the HD machine.

Prepump pressures are now used to determine whether the prescribed dialyzer blood flow can be delivered without generating excessive negative pressures. At high negative pressures, the collapse of the pump segment reduces the true flow and true flow may differ from "displayed" flow by up to 15%.[313,314] The degree of collapse is affected, in turn, by differences among manufacturer tubing sets.[315] These considerations are important in evaluating the relationship of flow to access pressure. Excessively negative pressures can result in hemolysis.[316] Differences in blood tubing performance are of obvious importance to manufacturers, leading to improvements. The newer generations available may show little differences with the improved blood flow delivered during dialysis, benefiting all patients.

When blood passes through the dialyzer, the blood traverses the venous drip chamber and returns to the patient's vascular access though the venous needle. The pressure required to infuse blood back into the access is recorded as the venous drip chamber pressure (VDP) or DVP. The original purpose of VDP was to detect infiltration or malpositioning of the needle because partial occlusion of the needle orifice or infiltration would quickly increase and sound an alarm. There still is no "alarm" for detecting accidental withdrawal of the needle outside the body; exsanguinations have occurred.

One of the components of the VDP is the actual IAP (P_{IA}). As shown in Fig 4, the IAP (P_{IA}) in a graft is usually less than 50% of MAP. Most of this pressure decrease occurs at the arterial anastomosis, unless there is intragraft stenosis. When outflow stenosis develops

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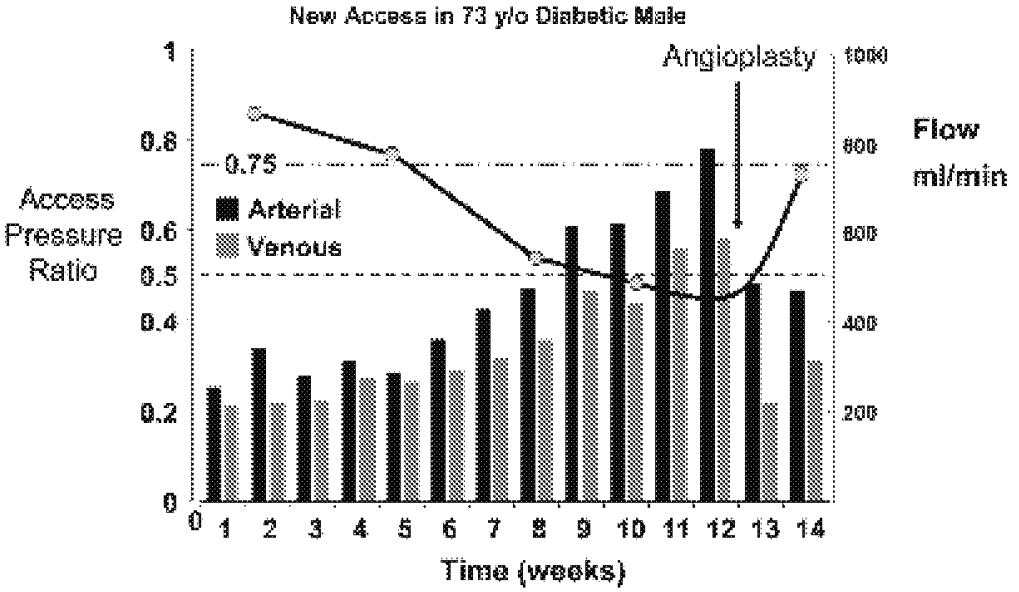
(eg, because of neointimal hyperplasia at or downstream from the graft-vein anastomosis), P_{IA} increases and flow decreases. When P_{IA} increases to greater than 50% of MAP (P_{IA}/MAP greater than 0.50), graft flow commonly has decreased into the thrombosis-prone range of 600 to 800 mL/min (Fig 6), and the presence of stenosis is likely. If a stenosis develops in the body of a graft between the areas used for arterial and venous limb cannulation, P_{IA} at the venous needle remains normal or can even decrease despite increasing stenosis.[270,271] Stenosis at the arterial anastomosis of both grafts and fistulae causes P_{IA} to decrease. Conversely, a high basal P_{IA} can be observed with a healthy artery in the absence of stenosis when the flow delivered is in excess of the venous system's initial capacity. Because of these pressure confounders, there is little correlation between a single measurement of flow and P_{IA}/MAP.[317] Serial measurements of pressure in each patient are more valuable than isolated measurements of either P_{IA} or P_{IA}/MAP ratio. This is illustrated in Fig 7. Note that the arterial pressure ratio is approximately 0.2 units higher than the venous ratio and the baseline initial value for both ratios is lower than usual because of the use of a 4- to 6-cm taper at the arterial anastomosis that limits inflow to prevent steal.

In fistulae, blood entering the venous system returns through multiple collateral veins. As a consequence, P_{IA}/MAP in a fistula is, on average, less than in a graft and may not increase with outlet stenosis. The test, therefore, theoretically is less valuable as a surveillance tool for stenosis in fistulae. However, most elbow-level fistulae do not have or lose collaterals and often behave hemodynamically like grafts. In both fistula types, elevation of P_{IA}/MAP indicates the development of a stenosis in the venous outflow from the access and is associated with an increased probability of access failure or need for revision to provide adequate blood flow for HD.[10,265,266,317]

Like access flow, measurement of P_{IA} has evolved.

Figure 7. Relationship of IAP ratio to access flow. Reprinted with permission: Besarab A: Blood Purif 2006;24:77–89 (DOI: 10.1159/000089442). S. Karger AG, Basel.



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Direct measurement of static pressure. Pressures in the access can be measured directly at the site of cannulation in the "arterial" and "venous" segments of the graft or fistula by using a pressure-measuring device. Although one can use a sophisticated electronic method (separate transducers placed in line with the dialysis tubing)[265-267] as originally reported, a much simpler technique uses a device consisting of a hydrophobic Luer-Lok connector that connects a standard dialysis needle to an aneroid manometer.[318]

IAPs also can be measured by using the pressure transducers of the dialysis machine. Under conditions of no blood flow and no ultrafiltration, the only difference between the pressure measured by an independent transducer and the machine transducer is that resulting from the height differential between the location of the machine transducers and the access. The two pressures can be equated by either moving the access to the level of the venous drip chamber or moving the drip chamber to the level of the access. Alternatively, the height difference, Δh, can be measured and the additional pressure ($0.76 \cdot \Delta h$) can be added to the machine transducer reading.[319]

Table 8 provides the sequence of steps for measuring static pressure. It is important that the pressure transducers be calibrated accurately.

Interpretation. Venous outlet stenosis can be detected with venous P_{IA} alone. Trend analysis is more useful than any single measurement. The greater the degree of stenosis at the outlet, the greater the venous pressure ratio. Strictures between the area of arterial and needle cannulation cannot be detected by measuring venous (P_{IA}) pressure alone.[271] Detection of these lesions requires simultaneous measurement of pressures from both the arterial and venous needles. Central stenoses that have collateral circulation may have "normal" pressures, but these usually present with significant ipsilateral edema. Accesses can be classified into the categories listed in Table 9. Using the equivalent P_{IA} ratios from the arterial or venous needles, the criteria must be met on each of 2 consecutive weeks to have a high likelihood of a 50% diameter lesion.

Patients who develop a progressive and reproducible increase in venous or arterial segment greater than 0.25 units more than their previous baseline, irrespective of access type, also are likely to have a hemodynamically significant lesion. Intra-access strictures usually are characterized by the development of a difference between the arterial and venous pressure ratios greater than 0.5 in grafts or greater than 0.3 in native fistulae. Because fistulae can remain patent at much lower flows than grafts, sequential measurement of conductance (ie, a blood pump/absolute value of prepump pressure), particularly at maximum prepump pressure permitted by the system, can detect fistula dysfunction and stenosis.[320,321]

Although measuring static pressure as described in Table 8 is straightforward, it is tedious, time consuming, and not "user friendly." Staff frequently bypass crucial steps, leading to poor-quality data being collected and recorded. This has led to a reevaluation of statistical methods to use the information within the dynamic pressure.

VDP or DVP and extraction of equivalent P_{IA}. DVP (also referred to as VDP under conditions of blood flow) is measured routinely during HD in the presence of extracorporeal blood flow. These pressures can be read off the dialysis machine or stored

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electronically with the blood pump running. One of the components of DVP is the actual IAP (P_{IA}) because the pressure needed to return blood into the access is the sum of that needed to overcome the needle resistance and IAP. DVP/VDP has been used to detect venous outlet problems,[322] but measurements are meaningful only if obtained at the beginning of dialysis and usually with low BFRs (50 to 225 mL/min) because at high BFRs, much of the resistance to flow is from the needle, and not the vascular access.

Measurement of DVP is less sensitive and specific than direct measurements of access flow rates or static pressure measurements. The reason for "poorer" performance results from many factors, including the lack of consistency about which flow should be the standard, varying in studies from 50 to 425 mL/min[322–325]; differences in needle design (wall thickness, actual length); and effects of viscosity affected chiefly by Hct. In addition, use of DVP as a method also requires that studies be performed to standardize the critical value as a function of needle gauge, length, and inner diameter (wall thickness). Consistency requires that a uniform flow value to test at be determined.

Indirect methods for determining P_{IA}. Most HD systems can store the blood pump values associated with DVP. A computerized algorithm has been developed that uses an empirical formula to calculate an equivalent P_{IA} from the DVP made during treatment. During a given treatment, many measurements at different flows can be made along with the simultaneous MAP, and an average equivalent P_{IA}/MAP can be calculated. The average values can be trended with each treatment and examined for an upward trend. When the ratio exceeds 0.55, the access has a greater risk for clotting.[326] This technique has been commercialized, providing monthly reports and trend analysis. Its ability to predict thrombosis is equal to that of direct measurement of P_{IA}. In the evolution of the IAP ratio to detect stenosis, the discriminator value has progressively increased from 0.4 using the ratio of systolic pressures, 0.45 using the ratio of mean pressures measured directly, 0.5 using transducers on the machine, and finally 0.55 when deriving P_{IA} from the dynamic pressure.

Recirculation: Method, Limits, Evaluation, and Follow-Up

Recirculation is the return of dialyzed blood to the dialyzer without equilibration with the systemic arterial circulation. The technique is not recommended as a surveillance tests in grafts. However, up to one third of dysfunctional fistulae will show an increase in recirculation that may be manifested as a decrease in urea reduction ratio (URR) or Kt/V, but this occurs late.

Access recirculation in a properly cannulated access is a sign of low access blood flow[192] and a marker for the presence of vascular access stenosis, particularly in fistulae. Such stenoses can be corrected, preventing underdialysis and decreasing the risk for access thrombosis.[327] Access recirculation can be measured accurately by using UDT[328] or conductivity.[299] A K^+-dilution method is more reliable than the 2-needle urea-based method and compared with UDT, has 100% sensitivity, 95% specificity, 91% positive predictive value, and 100% negative predictive value.[329] In analogy to access flow measurement, glucose infusion also has been used to measure recirculation.[330]

The amount of recirculation occurring with reversed needles usually is substantial (>20%), as confirmed when the tubings are deliberately reversed for access flow

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measurements. However, even with ideal sample timing and proper cannulation, laboratory variability in urea-based measurement methods will produce variability in calculated recirculation.[331] Therefore, individual recirculation values less than 10% by using urea-based methods may be clinically unimportant. The Work Group believes that they do not prompt further evaluation. Values greater than 10% by using urea-based recirculation measurement methods require investigation.

New loop grafts are at particular risk for reversed needle placement because of a lack of familiarity with the access anatomy. When possible, an access diagram that depicts the arterial and venous limbs should be obtained from the surgeon who constructed the access to aid in proper cannulation. If not available, the anatomy can be deduced by *temporarily* occluding the graft at its midportion. The portion retaining a pulse is the arterial limb.

Comparison of Surveillance Methods

Accuracy and Reproducibility

Only 1 study has directly compared many of the available flow techniques with regard to reproducibility.[332] Reproducibility is assessed by using duplicate measurement at unchanged conditions, whereas accuracy is determined under controlled change in a relevant measurement condition (2 different blood flows for ultrasound, changed sensor position in TQA). An accurate method produces the same result. In most studies using some form of dilution or concentration of an indicator, UDT is taken as the reference method for comparison because it most accurately separates cardiopulmonary from access recirculation and independently measures blood flow to the dialyzer. Ultrasonic flow is approximately 10% to 15% less than indicated by the blood roller pump, the magnitude correlating inversely with negative arterial blood tubing pressure.[333] It shows very high reproducibility, for measurement at the same extra corporeal blood flow, Q_B (correlation coefficient of duplicate measurement, $r = 0.97$; n = 58) and measurement at 2 different Q_B ($r = 0.97$; n = 24), justifying its current status of a reference method in Q_A evaluation.[334] The coefficient of variation usually is less than 8%.[327] Slightly lower reproducibility is found with thermal dilution (TD) or Fresenius BTM at the same Q_B ($r = 0.92$; n = 40) and 2 different Q_B ($r = 0.851$; n = 168); this inaccuracy can be overcome by increasing the number of measurements with averaging. Use of the simple Krivitski formula, $Q_A = Q_{BP}$ (1/R − 1) in TD (which measures total recirculation, ie, sum of access recirculation and cardiopulmonary recirculation) brings about underestimation of Q_A, which progressively increases from Q_A of about 600 mL/min upward. High correlation of TD versus UDT ($r = 0.95$; n = 54) makes TD a viable clinical alternative in Q_A evaluation. Consistently different Q_A values obtained at 2 different Q_Bs should prompt closer investigation of anatomic conditions of the access. Good correlation ($r = 0.87$; n = 27) also is found between Q_A measured by using DDU and UDT.[332,335]

The direct TQA method showed very high reproducibility ($r = 0.97$; n = 85); however, only for unchanged sensor position. Correlation of Q_A measured at 2 different sensor positions was much worse ($r = 0.73$; n = 22). Correspondence of TQA with UDT was satisfactory ($r = 0.81$; n = 36). Skilled and experienced operators are a must with this method. Similar results were found by others who reported, for triplicate measurements,

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coefficients of variation of 7.5% for differential conductivity by hemodynamic monitoring (HDM), 9.1% for UDT, and 17.4% for optodilution by ultrafiltration (OABF).[336] Repeatability data (variation among temporally separated measurements) showed values of 10.6% for HDM, 13.0% for UDT, and 25.2% for OABF. Fewer comparisons have been made with the other methods. Glucose pump test (GPT) flow measurements correlate well with UDT measurements and have acceptable replicability.[298]

Ionic dialysance or conductivity dialysance, as it frequently is referred to, is being used increasingly by clinicians to measure access flow in both the United States and Europe, particularly with Fresenius dialysis delivery systems, in which the methodology is built into the machines as on-line clearance. Major refinements have been made to increase the replicability and accuracy of this method at lower BFRs, but preliminary reports comparing the measurements with UDT have not yet been formally published.

Detection of Stenosis or Predicting Thrombosis

As important as accuracy of a method is, the goal of any surveillance method is to detect access stenosis in a timely way so that appropriate correction can be undertaken before thrombosis. A hemodynamically significant stenosis is the substrate for thrombosis by reducing flow, increasing turbulence, and increasing platelet activation and residence time against the vessel wall.

Table 11 summarizes the available studies in which the presence and degree of stenosis was confirmed by using angiography. As reflected by data in the table, DDU is most accurate because it can directly visualize the degree of stenosis. When DDU is used to measure flow, rather than identify anatomic stenosis, sensitivity and specificity decrease. A quick survey of the table clearly shows that none of the tests consistently achieves a sensitivity of 90% and specificity greater than 80%.

Because of the accuracy of DDU in detecting the presence of a 50% (by diameter) stenosis,[337] it has been used in some studies as the reference method, rather than angiography, to avoid invasive procedures. As shown in Table 12, Table 12 UDT has good accuracy, whereas physical examination has high specificity, but poor sensitivity.

Table 13 shows that DDU and UDT are equivalent in predicting thrombosis.

Data are still limited for some of the newer surveillance tests. Table 14 summarizes the observations. There is excellent correlation between flow measurements by means of GPT and UDT ($r > 0.9$).[298] GPT also has been validated recently as a surveillance technique in grafts. Using DDU to assess for the presence of stenosis, GPT picked up severe stenosis in 14 of 112 grafts (100% sensitivity) and performed better than UDT (86% sensitivity).[297] Specificity was less than 60% for both tests. Diagnostic efficiency (percentage of grafts with agreement between test result and factual situation) was 90% and 80% ($P = 0.056$) for GPT and UDT, respectively. MRA also can provide anatomic[338] and Q_A measurements, but it is prohibitively expensive. Intravascular ultrasounds (IVUSs) can be used to evaluate abnormalities in fistulae[297] and may find abnormalities not seen with angiography. However, it is too expensive for routine use, but may be a valuable adjunct in evaluating the efficacy or completeness of the intervention on the access.

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Table 11. Diagnostic Accuracy of Tests Used for Access Surveillance in the HD Population: Angiogram for Stenosis vs. Other Test

Author, Year	N	Type of Access		Applicability	Test 1 [a]	Threshold Value for Stenosis	Results				Quality
		AVF	AVG				Sens	Spec	AUC	CI	
Bosman 1997 [340]	42 (70 grafts)	0%	100%	↑↑	UDT	ND	-	-	0.72 [b]	(0.66, 0.78)	●
Tessitore 2003 [336]	127	100%	0%	↑↑	UDT	750 mL/min	84%	91%	0.91	(0.88, 0.94)	●
Schwarz 2003 [337]	66	100%	0%	↑↑	UDT	465 mL/min	68%	89%	0.79	(0.66, 0.91)	○
Schwarz 2003 [337]	66	100%	0%	↑↑	DDU	390 mL/min	76%	76%	0.80	(0.65, 0.94)	○
Gadallah 1998 [342]	56	34%	66%	↑↑	DDU	[c]	100%	100%			○
Robbin 1998 [341]	41	100%	0%	↑↑	DDU	[d]	92%	50% [e]			○
Bosman 1997 [340]	42 (70 grafts)	0%	100%	↑↑	Venous pressure	ND			0.83 [b]	(0.78, 0.88)	●
Laissy 1999 [338]	19	100%	0%	↑↑	MRA	[f]	92%	86%			○
Planken 2003 [339]	15	53%	47%	↑	MRA	[f]	Observer 1: 100%	0%	0.74		○
							Observer 2: 100%	20%	0.81		

AUC=area under curve; AVF=arteno-venous fistula; AVG=arterio-venous graft; CI=confidence interval; DDU=duplex Doppler ultrasound; MRA=magnetic resonance angiography; ND=no data; PSV=peak systolic velocity; Sens=sensitivity; Spec=specificity; UDT=ultrasound dilution technique.

a. This test is compared to the "reference standard", angiogram
b. Based on number of grafts
c. Access stenosis defined by > 50% narrowing or reduction of luminal diameter of vessel
d. Access stenosis defined by PSV ratio > 2.0 or > 50% stenosis
e. Derived specificity calculated based on data provided
f. Access stenosis defined by 50% vessel stenosis or 40% stenosis with turbulent flow

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Table 12. Comparison of Diagnostic Tests for Access Surveillance and Monitoring in the HD Population: Duplex Doppler Ultrasound As Reference

Author, Year	N	Type of Access		Applicability	Test 1 [a]	Threshold Value for Stenosis	Results	Quality
		AVF	AVG					
May 1997 [285]	170 (220 accesses)	22%	78%	↑↑↑	UDT [b]	ND	r = 0.79 P = 0.0001	●
Malik 2002 [124]	193 (258 exams)	72%	28%	↑↑	Physical exam	ND	Sensitivity = 36% Specificity = 93%	○

AVF=arterio-venous fistula; AVG=arterio-venous graft; ND=no data; r=correlation coefficient; UDT=ultrasound dilution technique.

a. This test is compared to the "reference standard", duplex US.
b. Access stenosis defined by doubling of systolic velocity in vessel narrowed more than 50%

Table 13. Comparison of Diagnostic Tests to Predict Thrombosis in Chronic Hemodialysis Patients

Author, Year	Study Design	N	Type of Access		Follow-up (maximum)	Applicability	Test 1	Test 2	Prediction Difference	Quality
			AVF	AVG						
Lok 2003 [200]	Prospective with historical control	401	63%	37%	NG	↑↑	DDU [a]	UDT [a]	NS [b]	○
May 1997 [285]	Prospective, uncontrolled	170 (220 accesses)	0%	100%	NG	↑↑	DDU	UDT	✚ [c]	○

AVF=arterio-venous fistula; AVG=arterio-venous graft; DDU=duplex Doppler ultrasound; ND=no data; NS=not significant; PTA=percutaneous transluminal balloon angioplasty; UDT=ultrasound dilution technique.

✚ Statistically significant beneficial effect of treatment compared to control (or intervention 1 vs. intervention 2)

a. Coupled with angiogram and PTA or surgery for those with access stenosis defined by doubling of systolic velocity in vessel narrowed more than 50%, or UDT flow < 650 mL/min for AVG or < 500 mL/min for AVF or 15% decrease from previous measurement
b. NS both AVG and AVF
c. UDT, but not DDU, predicts thrombosis in multivariate analysis

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Table 14. Comparison of Newer Tests to Established Tests for Stenosis Detection

Author, Year	N	Type of Access		Applicability	Test 1 [a]	Test 2	Results		P-Value or 95% CI	Quality
		AVF	AVG							
Arbab-Zadeh 2002 [344]	22	100%	0%	↑↑	Angiogram [b]	IVUS	Author's conclusion: IVUS feasible			O
Smits 2002 [45]	18	39%	61%	↑	Angiogram [a]	MRA	Mean difference in maximum stenosis between tests	Observer 1: 3.2%	(−26.7%, 33.1%)	O
								Observer 2: 4.1%	(−23.8%, 32.1%)	
							Mean interobserver difference	MRA: 3.2%	(−28.8%, 35.2%)	
								DSA: 3.6%	(−9.4%, 16.7%)	
Plankan 2003 [46]	15	53%	47%	↑	Angiogram [b]	MRA	Interobserver agreement on access stenosis	DSA: k = 0.69		O
								MRA: k = 0.81		
Ram 2003 [344]	33	24%	76%	↑	UDT	GPT	r = 0.901		<0.001	O

AVF=arterio-venous fistula; AVG=arterio-venous graft; DSA=digital subtraction angiography; GPT=glucose pump infusion technique; IVUS=intravascular ultrasound; k=kappa statistic for interobserver agreement; MRA=magnetic resonance angiography; PSV=peak systolic velocity; r=correlation coefficient; UDT=ultrasound dilution techniques; CI=confidence intervals

a. This test represents "gold standard" unless otherwise specified

b. Access stenosis defined by > 50% narrowing or reduction of luminal diameter of vessel

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An important issue in fistulae is the assessment of such abnormalities as aneurysms and extreme tortuosity in "well-functioning" fistulae. DU is a very valuable technique, particularly in fistulae; in addition to measuring flow and identifying stenosis directly, it can detect other abnormalities in presumably well-functioning accesses.[345] Pseudoaneurysms do not decrease access flow; Q_A is significantly greater than the mean (1,204 mL/min) in fistulae with aneurysms, calcifications, and tortuous vessels and, of course, less in those with stenosis. No correlation is noted between Q_A or the presence of stenosis with fistula age. Some degree of stenosis was detected in 64% of fistulae, with 57% of stenoses located in the anastomotic region; 22%, in the vein junction; 19%, at 1 or both ends of the aneurysm; and 2%, in the remaining region of the efferent vein.[345] Chronic venous occlusion with collateral veins was detected in 6% of fistulae.[345] Aneurysms were observed in 54% of fistulae with a mean diameter of 12.4 mm, with 96% of them located at puncture sites. Ten patients had a small thrombus in an aneurysm and at puncture sites. Thus, although a high level of abnormalities is present in well-functioning mature fistulae, the abnormalities are not sufficient to affect the functioning of the HD fistula and, in most cases, need only observation. More advanced lesions require therapy (see CPG 5).

DDU is a particularly useful modality to determine reasons for maturation failure of fistulae 4 to 12 weeks after construction,[346] even if preoperative vein mapping had shown adequate vein size (≥3 mm) and outflow. Using the criteria of peak systolic velocity ratio (SVR) of 2:1 or greater to detect a 50% or greater stenosis involving arterial inflow, and venous outflow and an SVR of 3:1 or greater to detect a 50% or greater anastomotic stenosis, DDU of 54 native fistulae (23 brachiocephalic, 14 radiocephalic, and 17 basilic vein transpositions) found that 20% were occluded and 26% were normal. The remainder showed a variety of lesions: 16 fistulae (42%), venous outflow; 13 fistulae (34%), anastomotic; and 2 fistulae (5%), inflow stenoses. In 7 fistulae (18%), branch steal with reduced flow was found. Sensitivity, specificity, and accuracy of DDU in detecting stenoses of 50% or greater were 93%, 94%, and 97% compared with fistulography, respectively. Because many of these fistulae cannot be studied by using other surveillance techniques, routine DDU surveillance of primary fistulae should be considered to identify and refer for correction of flow-limiting stenoses that may compromise the long-term patency and use of the fistula.

Inflow stenosis is more common than previously believed (ie, <5% of cases). An inflow stenosis is defined as stenosis within the arterial system, artery-graft anastomosis (graft cases), artery-vein anastomosis (fistula cases), or juxta-anastomotic region (the first 2 cm downstream from the arterial anastomosis) with a 50% or greater reduction in luminal diameter judged by comparison with either the adjacent vessel or graft. Such stenosis was found in nearly a third of 223 cases referred to an interventional facility serving several centers.[268] All referred accesses had a coexisting stenosis on the venous side. The frequency of inflow stenosis was less in grafts (29% of cases) than fistulae (40 of 101; 40%). Of these, 22 (54%) had a coexisting lesion on the venous side. Access inflow stenosis thus is much greater than traditionally reported in cases referred to interventional facilities with clinical evidence of venous stenosis or thrombosis.

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Attempts to combine the various surveillance techniques have been performed. One study found no difference in the ability to detect stenoses in grafts from using Q_A by UDT compared with static venous pressure ratios.[340] However, DVPs were of little use. Use of a P_{IA} compared with Q_A also was examined in 125 grafts followed up for 80.5 patient-years.[347] Standardized monitoring of either P_{IA}, Q_A, or the combination of both, followed by subsequent corrective intervention, decreased the thrombosis rate in grafts compared with a historical control rate.[348] Rates in 2 separate parts of the study for thrombosis not preceded by a positive test result were 0.24 and 0.32 episodes/patient-year at risk compared wth a historical rate greater than 0.7, respectively. The surveillance strategies were equally effective in decreasing thrombosis rates, and access survival curves were not significantly different between subgroups.[347] Again, DVP alone was not useful because either Q_A or P_{IA} turned positive before the dynamic pressure limit (>150 mm Hg at 200 mL/min) was reached. Unlike these 2 studies showing limited to no utility of DVP alone, another study was able to find some utility for DVP measurements for grafts.[349] Stenosis greater than 50% by diameter on fistulography or a thrombotic event was defined as a "vascular access impairment episode," whereas stenosis less than 50% or the absence of a thrombotic event was defined as "no vascular access impairment episode." By combined dynamic pressure readings and flow surveillance (DVP > 120 mm Hg; Q_A < 500 mL/min in fistulae and < 650 mL/min in grafts or a decrease in Q_A > 25% compared with the highest previously measured value were considered positive), improved sensitivity over flow alone for fistulae, but not grafts, was observed.[268] Sensitivity and specificity of the combined surveillance protocol for fistulae were 73.3% and 91%; in grafts, they were 68.8% and 87.5%, respectively. The rate of thrombotic events was less in patients with fistulae who underwent early repair, but in grafts, the addition of DVP did not decrease the thrombosis rate any further than surveillance based on Q_A alone. Finally, when UDT, DDU flow, DVP, and prepump pressure were examined as predictors of thrombosis in 172 grafts, DVP used alone was not predictive.[285]

In summary, available data suggest that the utility of DVP at flows of 150 to 225 mL/min to predict stenosis or thrombosis is limited or absent in grafts. Studies are needed to determine whether the method retains any utility in fistulae. Conversely, flow measurements, DDU assessment for stenosis, and static pressure measurements (direct or indirect by using computers) can detect hemodynamically significant stenosis in grafts and fistulae. Although the location of stenosis in fistulae (inflow) favors Q_A over P_{IA}, no direct comparisons have been made by using DDU anatomic imaging or contrast angiography to determine the accuracy of the techniques in this access type. If the prescribed Kt/V is not delivered in a patient who is using a fistula, measurement of access flow should be performed by using a recommended method (Table 7).

The Work Group believes there is insufficient evidence to suggest 1 surveillance technique from those listed in the guidelines as "preferred or acceptable" because the choice at a particular site is affected by many variables; chief among these are access type, technology, effect of operator, and cost (usually labor). Although DDU studies are predictive of access stenosis and the likelihood for failure,[350] frequency of measurement is limited

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by expense. In addition, interobserver variability in measurement of DDU flow in some instances can reduce the reliability of DDU flow measurement.[351] Variation in the internal software used for calculating DDU flow measurements by different manufacturers also is a factor preventing standardization. Magnetic resonance flow is accurate, but expensive. Both DDU flow and magnetic resonance are difficult to perform during HD sessions.

Conversely, flow measurements performed by using UDT and other techniques can be done on-line during HD, thereby providing rapid feedback. The same applies for P_{IA}. Both access flow and IAP techniques have been validated in prospective observational studies.[10,322,347,349,352,353] Measuring static venous pressures is the least expensive method of surveillance for stenosis.[322,354] Because of efficiency or cost, these methods are listed as preferred. In-line access flow measurements (DDU) are available and have been improved in terms of accuracy and replicability. However, there are no data yet on efficacy in detecting stenosis or effect on thrombosis rate.

The Work Group believes that recirculation is a relatively late predictor of access dysfunction and, if used, has a minor role in fistulae only. Non–urea-based recirculation measurements are very accurate, but require specialized devices.

Unexplained decreases in delivered dialysis dose, measured by using Kt/V or URR, frequently are associated with venous outflow stenoses.[355] However, many other factors influence Kt/V and URR, making them less sensitive and less specific for detecting access dysfunction. Inadequate delivery of dialysis dose is more likely to occur with a fistula than a graft.

In primary fistulae, inadequate flow through the access is the main functional defect predictive of thrombosis and access failure (defined as thrombosis or failure to provide adequate dialysis dose). Indirect measures of flow, such as dynamic and static venous dialysis pressure, may be less predictive of thrombosis and access failure in fistulae compared with grafts. However, measurement of recirculation becomes a more useful screening tool in fistulae compared with grafts because flow in fistulae, unlike grafts, can decrease to a level less than the prescribed blood pump flow (ie, <300 to 500 mL/min) while still maintaining access patency.[192,270,271] DDU may be useful in fistulae.[346] Comparative studies using HDM (Q_A, P_{IA}) and DDU need to be performed before firm recommendations can be made by the Work Group.

Regular assessment of physical findings (monitoring) may supplement and enhance an organized surveillance program to detect access dysfunction. Specific findings predictive of venous stenoses include edema of the access extremity, prolonged postvenipuncture bleeding (in the absence of excessive anticoagulation), failure of the vein to collapse with arm elevation, and changes in physical characteristics of the pulse or thrill in the graft.[108,354] Physical examination is a useful screening tool to exclude low flow (<450 mL/min) in grafts with impending failure.[275,277,278] In the context of proper needle position, an elevated negative arterial prepump pressure that prevents increasing the BFR to the prescribed level also is predictive of arterial inflow stenoses.

When a test indicates the likely presence of a stenosis, angiography should be used to definitively establish the presence and degree of stenosis. Currently, the Work Group is in agreement with the Society for Interventional Radiology, which recommends

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angioplasty if the stenosis is greater than 50% by diameter. Angioplasty by its very nature is a "disruptive" force on the vessel and can injure endothelium and underlying smooth muscle; each angioplasty can produce benefit or harm. However, there have been no large-scale trials to determine whether correction of only "hemodynamically" significant lesions (those associated with "low" access flows or "high" pressures or a change in access flow or pressure) is superior to correction of all stenosis greater than 50%. At the time of intervention, hemodynamic evaluation of each stenosis generally is not carried out.

Until such studies are conducted, the Work Group believes that the value of routine use of any technique for detecting anatomic stenosis alone—without concomitant measurement of access flow, venous pressure, recirculation, or other physiological parameters—has not been established. Stenotic lesions should not be repaired merely because they are present. If such correction is performed, then intraprocedural studies of Q_A or P_{IA} before and after PTA should be conducted to show a functional improvement with a "successful" PTA.

The Patient as His or Her Own Surveyor and Protector

The Work Group strongly advocates that all patients should be taught the "basics" *of how to take care of their vascular access*, including steps in personal hygiene, cleanliness, avoidance of scab picking, and so on, as discussed in Table 15. In addition, patients should be taught where and how to detect a "pulse," where and how to feel for a thrill, how to recognize infection, and—most importantly—when to notify a member of the dialysis staff of physician when the pulse or thrill is absent. Delay in recognizing loss of patency may influence the likelihood of restoring patency.

Table 15. Patient Education Basics

All patients should be taught how to:

a. Compress a bleeding access;
b. Wash skin over access with soap and water daily and before HD;
c. Recognize signs and symptoms of infection;
d. Select proper methods for exercising fistula arm with some resistance to venous flow;
e. Palpate for thrill/pulse daily and after any episodes of hypotension, dizziness, or lightheadedness;
f. Listen for bruit with ear opposite access if they cannot palpate for any reason.

All patients should know to:

a. Avoid carrying heavy items draped over the access arm or wearing occlusive clothing;
b. Avoid sleeping on the access arm;
c. Insist that staff rotate cannulation sites each treatment;
d. Ensure that staff are using proper techniques in preparing skin prior to cannulation and wearing masks for all access connections;
e. Report any signs and symptoms of infection or absence of bruit/thrill to dialysis personnel immediately.

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The patient must be taught the reason for avoiding "1-site-itis." Topical anesthetics should be used judiciously if they help the patient comply with the policy of rotation of needle sites. To avoid aneurysm formation, the patient should insist on site rotation unless a buttonhole method is being used in a native fistula. With the large staff turnover ratios prevalent in HD units in the United States, the patient must be diligent that staff uses the proper aseptic techniques whenever the access is palpated, inspected, or cannulated.

Surveillance and Thrombosis

Nonrandomized Trials

In dialysis AVGs, thrombotic events result primarily, but not solely, from progressive venous outflow stenosis.[10,24,105,300,354,356-358] Thrombotic events that cannot be resolved (ie, patency restored) are the leading cause of access loss. These stenoses are caused by intimal and fibromuscular hyperplasia in the venous outflow tract, typically at the graft venous anastomosis,[359-362] but can occur in the body of the graft, as well. The details of pathophysiology are beyond the limits of this discourse except to state that, to date, promising therapies in animal models have not yielded success in humans. Possible future therapeutic approaches have been summarized.[363]

As stenoses increase in severity, they produce a resistance to flow, increasing P_{TA} with an accompanying decrease in blood flow.[266,318] Cross-sectional studies using DDU or UDT showed a progressive increase in risk for access thrombosis during a follow-up interval of 1 to 6 months. The absolute value of the "critical or threshold" Q_A depends on the method used. Average access flow rates obtained by DDU are less (600 to 900 mL/min)[252,335,364] than those measured by using magnetic inductance (mean, 1,100 mL/min) or UDT (mean range, 900 to 1,200 mL/min).[336] Studies also showed that when access flow is measured repeatedly, trends of decreasing flow add predictive power for the detection of access stenosis or thrombosis.[284-286,300,311,318,349,364-371] Grafts with access blood flows less than 600 to 800 mL/min have a greater rate of access thrombosis than grafts with flow rates greater than 800 mL/min.[268,284,286,300,311,318,372] In addition to this absolute value, a decrease of 25% in access flow from a previous "stable" baseline greater than 1,000 mL/min has been suggested as a criterion for further diagnostic evaluation of grafts to detect the presence of at least one 50% (by diameter) stenosis within the access.[285,364,369-371] In general, the interval that is present to correct the lesion in grafts before the access thromboses varies inversely with the access flow, being less than 8 weeks at a flow less than 450 mL/min[371] and 3 months at flow rates of 600 to 800 mL/min.[285]

Although many centers refer patients directly for angiographic study without intermediate studies when a critical value is obtained, there may be a role for DDU anatomic scanning.[282] Because fistulae maintain patency at lower flows than grafts, criteria for intervention in fistulae are not as well established. Values of 400 to 650 mL/min have been proposed. Higher values increase sensitivity, but lose specificity. Some fistulae can maintain patency for years at flows less than 400 mL/min, but with high-efficiency/high-flux dialysis, the treatment time requires extension. Conversely, intervention with PTA almost invariably triggers a process of repeated need for PTA because the frequency of at least 1

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abnormality in an access is so high. Optimal care of a particular patient requires individualization, and not rigid application of protocols.

Because the development and severity of stenosis evolve to varying degrees among patients over time, the likelihood of detecting a hemodynamically significant stenosis increases if the surveillance test is repeated frequently. Therefore, surveillance should be performed at intervals of 1 month or less—depending on the complexity and cost—to detect access dysfunction early and permit sufficient lead time for intervention. The Work Group concluded that trend analysis could be as important as any individual value for any monitoring technique. Because access pressure measurements do not require complex technology, their frequency should be greater than that for access flow measurements. For direct measurement of access pressure, a frequency of twice a month appears sufficient. With methods more likely to produce variation under real-world clinical practice conditions (such as those from the HD system transducers), measurements once every 1 to 2 weeks are needed to detect a trend. The Work Group believes that measurement of static pressures every 2 weeks is the minimum frequency that is compatible with current HD staffing patterns. Derived static pressures need analysis from all available treatments for the month. Dynamic pressures should not be performed in grafts.

Measurement of access flow also was shown to be a valuable tool in determining the success of a therapeutic intervention. Failure to increase access flow by at least 20% after an intervention reflects failure of the intervention to correct the underlying problem.[282,369] In 1 study, values before PTA and ΔQ_A correlated with the subsequent decrease in Q_A ($P < 0.005$).[282] It was observed that Q_A increased after PTA (from 371 mL/min to 670 mL/min in a total of 65 grafts and 33 fistulae), but in a substantial percentage of cases, not to levels greater than 600 mL/min. Q_A values before PTA and the increase in Q_A values correlated with long-term outcomes, whereas angiographic results did not. Unfortunately, in many of the studies, the literature has admixed results for flow and outcome for both fistula and graft, making it impossible to sort out effects in grafts as opposed to fistulae. The Work Group believes there may be important differences in the response of fistulae (compared with grafts) to PTA, and surgical approaches also may influence outcomes. Research is needed in this area.

A large number of studies that used historical control data showed that prospective surveillance/monitoring to detect stenosis reduces the rate of thrombosis, although at the expense of increased procedures.[10,322,343,373,374] A seminal study showed that a prospective program of dynamic pressure surveillance could detect stenotic lesions, reduce thrombosis rates, and reduce access replacement rates.[322] In that study, fistulae and grafts were not differentiated with respect to efficiency of the test. Unfortunately, criteria developed with needles designed for low-efficiency dialysis (16 G; pressure > 150 mm Hg at a flow of 200 mL/min) were not adapted for larger bore needles (15 G and 14 G), and other investigators did not independently standardize their pressure criteria for the flow actually used (150 to 225 mL/min). Accordingly, results of this study generally were not duplicated.[340] Until such standardization is performed, DVP alone is not recommended. Additional studies using static pressure,[10] physical examination alone,[352,353]

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DVP combined with access recirculation plus physical finding,[373] DDU,[284,374] and Q_A[341,366,369,375] all showed a 41% to 67% reduction in thrombosis rate in grafts. A review suggested that the effect may be smaller in fistulae.[374]

Receiver operating characteristic (ROC) curve analyses have been performed to assess the overall performance of access flow and pressure in predicting thrombosis. Although in some studies, a good AUC of 0.84 to 0.9 was achieved for access flow, overall AUC for 10 studies was only 0.7.[376] Addition of a change in flow increased AUC slightly to 0.82, but not to the value of 0.9 that an excellent test would produce (90% sensitive and 80% specific).[377] The sum of Q_A and ΔQ_A did not perform any better than P_{IA}/MAP.

Unfortunately, the high baseline rate of thrombosis in grafts precludes a sensitive test that can unequivocally predict the likelihood of thrombosis or not over a specified time. During a 3-month observation period, grafts can clot in the absence of any stenosis and do so at flows equal to those that remain patent, 1,209 versus 1,121 mL/min.[270] In these cases, P_{IA} remains unchanged. Grafts that required intervention or that thrombosed because of an anatomic lesion had much lower access flows, 656 mL/min and 609 mL/min, respectively. At flows greater than the threshold, the incidence of thrombosis may be as high as 20% per 6-month period.[375] Even with flows in the highest quartile, greater than 1,395 mL/min, another study found a thrombosis rate of 9% during a period of 3 months (annualized risk, 36%).[285] Until more studies are performed that examine the frequency of thrombosis in the absence of stenosis and the frequency of patency in the presence of arterial or venous stenosis, the debate will go on.[378-381]

At the present time, the development of a surveillance abnormality should be correlated with other findings on physical examination and adequacy of HD. Any abnormality (Q_A, P_{IA}) must be confirmed before further referral for either DDU (stenosis characterization) or angiography.

Randomized Trials of Preemptive PTA in Response to Surveillance

To date, only a small number of studies have been performed prospectively to assess the impact of surveillance on outcome. These are summarized in Table 16. Table 16

The concept that prophylactic or preemptive PTA would decrease graft thrombosis initially was refuted.[382] In a study of 64 patients identified to have a 50% stenosis by using DDU and confirmed by using angiography, preemptive PTA produced no change in 6-month or 12-month patency. Because of confounding issues, a subanalysis was performed on 21 "virgin" grafts that had not previously clotted or required intervention.[383] Preemptive PTA from the time of diagnosis of stenosis reduced the thrombosis rate from 0.44 to 0.10 episodes/patient-year at risk. Both rates were much less than the rate of 0.91 in patients without virgin grafts. However, sample size was small (n = 19). It should be noted that in this study, only anatomic assessment was obtained; no hemodynamic assessment was performed.

The small number of patients in this and all other prospective studies has limited assessment of efficacy. One prospective study using P_{IA} was performed.[384] Although the study itself was well designed, it was flawed by the surveillance technique. A preliminary

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Table 16. Access Surveillance Studies with PTA Intervention

Author, Year	Study Design	Surveillance Test	N	Type of Access	Follow-up (maximum)	Applicability	Difference in Access Survival	Quality
Moist 2003 [306]	RCT	UDT	112	100% AVG	450 d	↑↑	NS	O
Ram 2003 [307]	RCT	UDT and DDU	101	100% AVG	800 d	↑↑	NS [a]	O
Dember 2004 [304]	RCT	Static venous pressure [b]	64	100% AVG	Median 8.1 mo for Surveillance test and 16.5 mo for control (3.3 yr)	↑↑	NS [c]	O
Lumsden 1997 [303]	RCT	DDU	64	100% AVG [d]	Mean 15.2 mo (24 mo)	↑↑	NS	O
Martin [e] 1999 [302]	RCT		21	100% AVG	3.5 yr	↑		
Tessitore 2003 [305]	Prospective with concurrent control	UDT vs. Clinical exam	60	100% AVF [f]	Median 17.5 mo for UDT 13 mo for no PTA (40 mo)	↑↑	+	○

AVF=arterio-venous fistula; AVG=arterio-venous graft; DDU=duplex Doppler ultrasound; NS=not significant; PTA=percutaneous transluminal balloon angioplasty; RCT=randomized controlled trial; UDT=ultrasound dilution technique.
Access Survival defined as time to abandonment or time to intervention.

+ Statistically significant beneficial effect of surveillance compared to "standard clinical evaluation"

a. UDT was ineffective; DDU for stenosis detection reduced thrombosis but increased PTA rates; no effect on graft survival
b. Static pressure ratio defined as systolic pressure in graft/mean arterial pressure; action level >0.4
c. Time to intervention was shorter in surveillance group. Proportion of patients with a thrombotic event was greater in the Observation group (72%) than in the Intervention group (44%) (P= 0.04), but overall thrombosis rates were similar in the 2 groups.
d. Inclusion criteria: functional stenotic AVG
e. Subgroup of Lumsden 1997 with "virgin" AVGs
f. Inclusion criteria: functional stenotic AVF

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study was performed in which monthly static venous pressure measurements were made during 2 consecutive HD sessions in all patients with a functioning upper-extremity graft in 2 HD units during a 16-month period. The method for deriving P_{IA} ratio differed significantly from that originally described[10] in that the ratio of systolic P_{IA} pressure to MAP was calculated instead of the ratio of systolic P_{IA} pressure/systolic blood pressure.[385] The net effect of this error is that the ratio would have been falsely elevated and the threshold value of 0.4 would not apply. In addition, measurements were performed less frequently than recommended. Not surprisingly, ROC analysis yielded curves with areas less than 0.64.[383] Subsequently, 64 patients with "elevated static venous pressure" measured in an upper-extremity graft were randomized to intervention (underwent angiography and repair of identified stenoses) or observation (underwent stenosis repair only in the event of access thrombosis or clinical evidence of access dysfunction), with the primary end point being access abandonment. Information on the fraction in the interventional group who had a stenosis is not provided. There was no difference in access abandonment (14 patients in each group) during the 3.5-year study period or in time to access abandonment. However, the proportion of patients with a thrombotic event was greater in the observation group (72%) than the intervention group (44%; $P = 0.04$), but overall thrombosis rates were similar in the groups (ie, there was a difference in mean number of thrombosis per graft in the intervention group in grafts that did thrombose). Not detailed was the number of PTAs that had to be performed in both groups during the entire study period.

Two randomized studies examined the role of access surveillance by using Q_A. In the first, it was found that stenotic lesions are detected more commonly by using Q_A ($Q_A < 650$ mL/min or 20% decrease in Q_A) than "routine surveillance" (physical examination plus DVP > 150 mm Hg) in a total of 112 patients, but elective PTA for lesions greater than 50% did not alter thrombosis rate.[386] Rates of graft loss, times to graft loss, and overall thrombosis rates did not differ between the 2 groups. However, interventions increased by 30% in the intervention group. In the second study, 101 patients were randomized to 3 groups: control, low surveillance Q_A (Transonics) monthly, or stenosis detection by using DDU quarterly.[387] Referral for angiogram was based on clinical characteristics in all, less than 600 mL/min in Q_A, and greater than 50% diameter in the DDU stenosis groups. Q_A was measured in all 3 groups, but only used for referral in the flow surveillance group. Baseline thrombosis rates were 0.7 and 0.9/patient-year in the control and Q_A groups, respectively. Results showed that Q_A increased PTA rate marginally (from 0.22 to 0.33/patient-year) and had no effect on thrombosis rate. Stenosis surveillance increased PTA to 0.65/patient-year and reduced thrombosis rates to 0.5/patient-year, but did not affect 2-year survival rate. Q_A less than 600 mL/min was found in 4 of 18, 4 of 31, and 3 of 11 in the control, Q_A, and stenosis groups in grafts that clotted (overall, 11 of 60). However, 26 of 35 in the stenosis group underwent PTA for "stenosis." In both studies, 20% to 25% of accesses clotted without a surveillance abnormality, ie, in a totally unexpected manner.

However, the overriding conclusion of the studies that surveillance using Q_A and PTA in response to a threshold value of Q_A did not alter graft survival has to be tempered

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by the small sample size of the studies, the comparator used, and the efficacy of the intervention. Graft survival studies require a sample size of approximately 700 patients to detect an increase in graft survival of 1 year or a 33% difference in survival by 3 years (H. Feldman, personal communication). None of the studies had 20% of this number. It also is important to assess the skill level of the staff. If the staff can reach a positive predictive value of 80% (when stenosis is present and needs intervention) through use of physical examination and clinical characteristics (monitoring), use of a surveillance method that has a sensitivity of only 80% will produce no benefit over good monitoring. Determining which lesions should undergo correction has already been addressed. Elastic recoil needs to be assessed.

In contrast to grafts, the role of Q_A surveillance appears to be more established in fistulae. In 1 study, the positive predictive value, negative predictive value, sensitivity, and specificity of ultrafiltration method for vascular access stenosis (OABF CritLine III) were 84.2%, 93.5%, 84.2%, and 93.5%, respectively. Vascular access thrombosis rates in 50 Q_A surveillance patients were less (2 of 50 patients; 4%) than in 94 patients not followed up with flow measurements (16 of 94 patients; 17%; $P = 0.024$).[242]

In a second study, a 5-year RCT of blood flow surveillance and preemptive repair of subclinical stenoses (1 or both of angioplasty and open surgery) with standard monitoring and intervention based upon clinical criteria alone was carried out in Italy.[388] Surveillance with blood pump flow (Q_B) monitoring during HD sessions and quarterly Q_A or recirculation measurements identified 79 fistulae with angiographically proven significant (>50% diameter) stenosis that were then randomized to either a control group (intervention done in response to a decrease in delivered dialysis dose or thrombosis; n = 36) or preemptive treatment group (n = 43). Kaplan-Meier analysis showed that preemptive treatment decreased the failure rate ($P = 0.003$) and the Cox hazards model identified treatment ($P = 0.009$) and greater baseline Q_A ($P = 0.001$) as the only variables associated with favorable outcome. Access survival was significantly greater in preemptively treated than control fistulae ($P = 0.050$), with greater postintervention Q_A as the only variable associated with improved access longevity ($P = 0.044$). This study provides evidence that active blood flow surveillance and preemptive repair of subclinical stenosis reduce the thrombosis rate and prolong the functional life of mature forearm fistulae and that Q_A greater than 350 mL/min before intervention portends a superior outcome with preemptive action in fistulae.

Finally, in a third study, a prospective controlled open trial to evaluate whether prophylactic PTA of stenosis not associated with access dysfunction improves survival in native virgin radiocephalic forearm fistulae, 62 stenotic functioning fistulae (ie, able to provide adequate dose of dialysis) were enrolled: 30 were allocated to control, and 32, to PTA.[389] Kaplan-Meier analysis showed that PTA improved fistula functional failure-free survival rates ($P = 0.012$) with a 4-fold increase in median survival and a 2.87-fold decrease in risk for failure. A Cox proportional hazards model identified PTA as the only variable associated with outcome ($P = 0.012$). It was found that PTA increased Q_A by 323 mL/min ($P < 0.001$), suggesting that improved fistula survival is the result of increased access flow. PTA also was associated with a significant decrease in access-related

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morbidity, halving the risk for hospitalization, central venous catheterization, and thrombectomy ($P < 0.05$). Because prophylactic PTA of stenosis in functioning forearm fistulae improves access survival and decreases access-related morbidity, it supports the use of a surveillance program for the early detection of these stenoses.

LIMITATIONS

At present, a vascular surveillance program to identify patients who may benefit from angiography and PTA appears to offer the most likelihood of benefit and may reduce thrombosis rates. However, we need additional studies to examine the characteristics of stenoses that produce incomplete responses to PTA so that patients are adequately treated at the time of their interventions.

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GUIDELINE 5. TREATMENT OF FISTULA COMPLICATIONS

Appropriate interventions for access dysfunction may result in an increased duration of survival of the AVF.

5.1 Problems developing in the early period after AVF construction (first 6 months) should be promptly addressed.

5.1.1 Persistent swelling of the hand or arm should be expeditiously evaluated and the underlying pathology should be corrected. (B)

5.1.2 A program should be in place to detect early access dysfunction, particularly delays in maturation. The patient should be evaluated no later than 6 weeks after access placement. (B)

5.2 Intervention:

Intervention on a fistula should be performed for the presence of:

5.2.1 Inadequate flow to support the prescribed dialysis blood flow. (B)

5.2.2 Hemodynamically significant venous stenosis. (B)

5.2.3 Aneurysm formation in a primary fistula. Postaneurysmal stenosis that drives aneurysm also should be corrected. The aneurysmal segment should not be cannulated. (B)

5.2.4 Ischemia in the access arm (B).

5.3 Indications for preemptive PTA:

A fistula with a greater than 50% stenosis in either the venous outflow or arterial inflow, in conjunction with clinical or physiological abnormalities, should be treated with PTA or surgical revision. (B)

5.3.1 Abnormalities include reduction in flow, increase in static pressures, access recirculation preempting adequate delivery of dialysis, or abnormal physical findings. (B)

5.4 Stenosis, as well as the clinical parameters used to detect it, should return to within acceptable limits following intervention. (B)

5.5 Thrombectomy of a fistula should be attempted as early as possible after thrombosis is detected, but can be successful even after several days. (B)

5.6 Access evaluation for ischemia:

5.6.1 Patients with an AVF should be assessed on a regular basis for possible ischemia. (B)

5.6.2 Patients with new findings of ischemia should be referred to a vascular access surgeon emergently. (B)

5.7 Infection:

Infections of primary AVFs are rare and should be treated as subacute bacterial endocarditis with 6 weeks of antibiotic therapy. Fistula surgical excision should be performed in cases of septic emboli. (B)

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RATIONALE

Initial Problems (CPG 5.1)

Minor swelling normally is found postoperatively after placement of an AVF regardless of location and type of anastomosis. This "physiological" swelling disappears within the first week. Swelling of the hand or area of the fistula should be treated with hand elevation and patient reassurance. Because prevention is always preferable to therapy, a major aspect of preventing postoperative swelling is to rest the arm. Persistent swelling requires further attention to exclude major outflow obstruction. Hematoma, infection, and venous hypertension also should be excluded by clinical examination[277,391,392]; noninvasive ultrasound examination helps confirm extravasations and hematomas or purulent infiltrations, as well as strictures/stenoses of the venous outflow tract.[45,124,393] Although angiography (fistulography) can show a venous stenosis causing venous hypertension, DDU is the preferred diagnostic method because it avoids any diagnostic cannulation of the newly created AVF and thereby avoids iatrogenic damage of the thin wall of the freshly arterialized vein. If a stenosis is found, it should be treated with a balloon angioplasty.

Persistent hand edema usually follows a side-to-side anastomosis for creating the fistula and invariably results from downstream stenosis forcing the flow through venous collaterals. This process can produce classic chronic venostasis with skin ulceration. The lesion should be treated early by ligation of the tributaries. If delayed healing of the wound is noted in patients, the surgical technique should be examined closely. The surgical technique to close the skin preferably should use degradable suture material in an exclusively subcutaneous position supported by externally applied sterile adhesive strips to minimize the thickness of the scar.

Risk for bleeding and hematoma formation is greatest in the early stages of use of a fistula and greater in brachiobasilic fistulae than other types of fistulae at the wrist or elbow.[77] Manifestations of an infiltration or hematoma aside from the obvious discoloration and swelling include the presence of high-frequency bruit on auscultation and a difference in intravascular pressure on palpation.[277,391,392] Because hematoma may lead to access loss,[77] hematomas should be treated surgically if they are compromising the lumen of the arterialized vein (producing stenosis).[388] In the absence of luminal compromise by physical examination or DDU, the access should be rested until the margins of the fistula are again well demarcated.

Proficiency in cannulating fistulae is suboptimal in the United States despite considerable efforts to remedy the situation.[120,394–396] One can improve needle design to minimize trauma[397] and develop methods to increase the efficiency of buttonhole development,[398] but it is for naught if the fistula cannot be cannulated consistently without infiltrations. Because an inability to "be sure of the location" of the 2 lateral borders of the fistula contributes to miscannulation (particularly in those who are obese or have deep fistulae) and is manifested by so-called clot aspiration and because DDU is very precise in depicting the borders of vessels (see CPG 1),[344,399,400] patients should be referred for access mapping and photography. A useful procedure is for the ultrasonographer to draw a map on the surface of the skin with a washable marker directly over the center of the lumen (or the 2 lateral

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borders), make a digital photo map of the fistula based on ultrasound, and send the photograph of the usable portion of the fistula access to the dialysis center. Alternatively, the access can be marked with indelible ink that permits the establishment of a series of subsequent successful puncture sites to demarcate the center of the vessels if the rotating-site system of cannulation is used (see CPG 3). These techniques both educate the staff and develop expertise and confidence. In addition, they should foster greater expertise in assessing fistulae during the first postoperative weeks for delayed maturation. Prospective studies are needed to demonstrate this opinion-based strategy.

The majority of fistula creations can be performed on an outpatient basis. A crucial element is the postoperative examination and surveillance follow-up that is scheduled by either the surgeon or a vascular access coordinator representing the interdisciplinary VAT. The primary purpose is to detect problems of maturation (see CPG 2). Although a variety of factors can produce maturation failure,[86,123,125] a greater than 70% successful fistula access rate can be achieved, even among patients who have diabetes[86,87,401,402] and women.[84] In a multiple logistic regression analysis of 148 grafts (60% forearm, 40% elbow), predictive factors of early failure were distal location (adjusted odds ratio [aOR], 8.21; 95% confidence interval [CI], 2.63 to 25.63; $P < 0.001$), female sex (aOR, 4.04; 95% CI, 1.44 to 11.30; $P = 0.008$), level of surgical expertise (aOR, 3.97; 95% CI, 1.39 to 11.32; $P = 0.010$), and diabetes mellitus (aOR, 3.19; 95% CI, 1.17 to 8.71; $P = 0.024$).[403] Much of the prevention of delayed fistula maturation must occur preoperatively (see CPG 1) through appropriate selection of arterial and venous vessels, as well as procedures most suitable for the individual patient. Although it is the vein that must dilate and accept higher flows, the artery must be healthy too. The resistive index of the artery used to construct the fistula is a strong predictor of early primary HD fistula failure.[404] However, despite selection of the best available artery and vein, maturation failure can still occur. By combining venous diameter (>0.4 cm) and flow volume (>500 mL/min) during DDU evaluation within the first 4 months after access construction, one can predict the likelihood of maturing a fistula,[72] ie, one that can be cannulated and provides sufficient blood flow for dialysis, with 95% certainty (19 of 20 fistulae). Women were less likely to have an adequate fistula diameter of 0.4 cm or greater: 40% (12 of 30) compared with 69% for men (27 of 39). However, of note, the accuracy of experienced dialysis nurses in predicting eventual fistula maturity was excellent at 80% (24 of 30).[72] This is more reason to have a protocol for regular clinical examination in place in dialysis centers to teach the skills of physical examination (see CPG 4) to all staff members and assess the developing fistula and not focus on only the access in current use. A new fistula should be monitored regularly during the postoperative 4 to 6 weeks for swelling, hematoma, infiltration, wound healing, and failure to mature.

Intervention (CPG 5.2)

Inadequate Flow

A primary fistula should be revised when it is unable to sustain adequate HD blood flow, manifested by the inability to achieve the prescribed Kt/V within a reasonable HD duration. Low access blood flow has a major effect on the delivery of dialysis: inadequate blood flow may result in inadequate dialysis, thereby increasing patient mortality and

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morbidity.[405,406] Impaired flow in fistulae is caused by impaired arterial inflow related to the site of cannulation. Location of the anatomic reason varies between arterial and venous lesions, as well as lesions within the anastomotic area.

Arterioatherosclerotic narrowing of the feeding artery with reduced flow and stenosis of the artery are found in an increasing portion of the elderly, patients with hypertension, and patients with diabetes. Therefore, careful preoperative evaluation should document data on anatomic and functional status of the arterial vasculature, including flow in the brachial artery (see CPG 1).

As stated, peripheral location of first fistula, female sex, diabetes mellitus, and, finally, surgical expertise are the main predictive factors of early fistula failure.[72] Because it is known that arterial calcification in patients with diabetes is more pronounced in the wrist than elbow region,[407] selection of a more proximally located site for creation of the AV anastomosis, eg, the proximal radial or beginning brachial artery in the proximal forearm, may be the better alternative. Inadequate flow in the area of the AV anastomosis is produced primarily by surgical factors. Two studies[403,408] emphatically stressed that the early failure rate of fistula may be 3-fold greater when constructed by "occasionally" working access surgeons compared with experienced surgeons.

However, an initially adequate artery may become inadequate in time. Four of 40 patients had brachial artery lesions contributing to access dysfunction.[409] In a larger series, 41 of 101 fistulae had arterial inflow lesions at the time of therapeutic intervention for dysfunction.[268]

In case of reduced flow caused by arterial inflow, 2 therapeutic options exist: stenosis of the feeding artery may require interventional angioplasty or surgical revision, or inadequate quality of the feeding artery (caused, eg, by calcification) may require a more proximally located new AV anastomosis. Although chronic arterial lesions in upper limbs bearing vascular access devices for HD most often manifest themselves as insufficient flow for HD treatment, the process may be severe enough to produce thrombosis and ischemia. For correcting stenoses, PTA is a safe and effective technique with a low rate of reintervention.[268]

Juxta-anastomotic venous stenosis is a commonly observed lesion. It occurs from the change in hemodynamic flow character from the artery into the vein and from devascularization of the venous wall during exposure, even after excellent surgery. Placement of the "arterial needle" downstream of this stenosis obviously supports the phenomenon of impaired flow. At times, it may be impossible to traverse the AV anastomosis by using the retrograde approach, and antegrade puncture of the brachial artery will be needed.[410] Although interventional procedures are successful with this type of lesion,[411] construction of a new AV anastomosis (revision) at a more proximal location is the preferred procedure.[112] However, the therapeutic strategy depends on the type of lesion and variability of local expertise.

Hemodynamically Significant Venous Stenosis

The commonly used parameter to characterize the hemodynamic relevance of a stenosis is a reduction in vessel diameter exceeding 50% based on angiographic and/or ultra-

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sonographic findings. In contrast to an exact diagnosis in a synthetic AVG with a known standard diameter, it may be difficult to describe reliably the percentage of narrowing in a native vein, particularly because this vein may present a prestenotic and/or poststenotic aneurysmic enlargement. The hemodynamic relevance of a 50% stenosis in a native AVF therefore should be supported by clinical symptoms, abnormal physical findings, and flow measurements (see CPG 4). The diagnosis of "hemodynamically relevant venous stenosis" based on a combination of clinical and technical findings should initiate a corrective procedure, either percutaneous or surgical intervention.

In AVFs, significant stenoses may not elevate dynamic or static pressures, although such lesions can result in decreased access flow and elevated recirculation (see CPG 4) that are associated with increased risk for thrombosis.[369] Treatment of hemodynamically significant venous stenosis prolongs the use-life of the AVF.[322,356,358,369,412] A study of 32 patients and 30 controls showed a beneficial effect on AVF survival of prophylactic angioplasty of stenoses.[390] Subsequent Kaplan-Meier analysis of a larger cohort of patients over 5 years showed that preemptive treatment decreased the failure rate ($P = 0.003$), and the Cox hazards model identified treatment ($P = 0.009$) and greater baseline access flow ($P = 0.001$) as the only variables associated with favorable outcome.[389] A significant increase in access blood flow rate was observed, as well as a significant decrease in access-related morbidity by approximately halving the risk for hospitalization, central venous catheterization, and thrombectomy. This group showed, in a population of 120 patients with AVFs, that UDT measurements were reproducible and highly accurate in detecting stenosis and predicting thrombosis in forearm AVFs. Neither Q_A/MAP nor ΔQ_A improved the diagnostic performance of Q_A alone, although its combination with ΔQ_A increased the test's sensitivity for stenosis.[339] These data support the value of monitoring and surveillance in AVFs (see CPG 4). In AVFs, 75% of stenoses producing low flow are at or near the AV anastomosis and 25% are in the outflow track.

Aneurysm Formation in a Primary Fistula

Progressive enlargement of an aneurysm eventually can compromise the skin above the fistula, leading to possible rupture. This can result in hemorrhage, exsanguination, and death. In the Work Group's opinion, large aneurysms can prevent access to the adjacent fistula for needle placement, thereby limiting potential cannulation areas.

Aneurysm formation in a primary fistula can be observed in the following situations:

1. Within the first postanastomotic venous segment in the presence of a hemodynamically relevant stenosis in the juxta-anastomotic position. The therapy of choice is a new AV anastomosis using a "healthy" venous segment located a few centimeters more proximally, but as close to the former anastomosis as possible, to preserve the maximum area for cannulation. Here, surgery may provide better results than angioplasty. Secondary patency rates may be very similar, although repeated angioplasty is far more expensive, with increased morbidity, risk for catheter placement, and inadequate HD sessions.
2. Within cannulation areas. This type of aneurysm is caused mainly by the so-called "1-site-itis" cannulation[413] and should lead to abandonment of the area for cannulation

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(see CPG 3) and strict enforcement of the "rope-ladder" cannulation method if a buttonhole does not seem practical. The latter is by far the best available method for prevention. For hemodynamic reasons, aneurysms of this type are combined at times with a preaneurysm stenosis, but more commonly with a postaneurysm stenosis.

Therapeutic options for managing the aneurysms include the following:

1. Cannulation should *not* be continued along any type of venous aneurysm, particularly in patients for whom the skin layer within the aneurysm is thin and prone to infection—a sign of impending perforation.
2. In cases of progression of aneurysm and stenosis, a series of surgical procedures are available, including: i) partial resection of the wall of the aneurysm and insertion of the resected material as patch along the stenosis, forming a patch from a segment of a venous branch; ii) mobilizing an adjacent venous branch for local repair by a "swing-by-technique"; and iii) other options. In all cases in which surgery can provide a (nearly) perfect inner diameter while preserving cannulation sites, angioplasty should be the second choice. Currently, stent insertion should be avoided along cannulation sites in fistulae.
3. Aneurysms along the venous outflow tract where cannulations are not performed routinely are found for anatomic reasons (eg, in junctions of veins, areas of venous valves with a rigid basic ring, and cases of old venous lesions caused by former venotomy, catheter insertion, and so on) as nucleus for a stenosis followed by a prestenotic aneurysm. Sometimes these lesions are caused by "1-site-itis," in which the same area is cannulated repeatedly without any attempt at buttonhole development. It is particularly prone to develop when intra-AVF pressures are high, as in arm AVFs with cephalic arch stenosis, or in high-flow AVFs. The therapy of choice for these stenoses is angioplasty; when elastic recoil occurs, PTA should be combined with stent insertion in these more central outflow veins. Recurrent stenoses should undergo surgery.

Indications for Preemptive PTA (CPG 5.3)

Preemptive PTA may be indicated in certain cases of abnormal physical findings (see Fig 8). These findings are more important than other criteria. See also the rationale for CPG 5.2. However, certain facets should be kept in mind. This may be particularly important in "underserved" areas where the dialysis staff has no choice other than to rely on abnormal physical findings.

Tools for physical examination have been described in CPG 4. However, Table 17 provides a quick summary.

To detect the early beginning of an abnormality requires continuous meticulous education and daily practice. When a high level of expertise is achieved, a definitive diagnosis can be achieved in approximately 60% to 80% of cases through the presence of abnormal physical findings that lead to an intervention. These findings should be documented and preserved in the chart and—if possible—electronically to continue the observation of the very earliest abnormality. In the remaining 20% to 40% of patients

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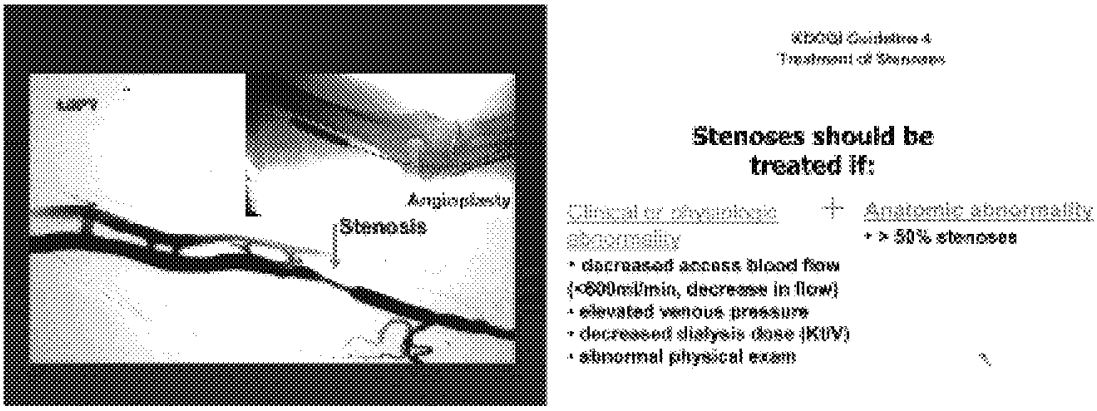
Figure 8. Treatment of stenosis. (Courtesy of Dr. Thomas Vesely)



without a definitive diagnosis after physical examination, further diagnostic steps should be undertaken using (preferably first) ultrasound followed by, if necessary, angiographic techniques, including the option of angioplasty during the same session; however, this is dependent on local availability and expertise.

Previous Thrombosis in the Access

It was shown repeatedly that thrombosis of AVFs is caused by anastomotic disorders, predominantly stenosis. Episodes of hypotension during HD may be contributory in some cases. No data exist to determine whether hypotension alone, even if for a few hours, can produce thrombosis in the absence of an underlying stenosis limiting flow into the access. Irrespective of type of treatment given for the previous episode(s) of access thrombosis, these patients should be considered at risk because anastomotic residuals or recurrent development of stenosis at the same site are common. Therefore, special attention should be taken to prevent recurrence of clinical signs. This strategy requires repeated continuous physical examination—a quick chairside procedure in the hands of experienced personnel preceding any cannulation procedure.

Persistent Abnormal Surveillance Test (see CPG 4.2)

Because surveillance test results at times are observer dependent, an abnormal isolated finding in any case should be supported by abnormal physical symptoms. Persistence of abnormal physical findings and surveillance test results (elevated pressures, low flows,

Table 17. Summary of Physical Examination

Inspection	Examine for erythema, swelling, gangrene, change of size of aneurysms over time.
Palpation	Feel for intravascular pressure along the veins; examine for segmental differences in quality. Feel for elevated/low skin temperature; check the quality of pulsation along arteries and veins. Check for pain caused by finger pressure.
Auscultation	Check for the presence of typical low-frequency bruit with systolic and diastolic components. Examine for abnormal high-frequency bruit produced by turbulence due to a stenosis.

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abnormal recirculation) require that further diagnostic steps be initiated to establish an exact diagnosis and lead to timely treatment (see CPG 4).

Stenosis (CPG 5.4)

In the absence of method errors, repeated failure to deliver the prescribed dialysis dose by using an AVF should result in immediate evaluation of the vascular access when other reasons can be excluded, eg, technical errors, timing errors, and so on. (See the Guidelines for HD Adequacy and also the rationales for CPG 5.1 and CPG 5.2.)

The degree of stenosis is graded by the percentage of narrowing of the access, the reference being the diameter of the immediately upstream or downstream "normal vessel." The reference diameter can be difficult to determine when the AVF is irregular or aneurysmal or at the confluence of 2 vessels. Grading of severity also can be done on the basis of the drop-off in systolic or mean pressure across the stenosis.[414,415] The degree of residual effacement tolerated varies among interventionalists. Some demand no residual at all unless it is the first PTA ever done. Swelling, local or generalized in the arm, caused by central venous stenosis may take additional time to resolve.

Dilation often is painful locally and local anesthesia may be needed at times. Venous stenosis in the outflow may be "rock hard" and require high-pressure balloons (bursting pressures of 25 to 30 atmospheres), as well as more prolonged inflation periods. Resistant stenoses are less common, usually less than 1% in forearm and 5% of upper-arm fistulae.[112] There is no convincing proof that such lesions respond better to cutting balloons[416] because studies have been small and not prospective. The Work Group recommends that high-pressure balloons be used first because cutting devices have not been studied adequately.

Thrombectomy (CPG 5.5)

In most patients, thrombosis is the final complication after a period of AVF dysfunction. Treatment of thrombosis should start as early as possible. The risk of delay is progressive growth of the thrombus that makes interventional/surgical procedures more difficult and risky with regard to long-term success. The vascular access should be reopened as soon as possible to resume regular dialysis treatment and avoid resorting to a short-term catheter. In addition, delay produces a longer period of contact between the surface of the thrombus and the vessel wall, thereby increasing the risk that extraction of thrombus may further damage the endoluminal layer. This could favor future thrombotic events. Early intervention increases the likelihood that the same AVF can be used to provide future dialyses.

Although thrombectomy procedures are more challenging in fistulae than grafts, results are more rewarding.[417] Better long-term patency has been achieved in the largest series to date as long as the underlying stenoses are sufficiently dilated: 1-year primary patency rates of 50% and secondary patency rates of 80% have been reported.[418] Results reported in the upper arm are not as good. The unmasking of stenoses in close to 100% of cases warrants stenosis-detection programs similar to those for grafts.[419]

After thrombosis is established, resolution depends on local expertise. Interventional thrombectomy and PTA of the underlying stenosis have gained wide acceptance. Nevertheless, there are no results from a larger series of surgical treatment of AVF thromboses

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available. This leads to the astonishing fact that there are no comparable data available in this important field of access care.

Thrombosed fistulae can be declotted by using purely mechanical methods (dilation and aspiration),[419] a thrombolytic,[420] or a combination of both.[421] Success rates are greater than 90% for the techniques. If a central vein stenosis is found, interventionalists frequently resort to the use of stents. Long-term results after dilation in the largest series are better in forearm native fistulae compared with grafts. Initial success rates for declotting are better in grafts compared with forearm fistulae, but early rethrombosis is frequent in grafts; thus, primary patency rates can be better for native fistulae after the first month's follow-up.[419] Although AVF function may be reestablished successfully as long as a week after thrombosis occurs, most should be treated as soon as possible.[422]

A variety of devices are available for mechanical thromboaspiration. With all, there are the issues of residual clots and cost-effectiveness of the devices over the simple procedure of catheter-directed aspiration. A meta-analysis should be performed.

Surgical thrombectomy is performed by using a Fogarty thrombectomy catheter, supported by retrograde digital expression of the thrombotic material and followed by correction of the stenosis by using a couple of techniques according to the individually varying condition. However, there are only scattered reports with initial success rates of only 65%[423] compared with 90% or better for endovascular techniques. In a small study of 29 patients, a primary patency rate of 50% at 4 months was reported.[424] Surgery seems to be the preferred technique to treat thrombosis in forearm AVFs with juxta-anastomotic stenoses, mainly by placement of a new anastomosis.[424] With more proximally/centrally located thromboses, preference should be given to interventional endoluminal techniques. Early recurrence of stenosis/thrombosis can be decreased by insertion of a stent. On occasion, when both the artery and vein are thrombosed, conversion from a side-to-side to end-to-side anastomosis can be attempted, with the goal of using the newly created fistula immediately. This procedure was successful in 57% of 72 patients, particularly those with thrombosis of the AVF to the first side branch only, with the remaining fistula maintaining patency through collateral flow.[425]

Access Evaluation for Ischemia (CPG 5.6.1)

This evaluation should be a part of regular monitoring conducted routinely in all dialysis facilities. Particularly elder and hypertensive patients with a history of peripheral arterial occlusive disease and/or vascular surgery, as well as patients with diabetes, are prone to develop access-induced steal phenomenon and steal syndrome. In any case, clinical examination is mandatory, followed by ultrasound or radiological evaluation, as necessary. The patient must be referred to a vascular surgeon to decide on additional procedures. Delay can lead to catastrophic gangrene and hand amputation. The importance of this type of monitoring will increase in the future because of demographic changes in the dialysis population.

An AVF normally produces an alteration in blood flow patterns, a "physiological" steal phenomenon,[426] that is seen in forearm AVFs and in a greater incidence in elbow/upper-arm AVFs.[427] Physiological steal occurs in 73% of AVFs and 91% of AVGs.[428] With the

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aging of the HD population and the increase in arterial changes caused by diabetes and hypertensive remodeling, the incidence of symptomatic peripheral ischemia to the hand/arm (pain, necrosis of ≥1 fingertips) is increasing, but fortunately is still uncommon (;1% to 4%).[48] Milder symptoms of coldness and some pain during dialysis may occur in up to 10% of cases and fortunately improve over weeks to months.[429] It also is more common with prosthetic bridge grafts; less than 2% versus 4%.[48,430] A decrease in distal perfusion pressures is found regularly and is more pronounced in patients with advanced arteriomedial sclerosis. In this type of patient, occurrence of a steal syndrome seems less dependent on access flow volume than on degree of the peripheral arterial obstructive disease.

Recently, staging according to lower-limb ischemia was proposed[48]:

1. Stage I, pale/blue and/or cold hand without pain;
2. Stage II, pain during exercise and/or HD;
3. Stage III, pain at rest;
4. Stage IV, ulcers/necrosis/gangrene.

It is important to differentiate the findings of hand ischemia from those of carpal tunnel compression syndrome, tissue acidosis, and edema from venous hypertension. Noninvasive evaluation should be performed, including digital blood pressure measurement, DDU, and—if available—transcutaneous oxygen measurement.[48]

Corrective results may be good at an early point in the process, but in any of these patients, one should be aware that the process of arterial damage could be progressive. Particularly in older patients with diabetes with an elbow/upper-arm AVF, monomelic ischemic neuropathy can be observed; an acute neuropathy with global muscle pain, weakness, and a warm hand with palpable pulses starting within the first hours after creation of the AVF.[431] Diagnosis of monomelic ischemic neuropathy is a clinical diagnosis, and immediate closure of the AVF is mandatory.

Emergent Referral to a Vascular Access Surgeon (CPG 5.6.2)

Although most ischemic manifestations occur early after surgery, in about a quarter of all patients, they can develop months to years after arterial constrictions. Fingertip necroses are an alarming symptom with an initially slow progression in most patients over weeks and a rapid final deterioration leading to necrosis and gangrene, indicating that one should aim for early intervention. If ischemic manifestations threaten the viability of the limb, the outflow of the fistula should be ligated.

Therapeutic options depend on the cause of steal syndrome. Arterial stenoses proximal to the anastomosis obstructing the arterial inflow may be dilated by angioplasty,[411] but not in the case of advanced general arterial calcification. High-flow–induced steal syndrome requires a decrease in AVF flow volume. Banding procedures of the postanastomotic vein segment using different techniques as practiced in the past were not as successful as expected.[432] It is more beneficial to decrease the diameter of the anastomosis or create a new AV anastomosis distally. The success of the procedure after surgery should be evaluated by using access flow measurements.

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In cases in which a physiological steal phenomenon becomes clinically symptomatic, ligation of the peripheral limb of the radial artery may be successful. Clinically symptomatic steal syndromes with normal or low BFRs represent the majority of cases with access-related peripheral ischemia. Since the new technique of the distal revascularization—interval ligation (DRIL) operation was published in 1988,[429] several groups have confirmed the good results.[48,433] In patients with a venous anastomosis to the brachial artery, with the DRIL procedure, the anastomosis is bridged by a venous bypass, after which the artery is ligated closely peripherally to the anastomosis. BFR into the AVF does not change substantially. Most patients do significantly better, presumably because of an increase in peripheral arterial perfusion.

In patients with low BFRs and signs of peripheral ischemia, the proximal AV anastomosis technique provides satisfactory results.[434] The idea is to ligate the preexisting anastomosis to the brachial artery in the region of the elbow or distal upper arm and place a new arterial anastomosis in the proximal upper arm, somewhere near the beginning of the subclavian artery. Blood volume is brought down to the vein through an interposed vein graft or small-diameter PTFE graft. Thus, a sufficient BFR into the vein is provided and peripheral perfusion pressure is reestablished; cannulation for HD can be continued immediately.

Infection (CPG 5.7)

Although infections of fistulae are rare, any episode of infection potentially is lethal in face of the impaired immunologic status of long-term dialysis patients.

Very rare access infections at the AV anastomosis require immediate surgery with resection of the infected tissue. Should an arterial segment be resected, an interposition graft using a vein can be attempted or a more proximal new AV anastomosis may be created with exclusive use of degradable suture material.

More often, infections in AVFs occur at cannulation sites. Cannulation at that site must cease, and the arm should be rested.

In all cases of AVF infection, antibiotic therapy is a must, initiated with broad-spectrum vancomycin plus an aminoglycoside. Based on results of culture and sensitivities, conversion to the appropriate antibiotic is indicated. Infections of primary AVFs should be treated for a total of 6 weeks, analogous to subacute bacterial endocarditis.[435] A serious complication of any access-related bacteremia is represented by metastatic complications, as described.[159]

LIMITATIONS

Considerably fewer data have been published regarding management of complications in fistulae compared with grafts. Some aspects are "accepted" as the standard of care because they are described in standard surgical textbooks and surgeons/interventionalists accept them.

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Appropriate management and treatment of AVG complications may improve the function and longevity of the vascular access.

6.1 Extremity edema:

Patients with extremity edema that persists beyond 2 weeks after graft placement should undergo an imaging study (including dilute iodinated contrast) to evaluate patency of the central veins. The preferred treatment for central vein stenosis is PTA. Stent placement should be considered in the following situations:

6.1.1 Acute elastic recoil of the vein (>50% stenosis) after angioplasty. (B)

6.1.2 The stenosis recurs within a 3-month period. (B)

6.2 Indicators of risk for graft rupture:

Any of the following changes in the integrity of the overlying skin should be evaluated urgently:

6.2.1 Poor eschar formation. (B)

6.2.2 Evidence of spontaneous bleeding. (B)

6.2.3 Rapid expansion in the size of a pseudoaneurysm. (B)

6.2.4 Severe degenerative changes in the graft material. (B)

6.3 Indications for revision/repair:

6.3.1 AVGs with severe degenerative changes or pseudoaneurysm formation should be repaired in the following situations:

6.3.1.1 The number of cannulation sites are limited by the presence of a large (or multiple) pseudoaneurysm(s). (B)

6.3.1.2 The pseudoaneurysm threatens the viability of the overlying skin. (B)

6.3.1.3 The pseudoaneurysm is symptomatic (pain, throbbing). (B)

6.3.1.4 There is evidence of infection. (B)

6.3.2 Cannulation of the access through a pseudoaneurysm must be avoided if at all possible and particularly so if the pseudoaneurysm is increasing in size. (B)

6.4 Treatment of stenosis without thrombosis:

Stenoses that are associated with AVGs should be treated with angioplasty or surgical revision if the lesion causes a greater than 50% decrease in the luminal diameter and is associated with the following clinical/physiological abnormalities:

6.4.1 Abnormal physical findings. (B)

6.4.2 Decreasing intragraft blood flow (<600 mL/min). (B)

6.4.3 Elevated static pressure within the graft. (B)

6.5 Outcomes after treatment of stenosis without thrombosis:

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After angioplasty or surgical revision of a stenosis, each institution should monitor the primary patency of the AVG. Reasonable goals are as follow:

6.5.1 Angioplasty:

6.5.1.1 The treated lesion should have less than 30% residual stenosis and the clinical/physiological parameters used to detect the stenosis should return to acceptable limits after the intervention. (B)

6.5.1.2 A primary patency of 50% at 6 months. (B)

6.5.2 Surgical revision:

6.5.2.1 The clinical/physiological parameters used to detect the stenosis should return to acceptable limits after the intervention. (B)

6.5.2.2 A primary patency of 50% at 1 year. (B)

6.6 If angioplasty of the same lesion is required more than 2 times within a 3-month period, the patient should be considered for surgical revision if the patient is a good surgical candidate.

6.6.1 If angioplasty fails, stents may be useful in the following situations:

6.6.1.1 Surgically inaccessible lesion. (B)

6.6.1.2 Contraindication to surgery. (B)

6.6.1.3 Angioplasty-induced vascular rupture. (B)

6.7 Treatment of thrombosis and associated stenosis:

Each institution should determine which procedure, percutaneous thrombectomy with angioplasty or surgical thrombectomy with AVG revision, is preferable based upon expediency and physician expertise at that center.

6.7.1 Treatment of AVG thrombosis should be performed urgently to minimize the need for a temporary HD catheter. (B)

6.7.2 Treatment of AVG thrombosis can be performed by using either percutaneous or surgical techniques. Local or regional anesthesia should be used for the majority of patients. (B)

6.7.3 The thrombectomy procedure can be performed in either an outpatient or inpatient environment. (B)

6.7.4 Ideally, the AVG and native veins should be evaluated by using intraprocedural imaging. (B)

6.7.5 Stenoses should be corrected by using angioplasty or surgical revision. (B)

6.7.6 Methods for monitoring or surveillance of AVG abnormalities that are used to screen for venous stenosis should return to normal after intervention. (B)

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6.8 Outcomes after treatment of AVG thrombosis:

After percutaneous or surgical thrombectomy, each institution should monitor the outcome of treatment on the basis of AVG patency. Reasonable goals are as follows:

6.8.1 A clinical success rate of 85%; clinical success is defined as the ability to use the AVG for at least 1 HD treatment. (B)

6.8.2 After percutaneous thrombectomy, primary patency should be 40% at 3 months. (B)

6.8.3 After surgical thrombectomy, primary patency should be 50% at 6 months and 40% at 1 year. (B)

6.9 Treatment of AVG infection:

Superficial infection of an AVG should be treated as follows:

6.9.1 Initial antibiotic treatment should cover both gram-negative and gram-positive microorganisms. (B)

6.9.1.1 Subsequent antibiotic therapy should be based upon culture results.

6.9.1.2 Incision and drainage may be beneficial.

6.9.2 Extensive infection of an AVG should be treated with appropriate antibiotic therapy and resection of the infected graft material. (B)

BACKGROUND

In this update of the KDOQI Guidelines, the Work Group did not perform a comprehensive literature and data review of recent studies of AVG complications. The primary change from previous versions of the KDOQI Vascular Access Guidelines is consolidation of related material on AVGs into a single unified guideline. However, the fundamental tenets are unchanged from previous editions. Newer references, including reviews, are included when appropriate.

RATIONALE

Extremity Edema and Stenosis (CPG 6.1)

The AVG, although decreasing in frequency of use, remains a major type of vascular access for HD in the United States.[2] The natural history of an AVG is the progressive development of neointimal hyperplastic stenoses in the outflow track. Although these stenotic lesions most commonly occur at the venous anastomosis, they also can occur at the arterial anastomosis and within the native veins that provide outflow from the AVG. This resulting increase in venous pressure leads to edema proximally and, in extreme circumstances, evidence of venous collateral flow. The presence of a hemodynamically significant stenosis can decrease the ability of the access to deliver adequate flow and increase the risk for AVG thrombosis. Early detection and treatment of hemodynamically significant stenoses is considered a primary tenet of a vascular access management program.

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Extremity edema persisting beyond 2 weeks (immediate postoperative period) after placement of an AVG may indicate inadequate venous drainage or central venous obstruction.[30,436] In many cases, the stenosis results from the prior placement of a subclavian catheter; risk for stenosis is increased by previous catheter infection.[170] PTA of the stenotic or obstructed venous segment can lead to resolution of the edema. However, acute elastic recoil may occur after angioplasty of large central veins.[437] Studies have shown that the use of stents may improve long-term patency of the central vein in certain circumstances.[438–442] Surgical treatment of central venous stenosis is associated with substantial morbidity and should be reserved for extraordinary circumstances.[443]

Graft Degeneration and Pseudoaneurysm Formation (CPG 6.2, CPG 6.3)

Repeated cannulation of an AVG may cause degeneration of the graft material that can progress to involve the subcutaneous tissues overlying the vascular access.[444,445] These degenerative changes may eventually compromise the circulation to the skin. Degeneration of the AVG and necrosis of the overlying subcutaneous tissue may lead to a progression of clinical problems, including difficulty achieving hemostasis upon needle withdrawal, spontaneous bleeding from cannulation sites, severe hemorrhage, and—ultimately—acute graft rupture. The degeneration of AVGs combined with a venous outflow stenosis fosters formation of a pseudoaneurysm. Progressive enlargement of a pseudoaneurysm produces thinning of the overlying skin, thereby accelerating skin necrosis that increases the risk for acute graft rupture. A large pseudoaneurysm can limit the availability of needle cannulation sites. Dialysis needles must not be inserted into a pseudoaneurysm. A severely degenerated graft or enlarging pseudoaneurysm should be repaired to decrease the risk for acute rupture and restore additional surface area for cannulation.

A pseudoaneurysm is treated most effectively by resection and segment interposition.[106,446] Pseudoaneurysms that are not resected may expand and rupture, resulting in significant blood loss. Pseudoaneurysms that exceed twice the diameter of the graft or those that are increasing in size should be surgically corrected because of their increased risk for rupture. At times, an endovascular covered stent option may exist.[447] Pseudoaneurysm expansion that threatens the viability of the skin places the patient at risk for graft infection. In these cases, surgical correction is indicated.

Treatment of Stenoses (CPG 6.4–6.8)

Venous stenosis is the most common lesion in AVGs, although in many cases, more than 1 lesion is present within the graft or at the anastomoses. Although previous studies suggested that arterial inflow lesions were uncommon (<5% of all lesions),[108,266] more recent experience suggests the arterial or arterial anastomotic lesion affecting blood flow into the AVG may be up to 20% to 25% of all lesions identified by angiography.

A hemodynamically significant outflow stenosis decreases intragraft blood flow and increases intragraft pressure.[10] The lower blood flow, in turn, may reduce the efficiency of HD treatment[327,355] and increase the risk for vascular access thrombosis.[285,287,322,340,347,364,376,448,449] Conversely, inflow lesions and intragraft lesions may be

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associated with low pressure in the body of the graft and venous outflow. A hemodynamically significant stenosis is defined as a 50% or greater reduction in normal vessel diameter accompanied by a hemodynamic, functional, or clinical abnormality (see CPG 4).[449,450] By means of angiography, about 90% of thrombosed grafts are associated with stenosis, predominantly in the outflow, at the venous anastomosis, and more centrally.[109,110,451,452]

PTA or surgical repair of a hemodynamically significant stenosis associated with a nonthrombosed AVG can maintain functionality and delay thrombosis of the vascular access.[269,453,454] Many nonrandomized trials have shown that preemptive treatment of stenoses reduces the rate of thrombosis[10,322,374,455] and perhaps prolongs the useful life span of the AVG.[10,322,374] A number of observational, but not randomized, studies show that a greater fraction of grafts remain free of interventions or thrombosis if the AVG is patent at the time of intervention.[111,112,269,354,456] The fraction of AVGs free of further intervention or thrombosis ranged from 71% to 85% among 4 studies if PTA was performed preemptively compared with only 33% to 63% if PTA was performed after thrombectomy of the graft.[10,322,374,455]

Although these results would suggest that elective correction of stenoses before thrombosis might increase the long-term survival of the AVG, recent studies suggested that prophylactic treatment of stenoses, although reducing thrombosis events, does not extend the useful life span of AVG rates.[384,386] Thus, the major reason for surveillance is the prevention of thrombosis (see CPG 4).

No convincing evidence exists showing that repair of an asymptomatic anatomic stenosis (>50% diameter reduction) improves function or delays thrombosis of the vascular access. Therefore, prophylactic treatment of a stenosis that fulfills the anatomic criteria (>50% diameter reduction), but is not associated with a hemodynamic, functional, or clinical abnormality, is not warranted and should not be performed.[10,322,354]

Arterial stenosis associated with diminished access inflow and frequently suspected by the presence of excessively negative dialysis circuit prepump pressures (arterial tubing to pump) should be evaluated and corrected when found.

After PTA, anatomic success is defined as residual stenosis less than 30%.[20,457] Published series have consistently reported a 6-month primary (unassisted) patency rate of 40% to 50% after PTA of stenoses associated with nonthrombosed AVGs.[108,111,112,269,354,456] The expected primary patency rate after surgical repair of stenoses associated with nonthrombosed grafts is less well established.[458] Previous Vascular Access Work Groups have determined that a 1-year primary patency rate of 50% after surgical revision should be the goal.

Individual patients may have a rapid recurrence of stenoses that requires repeated PTA.[108,453] In these patients, repeated angioplasty may not be cost-effective, and surgical revision may be beneficial. Previous Vascular Access Work Groups have defined rapid recurrence of a stenosis as the need for more than 2 angioplasty procedures within a 3-month interval.

Previous studies reported that the use of endovascular stents as the primary treatment for venous stenosis provides long-term results that are similar to those obtained with an-

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gioplasty alone.[382,459-461] Stents should be reserved for patients with contraindications to surgical revision and for treatment of angioplasty-induced venous rupture.[462-464]

Several studies have directly compared percutaneous thrombectomy with surgical thrombectomy with revision for treatment of AVG thrombosis.[465-470] A review of comparative and noncomparative studies reveals conflicting results and does not yield a definitive preference.[24,106,356,467-479] In the opinion of the Work Group, percutaneous thrombectomy or surgical thrombectomy with revision are both effective techniques for the treatment of AVG thrombosis and associated stenosis. The thrombectomy procedure should be performed expeditiously to avoid the need for a short-term catheter. Hospitalization and general anesthesia increase the cost and risk of the thrombectomy procedure and should be avoided when possible.

An underlying stenosis frequently (>85%) is the cause of AVG thrombosis.[108,480,481] Intraprocedural imaging should be used to evaluate the outflow veins for improved detection of significant stenoses.[382,470] Identification and treatment of all significant stenoses are essential to optimize long-term patency of the thrombectomy procedure. PTA of stenoses associated with AVG thrombosis correlates with poorer outcomes compared with nonthrombosed AVGs.[269] After percutaneous thrombectomy, the majority of reported 3-month primary (unassisted) patency rates range from 30% to 40%.[471,473,476,478,480,481] The Work Group believes that percutaneous thrombectomy should achieve a 3-month primary patency rate of 40%. After surgical thrombectomy, the achievable goals are a 6-month primary patency rate of 50% and a 1-year primary patency rate of 40%. Surgical procedures are held to a higher standard because the AVG usually is extended farther up the extremity when a surgical revision of a stenosis is performed, using up "venous capital."

Infection (CPG 6.9)

While cardiac causes account for almost half the deaths in adult patients with CKD stage 5, the second leading cause of death is infection, much of it related to the type of vascular access in use.[60] AVGs have a greater rate of infection than autologous fistulae, and, unfortunately, antibiotics alone frequently are inadequate and surgical procedures are needed.[482] Management of an AVG infection is a balance between achieving resolution of the infection while preserving the vascular access.[59,483] Superficial infections should be treated initially with broad-spectrum antibiotic therapy. Subsequent antibiotic therapy should be based upon the identification of the causative bacterial organism.[201,484] A more extensive AVG infection can lead to bacteremia, sepsis, and death. Surgical exploration and removal of infected graft material, combined with antibiotic therapy, often is necessary for complete resolution.[484]

Subclinical infection can develop in AVGs, typically resulting from retained graft material. Diagnosis may require performance of indium-labeled white blood cell or gallium scans. Such infection frequently is manifested as resistance to epoetin therapy, along with evidence of a systemic inflammatory response; frequently, it occurs in abandoned and nonfunctioning grafts. Epoetin responsiveness is restored only after removal of the graft.

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LIMITATIONS AND COMPARISON TO OTHER GUIDELINES

These updated CPGs are essentially unchanged in content from those of previous editions of the KDOQI Vascular Access Guidelines. More evidence now is available for the guidelines than in previous editions. However, there is still a paucity of RCTs to better define the effect of interventions on clinically important outcomes. These guidelines also are comparable to those recommended by the Society of Interventional Radiology,[457] American College of Radiology,[485] and a joint committee of several surgical societies.[458]

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GUIDELINE 7. PREVENTION AND TREATMENT OF CATHETER AND PORT COMPLICATIONS

Catheters and ports are essential tools for providing urgent and, in some cases, long-term vascular access. Prevention and early treatment of complications should greatly reduce associated morbidity and mortality.

7.1 Catheters and ports should be evaluated when they become dysfunctional. Dysfunction is defined as failure to attain and maintain an extracorporeal blood flow of 300 mL/min or greater at a prepump arterial pressure more negative than −250 mm Hg. (B)

7.2 The exception is pediatric or smaller adult catheters that are not designed to have flows in excess of 300 mL/min. (B)

7.3 Methods that should be used to treat a dysfunctional or nonfunctional catheter or port include:

7.3.1 Repositioning of a malpositioned catheter. (B)

7.3.2 Thrombolytics, using either an intraluminal lytic, intradialytic lock protocol, or an intracatheter thrombolytic infusion or interdialytic lock. (B)

7.3.3 Catheter exchange with sheath disruption, when appropriate. (B)

7.4 Treatment of an infected HD catheter or port should be based on the type and extent of infection.

7.4.1 All catheter-related infections, except for catheter exit-site infections, should be addressed by initiating parenteral treatment with an antibiotic(s) appropriate for the organism(s) suspected. (A)

7.4.2 Definitive antibiotic therapy should be based on the organism(s) isolated. (A)

7.4.3 Catheters should be exchanged as soon as possible and within 72 hours of initiating antibiotic therapy in most instances, and such exchange does not require a negative blood culture result before the exchange. (B) Follow-up cultures are needed 1 week after cessation of antibiotic therapy (standard practice).

7.4.4 Port pocket infections should be treated with systemic antibiotics and irrigation, in conjunction with the manufacturers' recommendations. (B)

RATIONALE

Evaluation of Dysfunction (CPG 7.1)

Catheter dysfunction can be attributed to many causes, and progression of dysfunction to nonfunction varies accordingly.[182] The most common complications are thrombosis and infection.[486,487] Even with care, fewer than half the catheters placed as "long-term access" are in use a year after their placement,[488] and about a third are removed because they fail to deliver adequate blood flow. The definition of adequate blood flow varies inversely with the "efficiency" of HD. High-efficiency dialysis as practiced in the United States requires

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dialyzer-delivered BFRs greater than 300 mL/min to achieve the target single-pool Kt/V of 1.2 (see the KDOQI HD Adequacy Guidelines). Conversely, in Europe, BFRs less than 300 mL/min frequently are used because dialysis treatment durations are longer.[203] Adequacy of dialysis is influenced additionally by the site of placement and degree of recirculation.[489,490] Recirculation in femoral catheters is significantly greater than that in internal jugular catheters (13.1% versus 0.4%; $P < 0.001$).[193] In addition, femoral catheters shorter than 20 cm have significantly greater recirculation (26.3%) than those longer than 20 cm (8.3%; $P = 0.007$). This length dependency may result from the ultimate tip position of longer catheters in the IVC as opposed to the common iliac vein with shorter catheters. The greater blood flow available to the catheter at the IVC site reduces recirculation. When dialysis dose delivery is a priority, placing the short-term catheter in the internal jugular vein is an advantage. Recirculation may increase when the "lines are reversed" (inversion of inlet and outlet lumens), even in "well functioning" nonsplit catheters (from 2% to 3% to >10%).[491] Although reversal of tubings may increase urea clearance by increasing blood flow temporarily,[184] it usually is at a BFR less than 300 mL/min and should never be used except temporarily until the problem is definitively corrected.

A dysfunctional catheter usually is easier to salvage than a nonfunctional catheter, thereby preventing complications of a new placement.[249] Early treatment also reduces the likelihood and minimizes the extent of inadequacy of dialysis caused by catheter dysfunction. Delivery of adequate dialysis dose is dependent upon blood flow and treatment duration. For any given dialyzer, low BFRs during HD extend treatment times and all too often still result in underdialysis (caused by unrecognized recirculation). A BFR less than 300 mL/min was noted in 15% of treatments with catheters.[249] Catheter dysfunction leads to 17% to 33% of untimely catheter removals,[487,488] and thrombosis of the catheter occurs in access loss in 30% to 40% of patients.

It is to be noted that the criterion for determining access dysfunction, ie, blood flow greater than 300 mL/min, is qualified by the prepump arterial pressure[182] factored for the length and lumen diameter of the catheter.[183,490] Prepump arterial pressure monitoring is essential to ensure valid blood flows, and adequacy is determined largely by the amount of blood pumped to and through the dialyzer.[189,191,200] Consequences of catheter dysfunction are many, including increases in morbidity and mortality,[20,248,258] increase in economic expenditures,[250] and a "real" concern to patients, 60% of whom report fear of thrombosis second only to pain in decreasing their QOL.[252]

In CVCs, the most likely cause for low BFRs is thrombotic occlusion. In the likely event that low BFR or occlusion will occur at some time during the useful life of a catheter, prospective monitoring is essential to detect dysfunction. Regular assessment of dialysis performance is strongly recommended to ensure dialysis adequacy.[189] Catheter performance parameters to consider are shown in Table 18 and include maximal consistently achievable BFR, resistance to blood flow indicated by arterial and venous pressures during HD, and blood recirculation rate.[492,493] Of these, the one favored by the Work Group is the ratio of dialyzer BFR achieved, factored by the prepump arterial limb pressure in absolute units.

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Table 18. Signs of CVC Dysfunction: Assessment Phase

Blood pump flow rates <300 mL/min
Arterial pressure ↑ (< –250 mm Hg)
Venous pressure ↑ (>250 mm Hg)
Conductance ↓ (<1.2) : the ratio of blood pump flow to the absolute value of prepump pressure
URR progressively <65% (or Kt/V <1.2)
Unable to aspirate blood freely (late manifestation)
Frequent pressure alarms—not responsive to patient repositioning or catheter flushing
Trend analysis of changes in access flow is the best predictor of access patency and risk for thrombosis.

Early detection of access dysfunction is most likely if all members of the VAT are involved.[198] The use of CQI in catheter access necessitates collaboration among team members, with specific tasks assigned to certain individuals, who then provide input and/or feedback.

The minimally accepted dialyzer BFR of 300 mL/min is easily achieved by using newer catheters that are capable of achieving rates of 400 mL/min or greater when properly placed.[494] Therefore, 300 mL/min is a conservative value in current adult practice and waiting until blood flow decreases to 300 mL/min may be too late to avoid loss of the catheter and unnecessary loss of the access site.

Prevention of catheter and access thrombosis by using antiplatelet agents and anticoagulation has not been successful (see Table 19).

Use of an antiplatelet agent is not recommended because it was not effective in grafts and was associated with more bleeding.[497] A similar conclusion was reached in a prospective nonrandomized comparison of warfarin to aspirin.[498] Use of a low fixed dose (1 mg) of warfarin also was found to be ineffective.[495] Further studies in this area with a higher target international normalized ratio (INR) are warranted.

The first step in assessing dysfunction is shown in Fig 9, which begins with a determination of the age of the catheter.

In catheters recently placed, inadequate blood flow usually is the result of mechanical obstruction, improper tip location affected by patient position, or a problem of catheter integrity, as shown in Table 20. [492]

The need to use a Trendelenberg position to achieve adequate blood flow from a catheter placed in great veins leading to the right atrium always implies that the catheter is improperly placed. If the problem is not obvious and not easily correctable, the patient should be referred to an interventional center for study to diagnose the cause. Although mechanical problems can develop acutely in catheters previously giving good performance, access dysfunction occurring after 2 weeks more likely is the result of progressive occlusion of the catheter tip by fibrin or thrombus. The location of obstruction may reside in the following areas:

1. *Intraluminal thrombus*—within lumen of catheter, partial or complete occlusion.
2. *Catheter tip*—in catheters with side holes at tip of arterial limb, thrombus may occlude or act like "ball valve."

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Table 19. Prophylaxis of TCC-Related Thrombosis

Author, Year	Study Design	N	Follow-up (maximum)	Applicability	Intervention 1	Intervention 2	Outcome	Results	P-Value	Quality
Mokrzycki 2001 [48]	RCT	105	12 mo	↑↑↑	Low dose Warfarin	Placebo	TCC failure	RR 0.8	NS	●
Schenk 2000 [49]	RCT [a]	12	8 mo	↑↑	Interdialytic rTPA lock	Heparin lock (1000 U/s/mL)	Blood flow increase [b]	ND	0.0301	○
							Thrombosis	0% (rTPA) vs. 20% (heparin)	ND	

ND=no data; NS=not significant; RR=relative risk; RCT=randomized controlled trial; rTPA=recombinant tissue plasminogen activator; TCC=tunneled cuffed catheter

a. Cross-over study
b. Flow is statistically significant without an estimator of effect size between the 2 treatment groups

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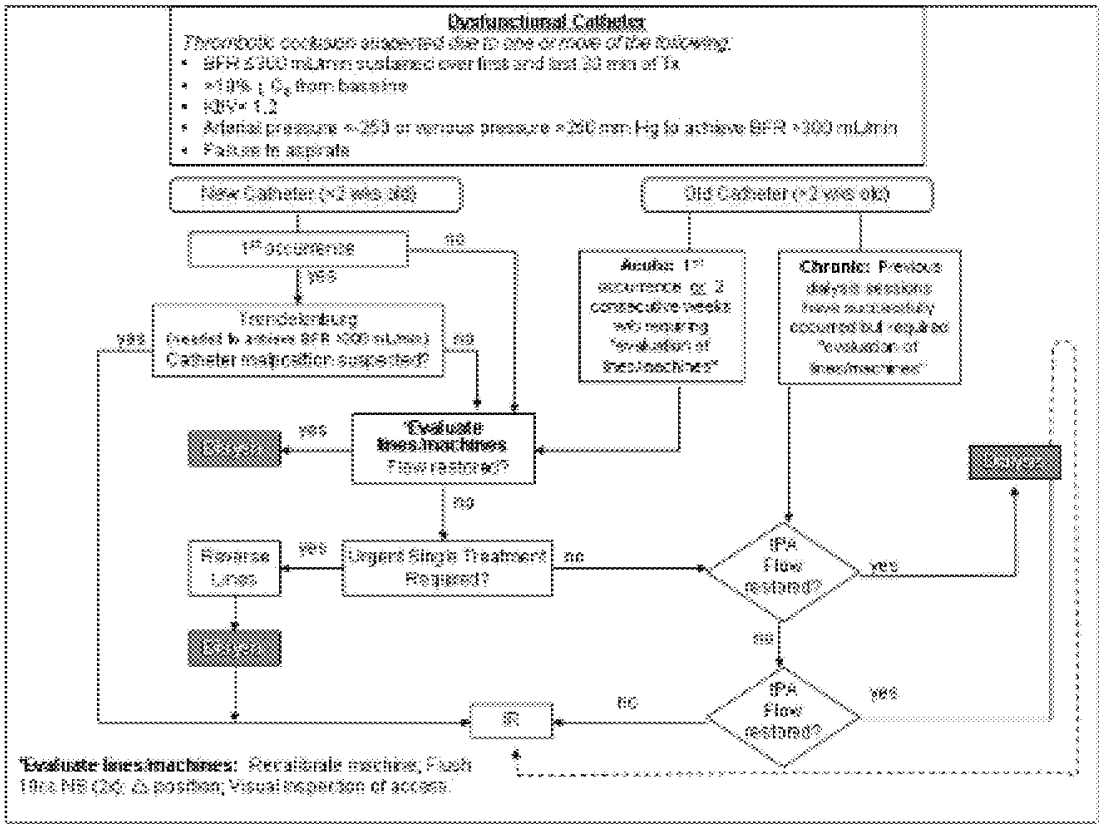
Figure 9. Assessing dysfunction of catheters. Symbols: IR, imaging for correct position. Abbreviation: tPA, tissue plasminogen activator; IR, intervention. (Courtesy of Drs Asif and Anatole Besarab).



3. *Fibrin sheath* (fibrin sleeve)—fibrin adheres to external surface of catheter, thrombus trapped between sheath and catheter tip.
4. *Fibrin tail* (fibrin flap)—fibrin adheres to CVC end, "ball valve" effect.

Methods That Should be Used to Treat a Dysfunctional or Nonfunctional Catheter or Port (CPG 7.3)

A catheter that has migrated out of the mid-right atrium should be repositioned. Catheters of inadequate length should be exchanged over a guide wire to the appropriate position or replaced.[499]

Table 20. Causes of Early Catheter Dysfunction

Mechanical
Kinks (angulation in tunnel)
Misplaced sutures
Catheter migration
Drug precipitation (some antibiotic locks or IV IgG)
Patient position
Catheter integrity
Holes
Cracks

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All catheters are "locked" with some anticoagulant. The purpose of the lock is to prevent thrombosis. Loss of anticoagulant by diffusive transport would be expected. However, it has been known for several years that some fraction of the anticoagulant will leak into the systemic circulation[500,501] by nondiffusive processes and increase the partial thromboplastin time, thus possibly contributing to minor or even major bleeding. In vitro simulations suggest an early leak within 30 seconds, followed by a slower loss of locking solution during the next 30 minutes.[502] The specific gravity of the locking solution likely also influences the rate of leak.[503] Locking solution lost is replaced by blood. It therefore is not surprising that thrombosis is so common in catheters because blood is likely to be in the lumen of the catheter for prolonged times interdialytically. The loss of anticoagulant permits the entry of clotting factors into the catheter lumen. The presence of these processes is manifested by a change in flow long before there is occlusion.

After assessment precludes mechanical dysfunction (see Fig 9), such as a kink or dislodgement, thrombotic occlusion—partial (poor flow on aspiration) or total (unable to aspirate or push)—is the most common cause of catheter dysfunction and/or occlusion.[151,504-506] Pharmacological intervention for catheter-occlusive dysfunction involves treatment with thrombolytics that convert plasminogen to plasmin. Thrombolytics are noninvasive, confer no additional trauma to the patient, have a high level of safety and efficacy, and are cost-effective.[507] A thrombolytic can be administered in the dialysis setting. Because of such advantages and the less practical alternative treatment options, thrombolytic therapy directed at salvaging the catheter should be considered before access replacement because it is the least invasive and least costly of all catheter salvage techniques.

A variety of thrombolytics have been used (Table 21), although at the present time, only tissue plasminogen activator (tPA) is approved by the Food and Drug Administration (FDA). Urokinase (UK) is still available (but is no longer manufactured), as is reteplase, but neither of these lytics currently is available in convenient dosages and must be aliquoted and frozen for use. Teneplase, another lytic, has not been used for access thrombosis. Formulations of some lytics have been tried in studies and are used "off label" at various institutions.

Thrombolytics have proved highly effective in opening partially and fully occluded lumens.[496,508-525] (See also: Abbott Laboratories, prescribing information for abbokinase [urokinase] Chicago, IL, 2003; Boehringer Mannheim GmbH, prescribing information for Reteplase® [reteplase], 2000; Genentech, prescribing information for Cathflo® Activase® [alteplase], 2001.[525A-C]) The most common use of lytics occurs late in the "dysfunction process," when prescribed blood flows are not attained and there is difficulty even in initiating a dialysis treatment. Currently, the package insert only describes the use of the agent for catheters in a timed dwell, based on clinical trials in nondialysis catheters.[526,527] The recent Cathflo Activase Pediatric Study has led the FDA to approve tPA as a thrombolytic in all age groups for the same indications as in the package insert.

In situations in which the obstructive process has progressed to a more severe state, dialysis is urgent, and the catheter is extremely dysfunctional (ie, unable to provide a BFR

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Table 21. Available Thrombolytics

Streptokinase [502,503]
- Highly antigenic
- Low fibrin affinity

Urokinase [151]
- Available for PE treatment
- No longer manufactured (11/2004)

Reteplase [504]
- Used in treatment of AMI
- Must be aliquoted and frozen

Alteplase, tPA [505]
- High Fibrin specificity
- FDA approved
- Available in single dose vials
- No antigenicity

of 200 mL/min), tPA reconstituted appropriately and instilled at a lumen fill volume permits resumption of dialysis in 50% to 90% of instances (see Table 22), although a second dwell may be required. Per the package insert, this lytic should be allowed to dwell for 1 hour or longer. Table 23 summarizes the major studies with tPA in totally occluded catheters.

In general, efficacy increases with longer dwell times with tPA as the lytic. Fewer studies are available with the other agents, but results are similar.[514,517] A recent study showed that a lower dose of 1 mg/lumen of tPA also is effective, restoring catheter patency in 72% with 1 dose, increasing to 83% with a second dose,[513] values only slightly lower than with the "standard" dose of 2 mg/lumen.

The Work Group believes that the use of lytics late in the thrombosis process without adequate prior diagnostic evaluation is in itself "dysfunctional" and *recommends* that the procedures described in Fig 9 be used to evaluate a catheter access on a recurrent basis. Tracking the relationship of prepump pressure, VDP, and flow (see Fig 9) can alert the clinician to the development of catheter dysfunction before late manifestations set in. The emphasis for managing catheter dysfunction should shift to intervention at an earlier stage of dysfunction.

Although endoluminal brushes have been used to clear thrombi from dialysis catheters,[528] there are no convincing data about efficacy and they are expensive. The Work Group does not currently advocate their routine use. Such brushes were originally developed to obtain biofilm specimens from catheters.

The management of fibrin sheaths is discussed further in CPR 7. Currently, the Work Group recommends change of catheter with disruption of the sheath by using a balloon. Fibrin sheath stripping rarely is used because of cost and increased patient morbidity.

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Table 22. Effect of Lytics in Occluded Hemodialysis Catheters

Author, Year	Dwells (n)	Catheters (n)	Patients (n)	Change in BFR (mL/min)	Success Rate Outcome	Dwell Time	Applicability	Quality
Zacharias, 2003 [526]	164	66	30	132 to 256	88%	30 min to 2 h	↑↑	●
Dashleigh, 2000 [488]	56	28	22	75 to 246	86% [a]	2-36 h	↑	●
Crowther, 2000 [509]	42	23	23	>250	65% [b]	272 h	↑	○
Paulsen, 1993 [521]	18	18	8	37 to 260*	83% [a]	30 min to 4 d	↑	○
O'Mara, 2001 [520]	62	25		111 to 243	58% [a]	30 min	↑	○

BFR=blood flow rate
a. Data for all catheters.
b. Successful completion of dialysis.
*Flow measured was that recorded at the blood pump

Table 23. Treatments of TCC Fibrin Sheath Occlusion

Author, Year	Study Design	N	Follow-up (maximum)	Applicability	Intervention 1	Intervention 2	Outcome	Results			Quality
								Urokinase	PFSS		
Gray 2000 [530]	RCT	57	100 d	↑↑	UK IV infusion for 4 h	Percutaneous fibrin sheath stripping	Primary patency rates	97%	87%	NS	●
							Angiogram patency	76%	87%	ND	
							Median secondary patency	32 d	42 d	ND	
							TCC patency [a]	Exchange	PFSS		
Merport 2000 [531]	RCT	30	120 d	↑↑	Exchange over wire	Percutaneous fibrin sheath stripping	Mean catheter life	52 d	25 d	+	●
							% patency at 1 mo	93%	31%	+	
							% patency at 4 mo	23%	0	+	

IV=intravenous; ND=no data; NS=not significant; PFSS=percutaneous fibrin sheath stripping; RCT=randomized controlled trial; TCC=tunneled cuffed catheter; UK=urokinase
+ Statistically significant beneficial effect of treatment compared to control (or intervention 1 vs. intervention 2)
a. Flow > 200 mL/min

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Treatment of an Infected HD Catheter or Port (CPG 7.4)

Definitions

Exit-site infection. Inflammation confined to the area surrounding the catheter exit site, not extending superiorly beyond the cuff if the catheter is tunneled, with exudate culture confirmed to be positive.

Tunnel infection. The catheter tunnel superior to the cuff is inflamed, painful, and may have drainage through the exit site that is culture positive.

Catheter-related bacteremia. Blood cultures are positive for the presence of bacteria with or without the accompanying symptom of fever.

The Work Group recommends the following CDC definitions for catheter-related infections.

Definite bloodstream infection: the same organism from a semiquantitative culture of the catheter tip (>15 colony-forming units per catheter segment) and from a peripheral or catheter blood sample in a symptomatic patient with no other apparent source of infection.

Probable bloodstream infection: defervescence of symptoms after antibiotic therapy with or without removal of catheter, in the setting in which blood cultures confirm infection, but catheter tip does not (or catheter tip does, but blood cultures do not) in a symptomatic patient with no other apparent source of infection.

Possible bloodstream infection: defervescence of symptoms after antibiotic treatment or after removal of catheter in the absence of laboratory confirmation of bloodstream infection in a symptomatic patient with no other apparent source of infection.

Although thrombotic occlusions leading to flow delivery problems are more common than infection, catheter-related infection has emerged as the primary barrier to long-term catheter use. The greater infection rate in catheters compared with grafts and fistulae is its major limitation. Infection is the leading cause of catheter removal and morbidity in dialysis patients.[148,156,201,532,533] The most recent USRDS data indicate that the rate of septicemia in HD patients continues to increase, and hospital admissions for vascular access infection doubled in the last decade.[235] The use of long-term HD catheters instead of short-term catheters has not yet translated into a significant reduction in the incidence of CRB and resultant infective endocarditis in our population.[234,534–539]

Accurate and early diagnosis is essential. A meta-analysis of 8 different methods comparing those that do and do not require catheter removal showed that paired quantitative blood cultures from the peripheral blood and the catheter are the most accurate,[540] but are not routinely performed. However, routine culture methods have negative predictive power (>99%), whereas the positive predictive value increases with the pretest probability for infection. Dialysis programs should monitor vascular access and especially catheter-related infections with attention to incidence, bacteriology, and outcomes.

Significant risk factors ($P < 0.05$) for bacteremic episodes include the presence of diabetes, peripheral atherosclerosis, a previous history of bacteremia, nasal carriage of *Staphy-*

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lococcus aureus, longer catheter use duration, more frequent UK catheter infusion, and local infection.[532,537] One report identified elderly women as being more at risk.[541]

Infection monitoring should be in place to identify outbreaks that can result from manufacturing defects.[542] A doubling of the rate is cause for concern.[542] One study provides a means to standardize the reporting of vascular access infection rates.[543] Analyzing nearly 40,000 dialysis sessions, infection rates were greatest among short-term catheters (recommended for in-hospital use only) and least among permanent native AVFs or synthetic grafts. Another analysis in Canada of 184 bloodstream infections in 133,158 dialysis procedures confirmed these findings.[232] AVFs were associated with the lowest risk for bloodstream infection (0.2/1,000 dialysis procedures; RR increased 2.5-fold with AVGs, 15.5-fold with TCC access, and 22.5-fold with uncuffed CVC access; all $P < 0.001$). Significant variation in infection rates was observed among centers, even when controlling for types of access used, suggesting that access-specific infection rates within and among centers could be used to develop quality improvement. Experience with femoral TCCs has been mixed. Some reports indicated no increase in infection rate,[544,545] but that has not been the experience of members of the Work Group. Even if there is no decrease in infection-free survival,[545] use of femoral catheters is associated with ipsilateral vein thrombosis in about 26% of patients that necessates use of anticoagulants with uncertain effects on the upstream iliac vein (see CPG 2).

All indwelling vascular catheters are colonized by microorganisms within 24 hours after insertion.[546] The formation of "biofilm" on the external and internal surface of vascular catheters is thought to have an important role in the colonization process. The biofilm is produced by a combination of host factors (eg, fibrinogen, fibrin, fibronectin, and extracellular polysaccharides) and microbial products (eg, glycocalyx or "slime") and has a critical role in bacterial antimicrobial resistance and recalcitrant infections.[547] Prevention of infection is the key first step, and the reader should consult the recommendations of the CDC.[222] Although documented by a variety of methods, the relationship of thrombin sheath to infection has not been evaluated clinically. Proteins in the fibrin sheath provide adhesions for organism binding, particularly by *S aureus.* Whether more aggressive prevention of fibrin sheaths could reduce the infection rate is unknown. Sporadic reports suggested that concomitant use of a lytic with antibiotics could salvage more catheters.

In general, uncuffed catheters have a greater rate of infection, 3.8 to 6.6 episodes/1,000 days, compared with TCCs, with 1.6 to 5.5 episodes/1,000 days.[534,542,544,548] This wide range obviously reflects differences in practice.[544] Rates as low as 1/1,000 days at risk have been achieved with detailed catheter protocols.[247] Programs with greater rates of infection in long-term catheters should institute CQI analysis techniques. Catheter infection usually requires replacement of the catheter in half the episodes despite antibiotic therapy.[532] Systemic antibiotics used to treat bacteremia do not penetrate into the biofilm and therefore do not eradicate it,[549] leading to potential treatment failures and eventual sacrifice of the catheter. Among uncuffed short-term catheters, femoral catheters have the highest infection rate, averaging 7.6 episodes/1,000 days, with more than 10% being infected by 1 week.[199]

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Catheter exit-site infections alone usually can be salvaged with topical and oral antibiotics without the need for catheter replacement.[148,149,151,550] CRB is the major reason for catheter loss[156] and has been associated with substantial morbidity, including metastatic infection.[159] It is a life-threatening condition requiring initial hospitalization and parenteral antibiotic therapy if the patient is clinically septic. The observation in a large trial of patients with CRB that systemic antibiotics alone were able to salvage less than 25% of catheters[533] led to the commonly used "salvage of site rather than salvage of catheter" approach.[551,552] Attempts to salvage the catheter in situ were associated with recurrence of infections soon after the antibiotics were discontinued.[533] Conversely, studies using catheter guide wire exchange in stable patients without tunnel involvement under the cover of antibiotics alone salvaged 80% to 88% of sites without apparent ill effects.[158,551,552] There is no advantage in delaying replacement of the catheter by several days.[553] A decision-tree hypothetical analysis showed that TCC exchange over a guide wire reduced net charges by approximately $5,200 and $750 (US dollars in year 2000) compared with TCC salvage and immediate TCC removal, respectively.[554] Expected 3-month patient survival for TCC guide wire exchange and immediate TCC removal were similar (93%), whereas survival for TCC salvage was worse.[554] A negative culture result is not required before catheter exchange.[551]

An alternative to this management of dialysis CRB (systemic antibiotics with catheter exchange, as well as removal of the infected catheter) is catheter salvage by combining systemic antibiotics in conjunction with antibiotic locks.[555-559] The former is burdensome at times and expensive and creates short-term problems for dialysis access if the infectious disease consultant demands that a 24- to 48-hour catheter-free period is needed before the catheter can be placed. As stated previously, bacterial biofilms form routinely in the catheter lumen and act as the nidus for bacteremic episodes. Instillation of a concentrated antibiotic-anticoagulant solution into the catheter lumen (antibiotic lock) at concentrations orders of magnitude higher than those achievable in the blood may permit successful eradication of the infection while salvaging the patient's catheter. A number of studies now confirm the validity of this approach,[556-559] with salvage of the catheter and without recurrence of infection in about 65% to 70% of cases, comparing favorably with the catheter-exchange approach. With the latter method, catheter replacement is necessary in patients with persistent fever or positive surveillance blood culture results. A direct head-to-head RCT of the 2 methods is needed (see Research Recommendations).

Bacteremia with tunnel-tract involvement should prompt catheter removal. Unstable patients require removal of the catheter for rapid response to therapy. The Work Group believes that a minimum of 3 weeks of systemic antibiotic therapy is needed to treat CRB and that new permanent access should not be placed until culture results have been negative for at least 48 hours after cessation of antibiotic therapy.

Prevention of CRB can be difficult despite the use of rigorous infection-control techniques. As shown in Table 24, silver impregnation of the catheter was ineffective,[560] whereas a gentamycin/citrate solution[561] and a taurolidine solution used as interdialytic

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Table 24. Prophylaxis for Dual-Lumen TCC-Related Infections

Author, Year	Study Design	N	Follow-up (maximum)	Applicability	Intervention 1	Intervention 2	Infection rate [a]			Quality
							Treatment	Control	Result	
Trerotola 1998 [33]	RCT	100	730 d	↑↑	Silver coated catheter	Non-silver coated catheter	1.1	1.4	NS	●
					Gentamicin + citrate					
Dogra 2002 [34]	RCT	83 (112 catheters)	288 d	↑↑	CLS (40 mg/mL and 3.13% citrate)	Heparin CLS (5000 U/mL)	0.3	4.2	+	●
					1.35% taurolidine and 4% sodium citrate CLS					
Allon 2003 [35]	Prospective with concurrent control	50	90 d	↑↑		Heparin CLS (5000 U/mL)	0.6	5.3	+	○

CLS=catheter lock solution; NS=not significant; RCT=randomized controlled trial; TCC=tunneled cuffed catheter.

+ Statistically significant beneficial effect of treatment compared to control (or intervention 1 vs. intervention 2)

a. Per 1000 catheter days.

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antibiotic locks were effective.[562,563] Minocycline/rifampin coating has not been tested in dialysis catheters.

The subject of antibiotic locking has been discussed extensively.[564] Other pharmacological measures that may be useful for prophylaxis against CRB include application of an antimicrobial ointment (mupirocin or polysporin) to the catheter exit site.[565,566] Subcutaneous port catheter devices do not reduce the frequency of CRB unless an antimicrobial solution is used with the device.[567] A preliminary study showed that a topically applied "Medihoney" was as effective as mupirocin in reducing catheter infection.[568] The former has a lower likelihood for selecting out resistant organisms. It unfortunately is forgotten that good practice and attention to "hub care" can significantly reduce CRB by 4-fold.[247]

However, with all preventive strategies other than good catheter care (see CPG 3), there are few long-term data on the development of antimicrobial resistance, and future studies are required. Until such data are available, it is unlikely that the use of such locks and ointments will receive official approval from the FDA.

LIMITATIONS

Considerable uncertainty exists about the most effective regimen for preventing catheter dysfunction by using lytics because there are no sufficiently powered studies to compare the efficacy and economics of different protocols. The same applies to prevention of CRB.

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GUIDELINE 8. CLINICAL OUTCOME GOALS

8.1 Goals of access placement:

8.1.1 Each center should establish a database and CQI process to track the types of accesses created and complication rates for these accesses.

8.1.2 The goals for permanent HD access placement should include:

8.1.2.1 Prevalent functional AVF placement rate of greater than 65% of patients. (B)

8.1.2.2 Cuffed catheter for permanent dialysis access (eg, not as a bridge) in less than 10% of patients. Long-term catheter access is defined as the use of a dialysis catheter for more than 3 months in the absence of a maturing permanent access—graft or fistula. (B)

8.2 The *primary* access failure rates of HD accesses in the following locations and configurations should not be more than the following:

8.2.1 Forearm straight grafts: 15%. (B)

8.2.2 Forearm loop grafts: 10%. (B)

8.2.3 Upper-arm grafts: 5%. (B)

8.2.4 Tunneled catheters with blood flow less than 300 mL/min: 5%. (B)

8.3 Access complications and performance:

8.3.1 Fistula complications/performance should be as follows:

8.3.1.1 Fistula thrombosis: fewer than 0.25 episodes/patient-year at risk. (B)

8.3.1.2 Fistula infection: less than 1% during the use-life of the access. (B)

8.3.1.3 Fistula patency greater than 3.0 years (by life-table analysis). (B)

8.3.2 Graft complications/performance should be as follows:

8.3.2.1 Graft thrombosis: fewer than 0.5 thrombotic episodes/patient-year at risk. (B)

8.3.2.2 Graft infection: less than 10% during the use-life of the access. (B)

8.3.2.3 Graft patency greater than 2 years (by life-table analysis). (B)

8.3.2.4 Graft patency after PTA: longer than 4 months. (B)

8.3.3 Catheter complications/performance should be as follows:

8.3.3.1 Tunneled catheter-related infection less than 10% at 3 months and less than 50% at 1 year. (B)

8.3.3.2 The cumulative incidence of the following insertion complications should not exceed 1% of all catheter placements: (B)

- **Pneumothorax requiring a chest tube**
- **Symptomatic air embolism**

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- **Hemothorax**
- **Hemomediastinum**
- **Hematoma requiring evacuation.**

8.3.4 Cumulative patency rate of TCCs: Not specified. (B)

8.4 Efficacy of corrective intervention:

The rate of certain milestones after correction of thrombosis or stenosis should be as follows:

8.4.1 AVF patency after PTA: greater than 50% unassisted patency at 6 months (and <30% residual stenosis postprocedure or lack of resolution of physical findings postprocedure);
AVF patency following surgery: greater than 50% unassisted patency at 1 year. (B)

8.4.2 AVG patency after PTA: please refer to CPG 6.5.1;
AVG patency after surgery: please refer to CPG 6.5.2;
AVG after either PTA or surgery: greater than 90% with postprocedure restoration of blood flow and greater than 85% postprocedure ability to complete 1 dialysis treatment. Please refer to 6.8. (B)

8.4.3 Surgical correction is set to a higher standard because of the use of venous capital. (B)

BACKGROUND

HD access failure is a major cause of morbidity and mortality for patients on HD therapy.[7,8,14–17] Expenditures for reconstituting patency are substantial and increasing.[2,8,9,12] Throughout this document, methods and recommendations have been proposed to improve vascular access results. These include:

1. Establishment of QA programs that track access complication rates and outcomes:
   a. Formation of VATs
2. Improvement of the skill set of staff:
   a. Physical examination of the accesses
   b. Cannulation techniques among staff
   c. Aseptic techniques
3. Increasing the percentage of patients with native or primary AVFs by implementing the FFBI. Key portions of the program include the following:
   a. Early identification and referral of patients with progressive kidney disease to nephrologists, allowing access construction well in advance of the need for HD
   b. Protection of veins
   c. Adequate artery and vein evaluation by using DDU and/or angiography
   d. Reevaluation for a native AVF after every access failure
4. Periodic monitoring of accesses to detect hemodynamically significant stenoses before thrombosis:
   a. Expeditious referral of patients for appropriate angioplasty or surgical revision after the detection and characterization of stenoses

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b. Documentation of functional improvement in access function after corrective intervention

5. Improved catheter care.

The following Clinical Outcome goals are target suggestions for measuring improvement in performance.

RATIONALE

Goals of Access Placement (CPG 8.1)

Data should be updated periodically and methods should be identified to increase the rate of AVF placement. Flow charts should be developed and root-cause analysis should be carried out to identify barriers to fistula placement, causes for excessive thrombosis rates, and reasons for excessive catheter-related infection.

These goals are greater than those previously recommended in the KDOQI Vascular Access Guidelines.[20,348] They represent the goals expected by CMS, which has set the target for fistula prevalence of 65% by 2009. Although there has been slow improvement in fistula rates since implementation of the FFBI, rates have increased only slowly (NVAII, www.fistulafirst.org; last accessed 2/20/2006). The Work Group believes that with the reimbursement of DDU procedures and early referral of patients by nephrologists for access evaluation and constructions, rates will improve. In some cases, this will require the use of brachial artery level constructions. An increase in percentage of native AVFs is accomplished best by early determination of the patient's preferred dialysis modality while dialysis therapy initiation is still months away (see CPG 1) because primary AVFs ideally need an extended period of 1 to 6 months to mature. However, those entering the CKD stage 5 program with inadequate or no prior medical care for CKD will continue to blunt the impact of such efforts.

These goals are achievable.[37,38,88,569] A primary AVF using the cephalic vein confers the best permanent access with the fewest complications (see CPG 2). Native accesses have the best 4- to 5-year patency rates and require fewer interventions compared with other access types. In many patients, a previous native or synthetic access produces dilation of arm veins, permitting construction of a new primary AV access at a site not previously available.

Catheter usage presents a conundrum. On one hand, catheters provide access that is immediately available; on the other hand, complications are high.[180,359] Blood flow frequently is inadequate, thrombolytics frequently are required, and the infection rate is an order of magnitude higher than with grafts or fistulae. Cuffed catheters are associated with lower BFRs compared with grafts and fistulae. As a result, long-term catheter use without appropriate adjustments in treatment duration can compromise dialysis adequacy. Compromise of dialysis adequacy is associated with increased morbidity and mortality. Systemic and local infections occur more frequently with cuffed catheters and account for some of the excess mortality associated with this access type. Finally, long-term catheter access is associated with a risk for central venous stenosis development, which can preclude the establishment of a permanent vascular access for HD (see CPG 2). The

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initial success, ease of use, and painless access to the patient's blood offered with a dialysis catheter may foster reluctance in some patients to accept more permanent access options with a fistula or graft despite the greater risk for infection and inadequate dialysis associated with long-term permanent catheter use. Patients should be educated on these issues and strongly encouraged to allow creation of a fistula for permanent access whenever possible.

When a catheter must be used either initially or to bridge the patient to the next permanent access, "time-urgency" for initiating/continuing HD therapy with a permanent access does not justify substitution of a graft for a fistula because cuffed catheters are an effective means of bridging the longer time necessary for primary AVF maturation.[148,178,184,200] Although catheters can be used for long-term dialysis,[187,189] they should be reserved for patients with comorbid conditions limiting life expectancy, those with systolic hypotension in whom attempts to create/maintain a permanent access have met with failure, and those in whom all available sites for fistula or graft (including chest-wall loop grafts) have been exhausted or are not feasible.

The Primary Access Failure Rates (CPG 8.2)

Primary failure is defined as the inability to use the graft at 30 days or obtain sufficient blood flow from the catheter within the first week after insertion. By proposing these goals for 30-day primary failure rates for various graft configurations, the Work Group does not wish to imply that upper-arm grafts should be elected over forearm grafts solely on the basis of these recommended primary failure rates. The Work Group encourages the creation and maintenance of access sites as distally as possible to preserve more proximal veins for future access options. For example, a forearm straight or a brachial loop graft may be used to develop a vein for fistula construction. The Work Group realizes that in some instances, a dialyzer BFR of 300 mL/min might be excessive and produce disequilibrium during the first or second treatment of a very uremic patient. However, by the third treatment, this should not be an issue, and a limit of 1 week is set to determine that the catheter can deliver adequate blood flow.

Primary access failure is considered failure of patency within the first 30 days after placement. Primary failure of dialysis AVGs is caused by technical problems or selection of inappropriate vessels (artery or vein). Neointimal hyperplasia is unlikely to be so virulent as to cause access graft failure within 30 days of construction. It is the Work Group's opinion that the primary failure rate reflects a center effect that is influenced by surgical access construction, patient demographics, adequacy of workup (see CPG 1 and CPG 5), comorbidities, and graft loss caused by premature cannulation and hematoma formation. Primary failure rates of dialysis AVGs at the same anatomic sites vary depending on whether the grafts are the primary, secondary, or tertiary access. The rates provided are derived from the published literature for first graft accesses constructed in a general HD population.[24-26,65,67,92,423,570] Failure of a graft before use reflects surgical construction problems. Prosthetic bridge graft survival is decreased in patients with diabetes, even at 30 days, and may be affected adversely by increasing age in patients without diabetes.[571] Patient demographics, characteristics, and comorbidities may differ across centers and

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explain some of the center effect. Each center should monitor its performance, recognizing the influence of some demographic factors, but tracking its own problems in access construction and use (see CPG 8.1.1). Marked deviations from the recommended patency rate should invoke a multidisciplinary evaluation of possible factors and their modification.

A modern properly placed catheter (see CPG 2.4 and CPG 7.1) can deliver more than 300 mL/min at a prepump pressure of −250 mm Hg in adults. A catheter that cannot deliver a flow of 300 mL/min is not being run at a sufficient negative pressure, is improperly positioned, or is dysfunctional for some other reason. Because blood flow with time is a major determinant of adequacy of dialysis, the cause must be determined quickly and corrected. The Work Group believes that catheter blood flow is an indicator of quality in a program. Data for performance should be collected and analyzed to improve quality and protect the patient from underdialysis.

Access Complications and Performance (CPG 8.3)

The Work Group believes that it cannot provide a reasonable estimate of expected cumulative patency of dialysis catheters. The use of cuffed catheters as permanent vascular access is discouraged, except in particular patient groups (see CPG 3).

The current national average rate of thrombosis of dialysis AVGs can only be approximated because there is no mandatory reporting. It is likely to be greater than the overall rate (all permanent accesses) of approximately 0.8 episodes/patient-year at risk[10,29] because these rates include the much lower rate of thrombosis of fistulae. In grafts, rates varying from 0.5 to almost 2 episodes/graft-year at risk have been reported in the absence of surveillance or monitoring programs.[10,29,374,572] The rate of graft thrombosis is determined largely by the presence of unrecognized hemodynamically significant stenosis.[10,266,572] Six published studies showing the value of surveillance reported baseline thrombosis rates varying from 0.5 to 0.8 episodes/graft-year at risk, which then decreased by 43% to 67% to rates of 0.2 to 0.4 episodes/graft-year.[10,322,343,352,373,374] Implementation of surveillance techniques should reduce stenosis and make a rate of 0.5 achievable, even in programs with greater than average rates of thrombosis Therefore, dialysis grafts should be monitored/undergo surveillance to permit early detection of hemodynamically significant stenosis with the goal of reducing the thrombosis rate to a maximum of 0.5 thrombosis/y for AVGs.

PTA is performed to dilate a stenotic lesion within a vascular access or its draining vein. Adequacy of the procedure is measured best by the duration of effect: ie, duration of subsequent patency until either another PTA is required for recurrence of stenosis or thrombosis occurs. A number of observational studies showed that a greater fraction of grafts remained free of interventions or thrombosis if the AVG was patent at the time of intervention (see CPG 6). The fraction of AVGs free of further intervention or thrombosis ranged from 71% to 85% among 4 studies if PTA was performed preemptively compared with only 33% to 63% if PTA was performed after thrombectomy of the graft.[373,374] After PTA of stenoses associated with nonthrombosed AVGs, published series consistently reported a 6-month primary (unassisted) patency rate of 40% to 50% (see CPG 6).

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The duration of effect after thrombectomy and correction of stenosis is considerably shorter. The 4-month criteria are meant to foster 2 processes: (1) preemptive PTA, and (2) assessment of the adequacy of the intervention (PTA or surgery) because inadequate correction typically is manifested by thrombosis or recurrence of the lesion within weeks.

The rate of fistula thrombosis is much less than that of grafts. Fistulae have the lowest rate of thrombosis,[57] require the fewest interventions,[57,58] and provide longer survival of the access.[3,57,58] For native fistulae, access events are only 14% to 33% of those observed in grafts.[3,57,58] Therefore, a fistula thrombosis rate that is half that of grafts should result in at least a 1-year longer access survival in well-functioning dialysis programs.

Infectious complications of accesses are a leading cause of morbidity and mortality in dialysis patients. The current national combined infection rates for permanent accesses for local and bacteremic infections are calculated to be 1% to 4% for primary AVFs and 11% to 20% for AVGs during their expected periods of use.[4,16,232,543,573-577] Significant variance among dialysis centers is noted.[232,543,575,577] Rates of 1% and 10% are the lower end of the published ranges and will demand more attention to aseptic technique (see CPG 3) by some centers.

The catheter infection rate is highly variable[532,578,579] and clearly depends on the duration of use.[156,211,533] At 2 weeks of catheterization, the incidence of infection of noncuffed central catheters generally is less than 8%.[580] One study reported a bacteremia rate of less than 5% in cuffed catheters used less than 3 months and a 50% removal rate for cuffed catheter infection at 12 months of use.[156] Other factors include being an incident patient, changing from 1 vascular access to another, and poor patient hygiene.[238] The National Nosocomial Infections Surveillance data show that national surveillance of health care–associated infections combined with an intervention prevention program can reduce infection rates, reduce morbidity and mortality, and improve patient safety.[581] Establishment of such health care–associated infection surveillance and prevention systems in countries throughout the world should be a priority.

The Work Group's recommendations are significantly less than the experiences of some centers. The Work Group believes infection rates can be decreased significantly through meticulous attention to detail and, in the case of catheters, following the recommendations in CPG 3 and CPG 7. Catheter infection rates can be decreased to less than 1.5 episodes/1,000 days by paying scrupulous attention to the hub,[247] a rate that is significantly less (<5%) than the 10% rate proposed. Infection rates also can be decreased by paying attention to skin preparation at the time of placement,[582] appropriate use of topical antibiotics,[578,583] and use of nonocclusive dressings.[584] Programs with high infection rates should consider the importance of nurse and patient training[585] (see CPG 3.5).

Complications related to the insertion of TCCs depend on operator skill. Cuffed catheters can be inserted with reference to anatomic landmarks, with or without ultrasound guidance,[151,579,586-588] but always with the use of fluoroscopy to verify proper positioning of the catheter tip (see CPG 2.4). Cuffed catheters can be placed by nephrologists, surgeons, or radiologists. Cumulative complication rates less than 5% are obtained routinely without ultrasound guidance.[151,579] A recommended complication rate less

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than 2% is less than values reported in the literature. However, published results are based on procedures obtained without benefit of ultrasound guidance. The RR for complication decreased 5-fold with the use of ultrasound.[587] In the Work Group's opinion, rates of 1% should be obtainable in almost all centers and should be the goal.

Double-lumen cuffed catheters are used as both temporary access while a permanent access is maturing and as permanent access in patients who have exhausted other options. This variation in intended use creates significant variation in catheter survival rates. A study reported a median cumulative catheter survival rate of 18.5 months; 65% of silicone dual-lumen catheters survived 1 year.[151,587] Conversely, another group reported a 1-year cumulative patency of 30%.[579] Another study using 2 single-lumen Silastic catheters (with the majority serving to bridge a period until permanent access was established) reported an average catheter survival of 57 days.[152] Others reported a 50% catheter survival rate at 12.7 months[156] and median survival period of 289 days.[186] Finally, 1 study reported an 80% survival rate at 1 year,[589] no doubt in part the result of an all-cause infection rate less than 2 episdes/1,000 days.

Numerous studies reported 1-year patency rates of grafts between 63% and 90%.[24,25,67,590] One report described an overall average patency rate of 70%.[4] Many investigators reported patency rates at 2 and 3 years, as well.[4,24,25,67,73] Outflow obstruction, followed by thrombosis, accounts for the majority of AVG failures. The Work Group believes that prospective surveillance and monitoring (see CPG 4) may improve this reported experience despite the aging of the population and increasing percentage of patients with diabetes or peripheral vascular disease. Thus, cumulative patency targets for grafts of 70% at 1 year, 50% at 2 years, and 50% at 3 years should be achievable. Because fistulae have a lower thrombosis rate, their cumulative survival should be greater. Despite the current problems with maturation and early failure, the Work Group believes that rates comparable to those in Europe can be achieved.[3,87,591,592]

With respect to grafts, there now has been sufficient time to assess the effect of the efforts made since the previous guidelines, at which the time the Work Group recommended that the primary failure rate of AVFs not be used as an indicator of quality. This was done for fear that during the learning curve of fistulae construction, patients with more complex vascular anatomy (ie, patients at greater risk for failure) might be discouraged. The Work Group recommended that primary failure of native AVFs be examined in dialysis centers as part of their QA/CQI vascular access programs. Since then, many studies documented the superior patency (with lower thrombotic rates) of fistulae compared with grafts.[3,37,57,570,593–598] The median patency of 3 years is based on current data and may improve if we can improve cannulation skills.

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II. Clinical Practice Recommendations for Vascular Access

CLINICAL PRACTICE RECOMMENDATIONS FOR GUIDELINE 1: PATIENT PREPARATION FOR PERMANENT HEMODIALYSIS ACCESS

Factors that may be helpful in preparing the patient for placement of a permanent HD access include the following:

1.1 The veins of the dorsum of the hand should be the preferred site for IV cannulation.

1.2 Sites for venipuncture should be rotated if arm veins need to be used.

1.3 Patients with CKD stage 5 should be educated on the risks and benefits associated with catheters and strongly encouraged to allow the evaluation for and creation of a fistula for long-term access when appropriate. Such discussions with the patient should be initiated months before the anticipated start of dialysis therapy.

1.4 Alternative imaging studies for central veins include DDU and magnetic resonance imaging/MRA.

RATIONALE

Venipuncture complications of veins potentially available for vascular access may render such vein sites unsuitable for construction of a primary fistula. Patients and health care professionals should be educated about the need to preserve veins to avoid loss of potential access sites in the arms and maximize chances for successful fistula placement and maturation. Subclavian vein catheterization is associated with central venous stenosis.[28-30] Significant subclavian vein stenosis generally will preclude the use of the entire ipsilateral arm for vascular access. Thus, subclavian vein catheterization should be avoided for temporary access in patients with kidney disease.[31] The incidence of central vein stenosis and occlusion after upper-extremity placement of PICCs and venous ports was 7% in 1 retrospective series of 150 patients.[32] PICCs also are associated with a high incidence of upper-extremity thrombosis. The incidence of upper-extremity venous thrombosis varies between 11% and 85%, which leads to loss of potential upper-extremity fistulae.[33-35] Because of the substantial risk for loss of useable upper-extremity veins and central venous stenosis with PICCs, the Work Group recommends strongly that PICCs not be used in patients with CKD.

Ideally, patients should have a functioning permanent access at the time of dialysis therapy initiation. Function implies that the access not only deliver adequate blood flow for dialysis, but also may be cannulated easily and repetitively. Timely attempts to create a primary fistula before the anticipated need for dialysis therapy will allow adequate time for the fistula to mature and sufficient time to perform another vascular access procedure if the first attempt fails, thus avoiding the need for temporary access. Early referral of a patient with CKD to a nephrologist is needed to facilitate CKD therapy with medications

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and diets that preserve kidney function. In addition, counseling patients on CKD treatment options is essential to plan for ideal access (ie, PD and HD access).

Duplex ultrasound is the preferred method for preoperative vascular mapping. Vascular mapping in preparation for the creation of a vascular access refers to the evaluation of vessels, both arterial and venous, of patients with CKD who selected HD in preparation for the creation of a vascular access. Vascular mapping should be performed in all patients before placement of an access. Preoperative vascular mapping was shown to substantially increase the total proportion of patients dialyzing with fistulae.[36-39] Several studies support the 2.0- to 2.5-mm vein diameter threshold for successful creation of a fistula.[36,39] Radiocephalic fistulae constructed in veins with a less than 2.0-mm diameter had only 16% primary patency at 3 months compared with 76% for those with veins greater than 2.0 mm.[36] In a pivotal study,[39] a threshold of 2.5-mm vein diameter assessed by using duplex ultrasound was used; this resulted in an increase in fistula creation of 63% compared with a retrospective 14% rate in the absence of vascular mapping.[22] A similar study using the same duplex ultrasound criteria showed a fistula increase from 34% in historical controls to 64%. Importantly, in this study, duplex ultrasound altered the surgical plan based entirely on the surgeon's clinical evaluation, resulting in increased placement of fistulae.[72]

Although angiography remains the standard for evaluating the central veins, the central veins may be assessed indirectly by using duplex ultrasound.[44] Compared with invasive venography, duplex ultrasound had a specificity of 97% and sensitivity of 81% for detecting central vein occlusion.[45] Alternatively, MRA may be used to evaluate central veins.[46]

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Recommendations for fistulae:

2.1 When a new native fistula is infiltrated (ie, presence of hematoma with associated induration and edema), it should be rested until the swelling is resolved.

RATIONALE

There are no studies evaluating the need to rest a fistula after an infiltration. Common sense dictates that cannulation should be avoided in the involved area until landmarks can be seen clearly. The most common reason for infiltration is poor cannulation. Successful cannulation and use of the fistula can be engendered by providing a digital photo map of the fistula based on ultrasound. This educates the staff and develops expertise. Dialysis units should develop a new AVF cannulation protocol to prevent trauma to the newly cannulated AVF, such as progressive evolution of needle gauge used for cannulation (see CPG 3). The needle gauge and BFR should be increased slowly to prevent infiltrations and should be detailed clearly in the fistula "break-in" cannulation protocol. The role of improving the cannulation needles requires further investigation.[397]

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3.1 Cannulation skill:

Staff should be appropriately trained and observed for technical mastery before cannulating any AV access. Only those with said technical mastery should be allowed to cannulate a new fistula. A protocol for minimizing vessel damage should be used for cannulation failure. Recannulation should be attempted only when the cannulation site is healed and the vessel is assessed to be normal and appropriate for cannulation. Heparin management should be reviewed on a case-by-case basis to minimize postdialysis bleeding.

3.2 Self-cannulation:

Patients who are capable and whose access is suitably positioned should be encouraged to self-cannulate. The preferred cannulation technique is the buttonhole.

3.3 Buttonhole:

Patients with fistula access should be considered for buttonhole (constant-site) cannulation. (See protocol in CPG 3.)

3.4 Elevation of arm for swelling:

The AVG access arm should be elevated as much as possible until swelling subsides, which may take as long as 3 to 6 weeks. Increase in symptoms requires urgent evaluation.

RATIONALE

Data from DOPPS[599] show that a functional fistula should have an outflow vein that can be successfully cannulated 1 month postoperatively. The previous KDOQI Vascular Access Guidelines recommendation of 3 to 4 months after access creation was opinion based as a result of anecdotes of early cannulation failure with resulting tissue infiltrations and vessel damage. Consideration should be given to marking, with the aid of ultrasound, veins that are difficult to see and feel, with accompanying measurements of the vein margins to prevent aspiration of clots when the needle is placed too close to the vein wall.

Many centers have higher doses of heparin for catheter-dependent patients than for patients with subcutaneous access. New fistulae are more likely to bleed for a variety of reasons: infiltrations, patient and staff inexperience with hemostasis, and lack of clarity regarding when to reduce the heparin dose if a patient is using both a fistula and 1 lumen of the catheter.

There is growing evidence that buttonhole (constant-site) cannulation may be less likely to infiltrate, may be pain free for the patient, may help preserve the integrity of the outflow vein,[244] and may be easier for patients to self-cannulate.

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4.1 Monitoring the access:

4.1.1 Access patency should be ensured before each treatment before any attempts to cannulate the access.

4.1.2 All caregivers, including fellows in training, should learn and master the methods for examining a vascular access.

4.1.3 Access characteristics, such as pulsatility and presence of thrill, as well as flow and pressure, should be recorded and tracked in a medical record and be available to all caregivers of the VAT.

4.2 Frequency of measurement is dependent on the method used:

4.2.1 It is not clear that access flow measurements performed at a monthly frequency provide sufficient data stability to make decisions. Until additional studies are performed to determine the optimal frequency, more frequent measurements are recommended.

4.2.2 Static pressure measurements require less technology and should be made more frequently than flow measurements. Direct measurements of static pressure ratios should be made every 2 weeks. Less-direct measurements should be made weekly. Dynamic pressures, if used (see CPG 4.2.3), should be measured with each dialysis treatment, but derivation of a static pressure should be attempted, rather than using the raw numbers.

4.2.3 Measurement of recirculation is not recommended as a surveillance technique in grafts.

4.3 Frequency of measurement for access complications:

4.3.1 Thrombosis in fistulae develops more slowly than in grafts. Flow measurements performed at a monthly frequency appear to be adequate. Until additional studies are performed to determine the optimal frequency, less frequent measurements are not recommended.

4.3.2 Because static pressure measurements are inherently less accurate in detecting access stenosis in fistulae, the frequency should not be less than in grafts. Direct measurements of static pressure ratios should be made every 2 weeks. Less-direct measurements should be made weekly. Dynamic pressures should be measured with each dialysis. Increased recirculation can indicate reduced effective blood pump flow, resulting in inadequate dialysis.

4.4 Diagnostic testing:

4.4.1 Characteristics of access (see CPR 4.1), as well as blood pump flow and pressure performance, should be recorded and tracked in medical records.

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4.4.2 Data should be analyzed at least monthly to evaluate access dysfunction.

4.4.3 After intervention, the surveillance parameter should be restored to normal.

4.4.4 Data should be analyzed to improve success rates and ensure that interventions are appropriately assessed. For example, PTA and surgical revision rates, recurrence rates, and number of procedures per patient year should be systematically analyzed in a CQI process.

4.4.5 A multidisciplinary team should be involved.

4.4.6 Preemptive correction of hemodynamically significant stenoses should remain the standard of care.

RATIONALE

There is considerable debate concerning whether PTA interventions improve long-term outcomes. Until sufficiently powered clinical studies are performed, the rationale for monitoring and surveillance are provided in CPG 4. It is the belief of the Work Group that physical examination and clinical evaluation are forgotten skills that, if restored, could be as valuable as any surveillance method.

The utility of any method develops on sequential assessment and evaluation. This requires collection and storage of observations and/or data. Because stenoses evolve over time, observations and data should change over time. Because observers may change, data must be available to all caretakers.

Quality and outcome improvement cannot be determined without analyses of data.

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5.1 If a new fistula access has vein margins that are difficult to discern on physical examination and cannulation frequently is associated with aspiration of clot, the patient should be referred for access marking by means of DDU to define the center of the vessel and depth of the fistula. A diagram of these findings should be sent to the dialysis unit.

5.1.1 The patient should be taught to examine his or her access daily, while at home, for thrombosis.

RATIONALE

Many patients present with an occluded access. In a fistula, successful declotting decreases with the duration of thrombosis (see CPG 5.4.2). Thrombus may propagate into side branches or become organized, increasing resistance to extraction. Most thromboses occur at home, and when questioned, many patients cannot recall when they last felt for the access thrill or pulse. The Work Group believes that this area is ripe for research on the efficacy of simple teaching on the early detection of thrombosis and the degree of early, as well as late, patency achieved by intervention.

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7.1 Treatment of catheter dysfunction:

Catheter dysfunction should be treated when a dialyzer blood flow of 300 mL/min is not being attained in a catheter previously able to deliver greater than 350 mL/min at a prepump pressure of −250 torr.

7.1.1 A dysfunctional catheter (blood flow < 300 mL/min) for 2 consecutive treatments should be treated in the HD unit by using an intraluminal interdialytic thrombolytic lock protocol between 2 dialysis treatments (ie, 35 to 69 hours).

7.2 Radiological evaluation:

Any dysfunction that cannot be managed in the dialysis unit should be sent for radiographic study to diagnose dysfunction and document the condition of the vessel.

7.2.1 Catheter imaging with contrast infusion can identify other correctable problems (eg, residual lumen thrombus, external fibrin catheter sheath, malpositioned catheter tip). Appropriate interventions may follow, such as:

7.2.1.1 Repositioning of the catheter.

7.2.1.2 Angioplasty of a vessel.

7.2.1.3 Replacement of a malpositioned catheter over guide wire.

7.2.1.4 Higher-dose lytic infusion for occlusive thrombus (eg, right atrial) or fibrin sheath.

7.3 Choice of thrombolytic and use of other modalities:

7.3.1 A special brush is used to remove thrombus from the lumens of a conventional catheter by using a protocol specific to this procedure.

7.4 Treatment of infection:

7.4.1 Catheter exit-site infections, in the absence of a tunnel infection, should be treated with topical and/or oral antibiotics, ensuring proper local exit-site care. In general, it should not be necessary to remove the catheter.

7.4.2 If a patient with bacteremia is afebrile within 48 hours and is clinically stable, catheter salvage might be considered by using an interdialytic antibiotic lock solution and 3 weeks of parenteral antibiotics in appropriate situations. A follow-up blood culture 1 week after completion of the course of antibiotics should be performed. (see Table 24)

7.4.3 Antibiotic lock with antibiotic to which the organism is sensitive is indicated when follow-up cultures indicate reinfection with the same organism in a patient with limited catheter sites.

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7.4.4 Short-term catheters should be removed when infected. There is no conclusive evidence to support a rationale for scheduled replacement except for those in the femoral area.

RATIONALE

Treatment of Catheter Dysfunction (CPR 7.1)

Locking with tPA maintains the conductance of a catheter better than locking with heparin.[496] Alternatively, intracatheter lytic infusion (eg, UK, 20,000 U/lumen/h for 6 hours,[600] or alteplase, 2.5 mg/lumen over 1 to 2 hours) during the dialysis can *restore* blood flow.[601,602]

Several studies evaluated the effect of tPA infusion in restoring patency to dysfunctional catheters. In general, infusion of 1 to 4 mg/lumen over 1 to 4 hours permits restoration of flow (>200 mL/min) sufficient to permit completion of a dialysis treatment,[601-603] permitting control of serum potassium levels and fluid removal. Infusion may succeed when a simple timed dwell fails. The difference in efficacy may result from the amount of lytic that gets to the fibrin/thrombus in a limited time. With the dwell technique, only the lytic at the catheter tip is biochemically active; the amount that has not leaked immediately must slowly diffuse to the fibrin or thrombus at the tip or exterior to the catheter. Conversely, push or infusion techniques more rapidly deliver the lytic in the lumen to the area of need. However, there have been no head-to-head comparisons. There should be little fear to use tPA as a long lock dwell or as infusions of doses less than 10 mg. The half-life of tPA is on the order of minutes, and it is only active when bound to fibrin. At the doses and infusion rates used, there is virtually no risk for systemic thrombolytic effect.

Very few head-to-head comparisons have been made among the available lytics.[525,604,605] Two studies showed an advantage of tPA over UK, but neither was randomized. In 1 of the studies, "the push" protocol was used as opposed to the "passive dwell."[525] The choice of agent to be used is governed by many factors, including availability, convenience, cost, and comparative efficacy.

Unfortunately, when the fibrin deposition/thrombus formation process is allowed to advance to a severe degree, the occlusive process recurs and repeated doses of lytic must be administered[496,516,517,523] at a median intertreatment interval of only 5 to 7 additional dialysis sessions.[516] This is believed to result from the presence of a fibrin sheath that, at times, is so extensive as to occlude the SVC.[606]

Endoluminal brushing, although not used widely in the United States, can remove clots effectively and also provides material for culture to rule out or confirm infection.[528]

Radiological Evaluation (CPR 7.2)

A fibrin sheath can only be diagnosed by performing a contrast study and requires partial pull back of the catheter. A representative example is shown in Fig 10.

A fibrin sheath can be treated in 1 of several ways: fibrin sheath stripping, guide wire catheter exchange, and lytic infusion.[156,157,579,607-609] Studies have shown the success of tPA infusion,[607,608] as well as stripping of the catheter.[156,609] No difference in outcome

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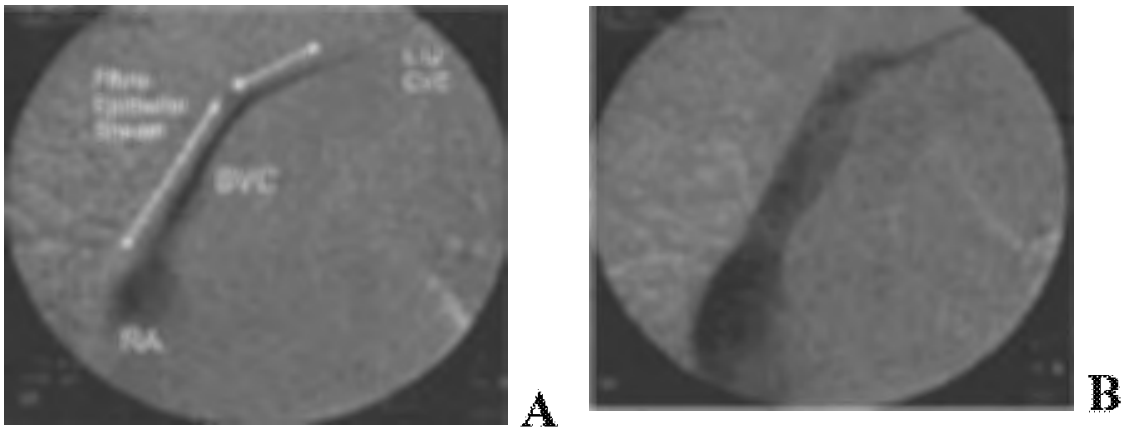
Figure 10. Fibrin sheath (A) prior to therapy; (B) after treatment with PTA. Abbreviations: LIJ, Left internal jugular; RA, Right atrium; SVC, Superior Vena Cava. (Courtesy of Dr A. Asim).



was found between percutaneous stripping and UK infusion.[530] See Table 24 in CPG 7.6 for additional information.

There have been no comparisons of sheath disruption with an angioplasty balloon compared with the other 2 techniques. It is intermediate in complexity. Until such studies are done, the Work Group's preferred intervention for a fibrin sheath is removal of the catheter over a guide wire, disruption of the sheath with a balloon, and placement of a new catheter (catheter exchange).[531]

Catheter Maintenance (CPR 7.3)

Increasing focus should be placed on prevention or control of growth of the fibrin sheath through periodic high-dose lytic infusion[600] triggered by a progressive decrease in achievable BFR. Also, some centers are using weekly instillation of tPA or UK to maintain flow characteristics of long-term catheters.[496,531] There is sufficient evidence of effectiveness for the Work Group to recommend these approaches for long-term catheter management with the proviso that this is an area for future research to optimize the best regimens that are cost-effective.

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CLINICAL PRACTICE RECOMMENDATION 8: VASCULAR ACCESS IN PEDIATRIC PATIENTS

8.1 Choice of access type:

8.1.1 Permanent access in the form of a fistula or graft is the preferred form of vascular access for most pediatric patients on maintenance HD therapy.

8.1.2 Circumstances in which a CVC may be acceptable for pediatric long-term access include lack of local surgical expertise to place permanent vascular access in small children, patient size too small to support a permanent vascular access, bridging HD for PD training or PD catheter removal for peritonitis, and expectation of expeditious kidney transplantation.

8.1.3 If surgical expertise to place permanent access does not exist in the patient's pediatric setting, efforts should be made to consult vascular access expertise among local adult-oriented surgeons to either supervise or place permanent vascular access in children.

8.1.4 Programs should evaluate their patients' expected waiting times on their local deceased-donor kidney transplant waiting lists. Serious consideration should be given to placing permanent vascular access in children greater than 20 kg in size who are expected to wait more than 1 year for a kidney transplant.

8.2 Stenosis surveillance:

An AVG stenosis surveillance protocol should be established to detect venous anastomosis stenosis and direct patients for surgical revision or PTA.

8.3 Catheter sizes, anatomic sites, and configurations:

8.3.1 Catheter sizes should be matched to patient sizes with the goal of minimizing intraluminal trauma and obstruction to blood flow while allowing sufficient blood flow for adequate HD.

8.3.2 External cuffed access should be placed in the internal jugular with the distal tip placed in the right atrium.

8.3.3 The BFR of an external access should be minimally 3 to 5 mL/kg/min and should be adequate to deliver the prescribed HD dose.

INTRODUCTION

Applicability of Previous KDOQI Vascular Access Guidelines to Pediatric Patients

Provision of validated evidence-based pediatric vascular guidelines is hampered by a number of pediatric CKD stage 5–related epidemiological issues. Most of the recommendations outlined in the first edition of the KDOQI Vascular Access Guidelines are pertinent to pediatric patients, although few published data exist to support more than opinion-based recommendations. Some pediatric HD vascular access descriptive and

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comparative clinical research has been conducted since the first edition of the KDOQI Vascular Access Guidelines, which provide data to formulate a first set of both evidence- and opinion-based recommendations for children receiving maintenance HD. Rather than restating the previous CPGs in their entirety with annotation of the few areas in which the emphasis may be different for pediatric patients, we have opted to present separate pediatric Vascular Access Guidelines based on the available pediatric literature. For specific vascular access areas not addressed in these pediatric guidelines, the practitioner should refer to the relevant adult KDOQI Guidelines.

RATIONALE

Choice of Access Type (CPR 8.1)

Kidney transplantation remains the preferred and predominant therapy for pediatric patients with CKD stage 5; therefore, many pediatric patients receive maintenance HD through an indwelling catheter in light of short deceased-donor waiting list times or a readily available living-related donor (see Fig 11).[610] Because fewer than 800 pediatric patients receive maintenance HD therapy in the United States, surgical expertise for placing fistulae or grafts in small patients may be limited by the infrequent need and sporadic caseload. Smaller patients, especially those less than 10 kg, present technical challenges in terms of both surgical and nursing skill; therefore, the majority of smaller patients receive PD for their maintenance dialysis modality.

Recent data show that AVFs and AVGs typically function longer[75,611-613] than catheters[614-616] in pediatric patients receiving maintenance HD therapy. Functional survival rates of AVFs and AVGs are similar to adult patient standards and those recommended by KDOQI Vascular Access Guidelines, with centers recently reporting 4-year functional survival rates of 40% to 60%. Despite this, the most recent CMS CPM and North American Pediatric Renal Transplant Cooperative Study data[617] show that 62% to 78% of pediatric maintenance HD patients have catheters as their vascular access. While reports of successful permanent vascular access in children less than 10 kg in size exist,[611,612,618] maturation can take up to 4 to 6 months, making routine permanent access placement impractical in many pediatric situations. Since the late 1970s, both AVFs and AVGs have been placed in children requiring maintenance HD.[619] The major complications of pediatric fistulae include a primary nonfunction rate of 20% to 33%, usually because of lack of maturation or clotting. Pediatric fistulae can develop stenosis anywhere along the fistula, most of which is amenable to either surgical correction or PTA.[620] Given the relatively long life expectancy for pediatric patients with CKD stage 5 (79% at 10 years and 66% at 20 years),[621] all efforts should be made to use distal sites for initial fistula creation, ie, the radiocephalic fistula configuration. For patients less than 10 kg in size with a creatinine clearance between 20 and 25 mL/min/1.73 m^2 in whom imminent dialysis is not required, microsurgical techniques should be used for fistula creation.[611,612] Fistulae in smaller children may require 4 to 6 months for adequate maturation.

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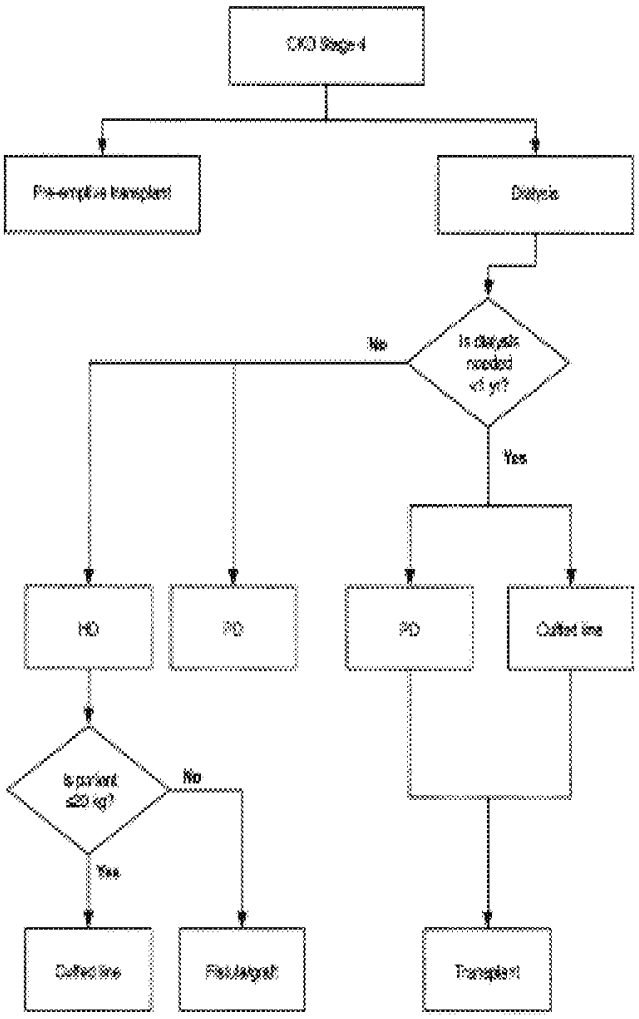
Figure 11. Pediatric progress from CKD stages 1 to 5 and KRT/access algorithm.



Stenosis Surveillance (CPR 8.2)

AVGs offer the advantage of more flexible surgical configurations, which include the use of thigh vessels. Recent data show that AVGs can function well in pediatric patients receiving maintenance HD, with functional survival rates similar to adult patient standards and KDOQI Vascular Access Guidelines.[613] As with AVFs, the more distal anatomic sites should be used for first access to preserve more proximal sites for access in later life. AVG venous outflow stenosis predisposes pediatric patients to AVG thrombosis. Recent pediatric data show that UDTs are very sensitive to predict venous stenosis.[365] A proactive ultrasound dilution venous stenosis assessment protocol directing patients to angioplasty with a corrected access flow less than 650 mL/min can lead to a significant decrease in AVG thrombosis rates.[622,623] One pediatric study found that static venous pressure

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monitoring did not help in the diagnosis of venous stenosis.[624] No data exist about the long-term effect of decreased thrombosis rates on AVG survival in children.

Catheter Sizes, Anatomic Sites, and Configurations (CPR 8.3)

The choice of catheter size and configuration depends on the size of the patient. Studies to date suggested that children as small as 4 to 5 kg can tolerate dual-lumen 8 Fr catheters, and as the child becomes larger in size, a larger volume access can be placed.[625] Table 25 serves as a guideline for matching catheter size to patient size. Choices often are limited based on availability, but considerations should include flow characteristic, recirculation risk, and ease of placement. Data suggest that for the appropriately sized patient, twin single-lumen catheters (the Tesio System) may provide better performance than standard dual-lumen catheters.[616] Longer and more narrow catheters result in greater resistance to flow.[626]

Catheter placement considerations in pediatrics are similar to those in adults, with a preference for internal jugular veins over subclavian veins. Right atrial placement may prevent inlet or outlet hole occlusion by blood vessels and thus allow for the high flow rates needed to provide adequate dialysis. Data have suggested that subclavian stenosis occurs in excess of 80% of patients in pediatrics who have subclavian catheters (Denis Geary, personal communication). Femoral access can be used when upper-anatomy venous access is no longer available.[627]

Flow rates for vascular access should be sufficient to result in a Kt/V greater than 1.2. Kt/V is influenced further by the recirculation rate. Because flow rates in pediatrics vary by the size of catheter, which varies by the size of the patient, a recommended flow rate of 3 to 5 mL/kg/min is acceptable in most patients.[628]

Table 25. Semipermanent HD Catheter and Patient Size Guideline

Patient Size (kg)	Catheter Options
<10 kg	Made on a case by case basis
10-20 kg	8 French dual lumen
20-35 kg	7 French twin catheter
20-40 kg	10 French dual lumen
	10 French Split catheter
	12 French twin catheter
>40 kg	16 French twin catheter
	11.5 or 12.5 French dual lumen

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III. Research Recommendations

PREAMBLE

RCTs are the optimal study design to answer intervention questions. A recent review concluded that between 1966 and 2002, the number of RCTs published in nephrology from 1966 to 2002 (2,779) is fewer than in all other specialties of internal medicine.[629] In addition, the overall quality of RCT reporting in nephrology is low and has not improved for 30 years. Issues identified included unclear allocation concealment (89%), lack of reported blinding of outcome assessors (92%), and failure to perform "intention-to-treat analysis" (50%). The challenges of improving the quality and quantity of trials in nephrology are substantial. We need to use standard guidelines and checklists for trial reporting, give greater attention to trial methods, and cease to focus on results of small underpowered studies. We must involve experts in trial design and reporting, expect multicenter collaboration, and do larger, but simpler, trials. Many of the research recommendations made in this section require multicenter trials to enroll sufficient patients to obtain clear-cut answers. Many will not receive external support from government or other grant agencies. However, they can be performed by collaboration between those in academic centers and those in clinical practice. We should emulate cardiology, for which there has been a 6-fold growth in clinical research trials, particularly in the number of patients (usually in the thousands) enrolled into the studies.

RANKING OF RECOMMENDATIONS

Research recommendations have been grouped into 3 categories: critical research, important research, and research of interest. These rankings were made by the Work Group based on current evidence and the need for research to provide additional evidence for the current CPGs and CPRs. No attempt was made to rank research recommendations within each of the 3 research categories.

Although the Vascular Access Work Group was restricted by the NKF to a thorough literature review in only 4 areas, the Work Group has developed research questions for all CPGs. These questions should not be viewed as comprehensive, but as a stimulus to the nephrology community to begin to ask, hopefully, better questions regarding vascular access with a goal of better outcomes for our patients.

CRITICAL RESEARCH RECOMMENDATIONS

Guideline 1. Patient Preparation for Permanent HD Access

Studies are required to determine the optimal vascular mapping criteria based on outcome goals of working fistulae.

Studies are needed to determine the optimal stratification of patients for fistula placement. Is there an age component to sizing of the artery and vein for fistula creation? Specifically, should the minimal vein diameter for such higher risk groups as female, diabetic, and elderly patients be larger to have acceptable working fistula outcomes?

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Randomized studies should be performed comparing 1-stage with 2-stage brachial basilic vein transposition fistula outcomes.

Studies are needed to determine the optimal surgical techniques for fistula creation with outcomes to identify factors that minimize the development of surgical swing segment stenosis in fistulae.

Guideline 2. Selection and Placement of HD Access

Patients should be considered for construction of a primary fistula after failure of every HD access. There is a paucity of information about the success of this strategy. If a forearm loop AVG is placed as initial access, does this lead to successful construction of elbow-level fistulae? How often? Do we need an RCT? In what patients would a graft before fistula be cost- and resource effective? None? Some? Would a PU "immediate use" type of graft be preferable to a catheter if one had to do immediate (ie, within days) dialysis?

How often is primary conversion of dysfunctional grafts to fistulae successful? Is it affected by the previous history of thrombosis or angioplasty (if applicable)? What are the guidelines for number of angioplasties/thrombectomies performed before compromising the ability to convert to a fistula? What is the optimal timing for conversion?

The preference for fistulae is based on lower morbidity associated with their creation and maintenance compared with other access types. Is this still true for the US CKD stage 5 population? Has this remained true as the population has grown older and the health care system in the United States has been stretched? Late referrals, lower skill sets in the staff delivering dialysis and cannulating accesses, increased comorbidity in the United States compared with Europe, Japan, or Canada—do these factors influence the selection of initial access and the progression and choices among different access types?

Guideline 3. Cannulation of Fistulae and Grafts and Accession of HD Catheters and Port Catheter Systems

Can intensive structured cannulation training lead to better access outcomes?

Can increased remuneration for expert cannulators lead to better access outcomes?

Can self-cannulation lead to better outcomes?

Guideline 4. Detection of Access Dysfunction: Monitoring, Surveillance, and Diagnostic Testing

Studies are needed to compare outcomes of physical examination with "high-tech" methods in determining the best timing for intervention.

The role of DDU as an intermediate diagnostic test should be examined to determine the "timing" for access intervention with PTA or surgery.

There may be important differences in the susceptibility of grafts and fistulae to thrombosis as a function of absolute access flow or change in access flow over time. The "best" therapy for the access also may differ according to type. Future studies should carefully separate the surveillance data, type of intervention (PTA or surgical), response

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to therapy, and both short-term and long-term outcomes according to access type, either graft or fistula. Because more proximal accesses have greater flow rates, data also should be categorized to access location, primarily the feeding artery (radial or ulnar versus low brachial, high brachial, and axillary for the upper arm and femoral for the thigh).

Studies are needed to establish objective criteria for endovascular intervention.

Guideline 5. Treatment of Fistula Complications

The efficacy of physical examination in detecting abnormalities in accesses difficult to cannulate should be studied.

Comparative trials are required to assess interventional versus surgical modalities to correct maturation failure with measurement of access flow longitudinally before and after correction.

Studies should examine the effect of intervention on: recurrent stenosis, elastic recoil, and juxta-anastomotic stenoses.

Guideline 6. Treatment of AVG Complications

Assessing adequacy of the intervention. Is PTA an effective intervention for treatment of vascular access–related stenosis? We cannot answer this question. A fundamental problem is our inability to reliably predict the outcomes of our percutaneous and surgical interventions. The true determinants of HD graft patency and longevity remain unknown. It certainly is a complex and multifactorial process. The primary determinants of graft failure likely are regulated by both physiological and genetic factors and therefore are variable within the patient population. To add to the confusion, neointimal hyperplastic stenoses develop simultaneously and sequentially in multiple locations. Our success in treating 1 stenosis is negated by the rapid development of another lesion. And there is another important variable: delayed elastic recoil can cause rapid recurrence of the stenosis after an apparently successful angioplasty procedure. This phenomenon can occur minutes to hours after balloon dilation, and our anecdotal experience suggests that elastic recoil of a stenosis may happen after 10% to 15% of our angioplasty procedures. Our current challenge is to identify the determinants for successful angioplasty and optimize our techniques to improve our clinical outcomes. In addition, we need to develop pharmacological means to reduce/prevent the recurrence of neointimal hyperplasia after successful angioplasty.

Criteria for success. An end point is used to define the successful completion of a procedure. The definition of a successful procedure can be viewed from several different perspectives. For example, the end point for clinical success is alleviation of the patient's symptoms. Hemodynamic success is restoration of normal blood flow throughout the treated vascular segment. And for treatment of stenoses, the end point for anatomic success is less than 30% residual diameter reduction. These clinical, hemodynamic, and anatomic end points serve as the determinants of a successful endovascular intervention. Our clinical experience has shown that these commonly used end points are *unreliable* for predicting the long-term patency of an HD graft or fistula. Although we use end points

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to define immediate success, there is no postprocedural end point that correlates with long-term patency. Our inability to predict the long-term outcome of our endovascular procedures continues to frustrate both the physician and patient.

After an endovascular intervention, the standard definition of anatomic success is a residual stenosis with less than 30% diameter reduction. Although there are well-recognized physiological concepts that support the use of 50% stenosis as the definition of a hemodynamically significant lesion, there is no such scientific basis for the use of less than 30% residual stenosis to define a successful treatment. A consensus committee reached the value of 30% with representatives from interventional radiology and vascular surgery. This well-accepted standard end point (<30% residual stenosis) has no hemodynamic or physiological meaning. In addition, the residual stenosis does not allow for proper remodeling of the vein and may contribute to recurrence of stenosis. Therefore, it is not surprising that use of this parameter as a determinant of success is not predictive of the long-term patency of an HD graft or fistula. This poor correlation between degree of residual stenosis and subsequent patency was substantiated in a study that reported analysis of 96 interventions performed in native AVFs.[630] After angioplasty, 17 lesions had greater than 30% residual stenosis and, by definition, had failed treatment. However, there was no difference in the long-term patency of this group compared with patients who had lesions with less than 30% residual stenosis on final fistulography.

Obviously, criteria used for success need to be examined by well-designed outcome studies.

Multiple lesions and criteria for intervention. According to the KDOQI guidelines, lesions with less than 50% stenosis should not be treated. However, it is not uncommon for a graft or fistula to have multiple areas of endoluminal irregularity that, when measured individually, represent less than 50% stenosis and therefore should not be treated. However, a hemodynamic abnormality may still exist. The basic principles of hemodynamics state that the effects of multiple stenoses are additive, similar to an electrical circuit with a series of multiple resistors. Therefore, our current concepts that emphasize the evaluation of individual stenoses using anatomic criteria are flawed.

New methods[54] that provide a more global assessment of the entire vascular access circuit suggest that subtle lesions can have substantial hemodynamic effects. The assessment of intragraft blood flow during angioplasty procedures may provide additional information regarding the hemodynamic importance of lesions that are greater than 30% but less than 50% stenosis.

We need to identify physiological/objective criteria for successful intervention.

IMPORTANT RESEARCH RECOMMENDATIONS

Guideline 1. Patient Preparation for Permanent HD Access

Studies are needed to determine the optimum timing of access placement.

Studies should be performed to examine the effect of exercises to mature vessels (arterial and venous) before and after fistulae are constructed.

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The use of diluted contrast to characterize the venous system peripherally and centrally in patients with CKD and the effect on residual kidney function should be studied.

Additional studies are needed to compare the accuracy of MRA and DDU in evaluating central veins.

How can we align incentives for the creation of fistulae for all stakeholders: patients, nephrologists, surgeons, and dialysis providers?

Guideline 2. Selection and Placement of HD Access

What is the relative benefit of arm exercises performed before or after fistula construction and maturation or both?

We need RCTs to determine the effect of exercise either before or after access construction, alone or combined, on access maturation, time to cannulation, primary and secondary patency, ease of cannulation, number of procedures needed during the life span of the access, and cost analysis. Is pressure inside the fistula important in the maturation process? Is it flow or intraconduit pressure or both that allow an access to tolerate cannulation without infiltration? Should a nonocclusive tourniquet be used during exercise? Do we use/measure mere clinical end points for these studies or does fistula flow need to be measured as well, or does it not matter what the flow is? Brachial artery flow can be measured as a surrogate for access flow.

If intrafistula flow is important, what flow is needed to mature a fistula?

Guideline 3. Cannulation of Fistulae and Grafts and Accession of HD Catheters and Port Catheter Systems

Additional studies are needed of disinfectants, the role of antibiotic locks, and which patients may benefit most from CVC salvage. Risk-benefit outcomes, as well as long-term antibiotic susceptibility studies, should be done to detect resistance.

Studies are needed to examine the effectiveness of data on rotation of sites, buttonhole, flow/pressure curves, and so on.

Does the bevel-up cannulation method decrease access complications?

What needle tip-to-tip measurements minimize recirculation or prevent erroneous access flow measurements?

Can buttonhole (constant-site) cannulation be used in biografts?

Should an infiltrating needle be removed after the patient undergoes sytemic anticoagulation with heparin?

How should the timing of flushing and locking of heparin in a catheter occur in a patient who is using 1 needle in the fistula and 1 side of the catheter for return?

Do transparent dressings, where the exit site is clearly visualized, need to be changed at each dialysis treatment?

Guideline 4. Detection of Access Dysfunction: Monitoring, Surveillance, and Diagnostic Testing

Further evaluation of the acoustic stethoscope is needed in detecting hemodynamically significant stenoses.

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The relationship of access flow to pressure varies among individuals, affected chiefly by the health and capacity of the artery to deliver flow into the access. Within a population, there may be no obvious relationship between access flow and P_{IA} if measurements are made cross-sectionally because the important determinant in an individual is baseline flow (which may vary from 500 to 3,000 mL/min), the presence of 1 or more stenoses, their location, and the rate of evolution of the stenosis or stenoses. Additional studies are needed to determine the natural course of stenoses in grafts and fistulae. Stable stenoses may need no intervention if they are not associated with increased risk for thrombosis. Conversely, there may be significant risk for thrombosis, even with access flows exceeding 1,000 mL/min. Noninterventional trials should be conducted with the clock starting from the time of construction.

Large-scale trials are required to determine whether correction only of "hemodynamically" significant lesions (those associated with "low" access flows or "high" pressures or a change in access flow or pressure) is superior to correction of all stenosis greater than 50%.

Guideline 5. Treatment of Fistula Complications

Studies are required to compare strategies for treating aneurysms in fistula: surgery with new anastomosis versus surgical creation of new anastomosis. Cost and outcome analyses should be performed.

Studies are needed to examine the efficacy of endoluminal interventional versus surgical procedures for the management of aneurysms in fistulae.

Comparative trials should be performed to study the efficacy of surgery compared with interventional endoluminal procedures in correcting stenoses/thrombosis, with the same methods used for outcomes.

The role of thrombolytics in reestablishing or maintaining patency after fistula thrombosis should be examined. Low doses of thrombolytics have been used to keep costs controlled—does it make a difference in outcomes?

Data from RCTs are needed on the duration of thrombosis and success in reestablishing/maintaining patency. Is surgery more effective early or later?

Guideline 6. Treatment of AVG Complications

Assessing effectiveness of interventions. It is well accepted that a stenosis causing greater than 50% diameter reduction is considered to be a hemodynamically significant lesion. This value is based on both experimental modeling of flow stenosis[631] and correlation of thrombosis rates and degree of stenosis.[10] This value is based upon the physiology of a "critical arterial stenosis."[450,451] A 50% reduction in luminal diameter corresponds to a 75% reduction in cross-sectional area, the critical point at which blood flow begins to dramatically decrease.

Measuring technical success. What determines technical success for endovascular interventions? Should technical success be based upon anatomic criteria, the measurement of which is both subjective and fraught with error and usually not assessed in 2 orthogonal views? Or should it be based upon normalization of a hemodynamic

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parameter that is less subjective and more reflective of vascular access performance? Possibilities include the use of flow measurements, static pressure, or ultrasound imaging during the PTA procedure or angioscopy after the procedure. Continued clinical investigation hopefully will provide scientific support for the use of hemodynamic end points, not anatomic end points.

Endovascular stents would seem to be an ideal method to treat angioplasty failures. Stents can oppose elastic recoil and optimize endoluminal dimensions, thereby improving intragraft blood flow and prolonging graft patency. However, the majority of clinical studies showed that the routine use of stents does not provide an additional benefit compared with angioplasty alone.[460,461] The neointimal hyperplastic tissue continues to grow unabated through the meshwork of the metallic stent. For these reasons, use of endovascular stents to treat HD-related stenoses continues to be a controversial subject. A recent study reported that use of nitinol stents provided superior results compared with stainless steel stents.[632] Continued improvements in stent design, the use of stent grafts, or the use of drug-eluting stents may provide better long-term results. Covered stents have been used to salvage AVGs, but efficacy has not been compared with other strategies.

Balloon sizing and selection. Balloons are now available in various sizes, have cutting edges, and are capable of delivering drugs. The proper selection and use of these balloons requires additional studies.

Mechanical thrombectomy devices. Comparative studies are needed on efficacy and cost. A reanalysis of existing data with differing devices should be performed.

Thrombolytics and anticoagulation. Although heparin typically is used during an endoluminal thrombectomy procedure, the proper role of thrombolytics is unknown. The spectrum has shifted from pharmacolytic to mechanical thrombectomy. Whether some lytics and their efficacy are superior to others in terms of outcomes is unknown. Several small series also suggested that dialysis within hours of thrombectomy influences patency.

Comparison of intervention methods. Do percutaneous and surgical techniques provide similar results or are we using percutaneous techniques simply because of the unavailability of surgical manpower for performing large numbers of vascular access–related procedures in an expedient manner? From another perspective, are we sacrificing long-term patency of the AVG to avoid insertion of an HD catheter?

Several reasonable studies reported that surgical techniques for AVG repair can provide substantially better outcomes compared with percutaneous techniques.[467,468,472] By establishing substantially higher primary patency goals after surgical repair, the KDOQI guidelines have acknowledged the superiority of surgical techniques. However, because of a variety of factors, including the unavailability of surgeons, the growth of interventional nephrology, the trend toward outpatient vascular access services, and the profitability of percutaneous procedures, the superiority of surgical techniques seems to have been forgotten.

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Do surgical techniques for AVG repair provide more durable results with better long-term patency compared with percutaneous techniques? Is this a political issue, a manpower issue, or a financial issue?

Prevention of stenosis. This is a particularly important area. Both basic studies and pharmaceutical interventions are needed.

Guideline 7. Prevention and Treatment of Catheter and Port Complications

The ideal catheter diameter is not established. Are there concomitantly increased complications associated with larger diameter catheters?

Studies are needed to evaluate the risk versus benefit of higher dose warfarin therapy (INR > 1.6) on catheter patency.

A comparison of lytic treatments is needed to examine:

- "Dwell" versus push versus infusion for catheters unable to deliver BFR of 300 mL/min
- Comparison of lytic agents for efficacy, cost, and long-term performance
- A number of studies on "anticoagulant locks" should be done in which primary outcome parameters of maintained access flow, resource use, and cost of care are evaluated. These include:
  1. Comparison of heparin at different concentrations (1,000 U and 5,000 U/mL) for all 3 dialysis sessions per week versus substitution of one of the heparin locks by tPA lock
  2. Use of high dose tPA (2.5–5 mg/lumen) where the catheter blood flow delivered at −250 mm Hg falls to <300 mL/min or decreases by 100 mL/min from its best flow ever

A definitive study should be performed to determine the natural history of catheter/port-related complications in the central veins, by using central venograms, that begins with de novo catheter placement, every 6-month follow-up, and with eachthe lowest rate in the last four decadescatheter complication (CRB, fibrin sheath, and all other types of catheter dysfunction).

Studies are needed to determine the association between infection and fibrin sheaths in catheters.

The optimal duration of antibiotic therapy for catheter-related infections should be examined.

Prospective studies are needed to examine antibiotic locks as an adjunct to save catheter versus "site salvage." Outcomes as primary and economics as secondary factors should be considered.

RESEARCH RECOMMENDATIONS OF INTEREST

Guideline 1. Patient Preparation for Permanent HD Access

Does patient education on the various risks/benefits of catheters versus fistulae/grafts alter success in placement? Is it an ethical study?

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What demographic variables influence the likelihood of permanent access construction among a cohort of patients seen in a CKD clinic?

Guideline 2. Selection and Placement of HD Access

Studies are needed to determine the optimum duration of rest of a young (in use for <3 months) fistula after it has been infiltrated (ie, presence of hematoma with associated induration and edema). What parameters should be examined and how should such a study be designed?

The effects of catheter tip location on catheter or port catheter system performance should be studied—in the SVC/right atrium, common iliac, low IVC, and high IVC/right atrium. For the same French and luminal diameter, pressure flow curves should be performed keeping catheter design constant (ie, without mixing stepped and split catheters).

Studies are required to examine the effect of jets from catheter tips on central veins.

Guideline 3. Cannulation of Fistulae and Grafts and Accession of HD Catheters and Port Catheter Systems

What effect does correction of anemia have on access flow in fistulae? Prospective observational studies are needed.

Guideline 4. Detection of Access Dysfunction: Monitoring, Surveillance, and Diagnostic Testing

Research is needed on portable ultrasound devices for assessing flow easily and repetitively without operator effects.

Studies are needed to determine whether a properly performed DVP test retains any utility in detecting stenoses in fistulae.

Comparisons of surveillance techniques (access flow, DVP, P_{IA}) are required in fistulae using DDU anatomic imaging or contrast angiography to determine sensitivity and specificity. Low-end techniques (physical examination + derived P_{IA} ± flow achieved/prepump pressure) should be compared with high-end methods (Q_A by UDT or GPT alone ± flow by in-line dialysance, DDU).

Guideline 5. Treatment of Fistula Complications

Comparative trials are needed to examine interventional versus surgical modalities to correct maturation failure, with measurement of access flow longitudinally before and after correction.

Guideline 6. Treatment of AVG Complications

Treatment of infection. There are few informative data on the treatment of infected grafts. Decisions on using antibiotics, removal or not of the AVG, and duration of antibiotic use usually are made based on experimental considerations and recommendations from infectious disease consultants and CDC publications. Most of these recommendations are extrapolations and are not based on specific studies of dialysis patients with AVGs.

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Arterial lesions and steal. In an increasingly older population with a greater incidence of diabetes, arterial lesions are not uncommon in patients undergoing vascular access constructions.[409] Steal occurs with high-flow fistulae. Prediction of its occurrence[80,633] and means to prevent its development[634] require prospective outcome studies. Once developed, several methods can be used to correct the problem,[411,431,433,635,636] but without consensus about the best procedure.[48,637] When distal digital ischemic changes or gangrene appear ipsilateral to a functioning graft, we need more studies to determine whether the problem is purely "ischemic" or perhaps embolic.[431,638]

Prediction of successful AVG function. A multitude of factors probably influence the longevity of AVG function,[143] including the individual's genetic predisposition for neointimal hyperplasia, surgical techniques, cannulation, and so on. These factors have not been systemically studied.

Guideline 7. Prevention and Treatment of Catheter and Port Complications

Studies should examine the value of sequential measurement of dialyzer flow rates and delivered and prepump arterial pressures during sequential dialysis treatments in detecting problems while they are still amenable to pharmacological or mechanical intervention. With modern catheters, what is the value of the conductance (BFR/arterial prepump pressure) in predicting catheter dysfunction?

Research is needed to define the optimum value of flow rate: 300 versus 350 mL/min if the initial flow is greater than 400 mL/min. Outcome parameters should include effects on adequacy, manpower utilization, and cost of intervention.

Studies should culture the tips of all catheters removed for both CRB and fibrin sheath disruption to determine the frequency of occult "silent" infection.

Additional studies are required to define the agents and concentrations of antibiotic locks that can be used, including studies of systemic levels during prolonged periods.

Long-term studies are needed on antibiotic and antimicrobial resistance to antibiotic locks and ointments used to prevent infection.

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Acronyms and Abbreviations

AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BP	Blood pressure
CHF	Congestive heart failure
CPR	Clinical Practice Recommendations
CrCl	Creatinine clearance
CVD	Cardiovascular disease
DOQI	Dialysis Outcomes Quality Initiative
GFR	Glomerular filtration rate
HD	Hemodialysis
HTN	Hypertension
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/V	Measure of dialysis adequacy calculated from K (dialyzer clearance), t (time) and V (volume of body water in a given patient)
LVH	Left ventricular hypertrophy
NKF	National Kidney Foundation
PD	Peritoneal dialysis
RCT	Randomized controlled trial
ROC	Receiver operating characteristics
SGA	Subjective global assessment
TPA	Tissue plasminogen activator
UOP	Urine output
UrCl	Urea clearance
US	Ultrasonography

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Appendix 1. Methods for Evaluating Evidence

AIM

The overall aim of the project was to update the 2000 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines on Hemodialysis and Peritoneal Dialysis Adequacy, and Vascular Access. The Work Group sought to update the guidelines using an evidence-based approach. After topics and relevant clinical questions were identified for the updates, the available scientific literature on those topics was systematically searched and summarized.

OVERVIEW OF PROCESS

Update of the guidelines required many concurrent steps to:

- Form the Work Groups and Evidence Review Team that were to be responsible for different aspects of the process;
- Confer to discuss process, methods, and results;
- Develop and refine topics;
- Define exact populations of interest;
- Create draft guideline statements and rationales;
- Create data extraction forms;
- Create and standardize quality assessment and applicability metrics;
- Develop and perform literature search strategies;
- Screen abstracts and retrieve full articles;
- Review articles;
- Extract data and perform critical appraisal of the literature;
- Tabulate data from articles into summary tables;
- Write guideline statements and rationales based on literature and Work Group consensus.

Separate Work Groups were created for each subject area: hemodialysis adequacy, peritoneal dialysis adequacy, and vascular access. The 3 groups worked in parallel to create the guidelines. The Work Group Chairs conferred regarding overlapping topics across guidelines. The Evidence Review Team, comprised of experts in systematic review and guideline development, guided the Work Groups in all methods and aspects of guideline development.

Creation of Groups

The KDOQI Advisory Board selected the Work Group Chairs and the Director of the Evidence Review Team then assembled groups to be responsible for the development of the updates. These Work Groups and the Evidence Review Team collaborated closely throughout the project.

The Work Groups consisted of domain experts, including individuals with expertise in nephrology, surgery, radiology, pediatrics, nursing and nutrition. For each guideline

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update, the first task of the Work Group members was to define the overall topics and goals of the updates. They then further developed and refined each topic, literature search strategies, and data extraction forms (described below). The Work Group members were the principal reviewers of the literature, and from their reviews and detailed data extractions, they summarized the available evidence and took the primary roles of writing the guidelines and rationale statements. Completed data extractions were posted on a National Kidney Foundation (NKF) website for direct access by Work Group members.

The Evidence Review Team consisted of nephrologists (1 senior nephrologist and 2 nephrology fellows), methodologists, and research assistants from Tufts-New England Medical Center with expertise in systematic review of the medical literature. They instructed the Work Group members in all steps of systematic review and critical literature appraisal. The Evidence Review Team also coordinated the methodological and analytical process of the report, defined and standardized the methodology of performing literature searches, of data extraction, and of summarizing the evidence in summary tables. They organized abstract and article screening, created forms to extract relevant data from articles, organized Work Group member data extraction, and tabulated results. Throughout the project the Evidence Review Team led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, and grading of the quality of the body of evidence and the strength of guideline recommendations.

Refinement of Update Topics and Development of Materials

The Work Group reviewed the 1995 Dialysis Outcomes Quality Initiative (DOQI) Clinical Practice Guidelines and the 2000 KDOQI updates and decided which of the guideline recommendations required updates and which should remain unchanged. These assessments were based primarily on expert opinion regarding the currency of the previous guidelines and the likelihood of availability of new evidence. Preliminary literature searches were made to inform this process. To allow for timely review, it was determined that each set of guidelines would be able to have systematic reviews on only a limited number of topics. After literature review, the experts decided which recommendations would be supported by evidence or by opinion. As described below, recommendations based on adequate evidence were categorized as Guidelines (CPGs), while opinion-based statements were categorized as Clinical Practice Recommendations (CPRs).

The Work Groups and Evidence Review Team developed: a) draft guideline statements; b) draft rationale statements that summarized the expected pertinent evidence; and c) data extraction forms containing the data elements to be retrieved from the primary articles. The topic refinement process began prior to literature retrieval and continued through the process of reviewing individual articles.

Literature Search

Based on the draft guideline statements, the Work Group members agreed on topics that would be systematically reviewed and formulated questions defining predictors, interventions, comparators, and outcomes of interest. Search strategies were developed based

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on these questions and topics, in addition to the study designs and years of publications of interest to the Work Group. Articles of interest were identified through MEDLINE searches of English language literature of human studies in May through July 2004. Broad search terms were used to avoid missing potentially pertinent articles. The searches were supplemented by articles identified by Work Group members through June 2005.

Only full journal articles of original data were included. The searches were limited to studies published since January 1997 since earlier publications were reviewed in the previous DOQI guidelines. Editorials, letters, abstracts, and unpublished reports were not included. Selected review articles, however, were included for background material. No systematic process was followed to obtain review articles.

Abstracts and titles from the MEDLINE search results were prescreened by members of the Evidence Review Team for general relevance. A second round of screening was performed on the abstracts by Work Group members for relevance using predefined eligibility criteria, described below. Articles were retrieved by the Evidence Review Team and then rescreened by Work Group members and/or the Evidence Review Team. Eligible studies were extracted using standardized extraction forms. Domain experts made the final decisions regarding the eligibility of all articles.

Generation of Data Extraction Forms

Data extraction forms were designed to capture information on various aspects of the primary articles. Forms for all topics included study setting and demographics, eligibility criteria, causes of kidney disease, numbers of subjects, study design, study funding source, dialysis characteristics, comorbid conditions, descriptions of relevant risk factors or interventions, description of outcomes, statistical methods, results, study quality (based on criteria appropriate for each study design (see below), study applicability (see below), and sections for comments and assessment of biases. Training of the Work Group members to extract data from primary articles occurred by emails and teleconferences. Work Group members were assigned the task of data extraction of articles.

Generation of Evidence Tables

The Evidence Review Team condensed the information from the data extraction forms into evidence tables, which summarized individual studies. These tables were created for the Work Group members to assist them with review of the evidence and are not included in the guidelines. All Work Group members (within each Update) received copies of all extracted articles and all evidence tables. During the development of the evidence tables, the Evidence Review Team checked the data extraction for accuracy and rescreened the accepted articles to verify that each of them met the initial screening criteria determined by the Work Group. If the criteria were not met, the article was rejected, in consultation with the Work Group.

Format for Summary Tables

Summary Tables describe the studies according to the following dimensions: study size and follow-up duration, applicability or generalizability, results, and methodological quality. Within each table, the studies are first grouped by outcome type.

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Data entered into Summary Tables were derived from the data extraction forms, evidence tables, and/or the articles by the Evidence Review Team. All Summary Tables were reviewed by the Work Group members.

Within each outcome, studies are ordered first by methodological quality (best to worst), then by applicability (most to least), and then by study size (largest to smallest). When relevant, outcome thresholds (eg, of access flow measurement) are included. Results are presented by using the appropriate metric or summary symbols, as defined in the table footnotes.

Systematic Review Topics, Study Eligibility Criteria, and Studies Evaluated

The topics for each Update were selected by the respective Work Group members for systematic review (Table 1, Table 2, Table 3). The eligibility criteria were defined by the Work Group members of each Update in conjunction with the Evidence Review Team.

Literature Yield for Hemodialysis Adequacy (Table 4)

A total of 2,526 citations were screened, of which 319 were review articles and 14 were added by Work Group members. There were 223 articles (191 studies in adults and 32 in children) that were potentially relevant. These articles were retrieved for full review. Of these, 87 adult articles were accepted for full data extraction by the Work Group members. Eight articles in children were formally data extracted by a pediatric nephrologist on the Work Group. Articles in adults were randomly assigned to individual Work Group members for data extraction. Of these, 23 studies answered questions pertinent to topics chosen for systematic listing in Summary Tables.

Literature Yield for Peritoneal Dialysis Adequacy (Table 4)

A total of 2,307 citations were screened and 7 were added by Work Group members. There were 293 articles (263 studies in adults and 30 in children) that were potentially relevant. These articles were retrieved for full review. Of these, 101 adult articles were accepted for full data extraction by the Work Group members. Nine articles in children were formally data extracted by a pediatric nephrologist on the Work Group. Articles in adults were randomly assigned to individual Work Group members for data extraction. Of these, 27 studies answered questions pertinent to topics chosen for systematic listing in Summary Tables.

Literature Yield for Vascular Access (Table 4)

A total of 2,892 citations were screened, of which 388 were review articles. There were 112 articles (89 studies in adults, 13 in children, 10 review articles) that were potentially relevant. These articles were retrieved for full review. Of these, 58 articles were accepted for full data extraction by the Work Group members. Because of small sample sizes, articles in children were not formally data extracted but reviewed in detail by the 2 pediatric nephrologists on the Work Group and used to write the narrative summary in the pediatric section. Articles in adults were randomly assigned to individual Work Group members for data extraction. Five additional articles were added by Work Group experts and the Evidence Review Team. Finally, 24 studies answered questions pertinent to topics chosen for systematic listing in Summary Tables.

Search terms for all updates are shown in Appendix 2.

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Table 1. Topics and Eligibility Criteria for Systematic Review: Hemodialysis Adequacy, Update 2006

Topic 1 (guideline 5)	**What is the role of residual kidney function compared to dialysis dose for clinical outcomes, including hospitalization and mortality?**
Population	Patients on HD
Predictor/Intervention	Direct comparisons of dialysis dose versus residual kidney function
	Direct comparisons of including or excluding residual kidney function in calculating dialysis dose
Outcomes	Clinical outcomes (death, hospitalization, CVD/CHF events, other events)
Screening Criteria	Minimum duration: 6 months
	Any study design (prospective or retrospective)
Topic 2 (guideline 4)	**What should be the recommended minimum dose for adequate dialysis using urea kinetics? Should separate goals be set for specific subgroups of patients such as race, gender, age or residual kidney function?**
Population	Patients on HD
Predictor/Intervention	Kt/V
Outcomes	Clinical outcomes (death, hospitalization, CVD/CHF events, other events)
Screening Criteria	Minimum duration: 6 months
	Any study design (prospective or retrospective)
Topic 3 (guideline 5)	**Does the use of a particular type of dialyzer reuse (or lack of reuse) have either an adverse or beneficial effect on either intermediate outcomes or mortality? Are these benefits seen only in specific subgroups of patients, such as race, gender, age, or residual kidney function?**
Population	Patients on HD
Predictor/Intervention	Dialyzer reuse or lack of reuse, and method of "cleaning" for reuse
Outcomes	Clinical outcomes (death, hospitalization, CVD/CHF events, other events)
	Adverse events (allergy, toxicity, etc.)
	Intermediate outcomes (clearance and filtration measures)
Screening Criteria	Clinical Outcomes
	Minimum follow-up 6 months; Direct comparisons only; Prospective or retrospective
	Adverse events
	No minimum follow-up; Any study design
	Intermediate outcomes
	No minimum follow-up; Direct comparisons only; Prospective or retrospective

Grading of Individual Studies

Study Size and Duration

The study (sample) size is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to be generalizable; however, large size alone, does not guarantee applicability. A study that enrolled a large number of selected patients may be less generalizable than several smaller studies that included a broad spectrum of patient populations. Similarly, longer duration studies may be of better quality and more applicable, depending on other factors.

Applicability

Applicability (also known as generalizability or external validity) addresses the issue of whether the study population is sufficiently broad so that the results can be generalized

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Table 2. Topics and Eligibility Criteria for Systematic Review: Peritoneal Dialysis Adequacy, Update 2006

Topic 1 (guideline 2)	**What is the association between achieved (or target) clearance values and clinical outcomes?**
Population	Patients on PD
Predictor/intervention	Clearance measured as achieved total Kt/V (including residual kidney function), CrCl, or prescription (dialysis dose)
Outcomes	Clinical outcomes = death, hospitalization, technique survival, nutrition (albumin, SGA, possibly others), growth (pediatrics), cognitive (pediatrics), allowed other pediatric outcomes
Screening Criteria	Study design: Longitudinal cohorts and RCTs Minimum Duration: Death, Hospitalization/Technique survival: 1 year; Others: 1 month
Topic 2 (guideline 2)	**What is the association between achieved (or target) level of fluid/Na removal parameters and clinical outcomes?**
Population	Patients on PD
Predictor/intervention	Net fluid/volume removal (+/- residual kidney function) Net sodium removal (including dietary Na restriction) Ultrafiltration volume; Volume status; Blood pressure
Outcomes	Clinical outcomes: death, hospitalization, technique survival, nutrition (albumin, SGA, possibly others), growth (pediatrics), cognitive (pediatrics), allowed other pediatric outcomes, EPO/HTN, LVH
Screening Criteria	Study design: Longitudinal cohort studies (RCTs if available) No minimum study duration (except >= 1 year for mortality) Search: 1989-2004
Topic 3 (guideline 3)	**What treatments are effective to preserve residual kidney function and maximize urine output? Among studies that answer this question, is there evidence that the treatments affect clinical outcomes?**
Population	Patients on PD
Predictor/intervention	Pharmacological interventions
Outcomes	Kidney: Residual kidney function for solute clearance (GFR from U/Cr and CrCl), salt and water excretion (UOP) Clinical: death, hospitalization, technique survival, growth (pediatrics), cognitive (pediatrics), allowed other pediatric outcomes
Screening Criteria	Study design: Direct comparisons only (either RCT, uncontrolled parallel comparison, observational single cohort cross-over (from solution A to solution B, no minimum washout period) Minimum study duration: shorter for residual kidney function and longer for clinical outcomes (determine exact thresholds upon reviewing available studies) Search: 2000-2004

to the population of interest at large. The study population is typically defined primarily by the inclusion and exclusion criteria. The target population was defined to include patients with kidney failure, specifically those on dialysis. A designation for applicability was assigned to each article, according to a three-level scale. In making this assessment, sociodemographic characteristics were considered, as well as comorbid conditions and prior treatments. Applicability is graded in reference to the population of interest as defined in the clinical question. For example for the question of treatment of catheter-related infections the reference population is that of HD patients with infected cuffed tunneled HD catheters.

Sample is representative of the target population, or results are definitely applicable to the target population irrespective of study sample.

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Table 3. Topics and Eligibility Criteria for Systematic Review: Vascular Access, Update 2006

Topic 1 (guideline 1)		**Effectiveness of preoperative venous imaging/mapping for planning AVF construction**
	Population	Patients on HD or for future HD, undergoing imaging study in preparation for AVF construction
	Predictor/Intervention	Duplex US
	Outcomes	Maturation and function of new AVF, as defined in study (if several outcomes were reported, the following were extracted: successful use for first dialysis and delivery of adequate dialysis dose for at least 1 month) Change in approach to access placement
	Screening Criteria	Longitudinal studies, prospective or retrospective, including before / after comparisons, any duration Exclude studies of "feasibility or diagnostic accuracy (sensitivity/specificity) Exclude studies with venograms as predictor
Topic 2.1 (guideline 7)		**Treatment of catheter-related infection and the use of antibiotic locks**
	Population	HD patient with cuffed, tunneled HD catheter and catheter-related infection, as defined by the Centers for Disease Control and Prevention, including bacteremia
	Predictor/Intervention	Catheter removal versus no catheter removal with or without use of antibiotic locks Different methods of removal; Different durations of line holiday prior to intervention
	Outcomes	Infection clearing rates; Reinfection rates
	Screening Criteria	Prospective controlled trials of any duration
Topic 2.2 (guideline 7)		**Prophylaxis of catheter-related infection and the use of antibiotic locks**
	Population	HD patient with cuffed, tunneled HD catheter without current catheter-related infection
	Predictor/Intervention	Prophylaxis with "antibiotic lock" (an ounce of antibiotic and coagulant placed into catheter)
	Outcomes	Infection free time; Catheter survival; Infection rate/1000 patient days
	Screening Criteria	Prospective controlled trials Minimum 1000 days at risk (total)
Topic 3.1 (guideline 7)		**Treatment of malfunctioning cuffed tunneled HD catheter with thrombolytics**
	Population	HD patient with cuffed, tunneled HD catheter, which is malfunctioning
	Predictor/Intervention	Treatment with: TPA, Retaplase (Retavase); Urokinase; Other investigational agents in phase 3 studies; Any methods of fibrin sheath stripping (including continuous infusion, catheter exchange, angioplasty)
	Outcomes	Re-establishment of patency/function, ability to restart HD treatment, access survival
	Screening Criteria	Prospective controlled trials of any duration Only cuffed/tunneled catheters, not uncuffed For fibrin sheath stripping studies, only those with radiographic evidence of fibrin sheath Exclude studies using streptokinase
Topic 3.2 (guideline 7)		**Prophylaxis of cuffed tunneled HD catheter malfunctioning with thrombolytics**
	Population	HD patient with functional cuffed, tunneled HD catheter
	Predictor/Intervention	Prophylaxis with: TPA, Retaplase (Retavase); Urokinase; Other investigational agents in phase 3 studies; Any methods of fibrin sheath stripping (including continuous infusion, catheter exchange, angioplasty)
	Outcomes	Maintenance of patency/function, blood flow achieved, access survival
	Screening Criteria	Prospective controlled trials Minimum 1000 days at risk Only cuffed/tunneled catheters, not uncuffed Exclude studies using streptokinase
Topic 4 (guideline 4)		**Performance of different techniques for access surveillance and efficacy of periodic access monitoring for prolonging access life and maintaining access function**
4.1		**How do different tests compare to each other?**
	Population	HD patient with functional AVFs or AVGs
	Predictor/Intervention	Diagnostic test studies comparing performance of one technique of measuring access function with another reference test
	Outcomes	Sensitivity, specificity ROC curves
	Screening Criteria	Cross-sectional diagnostic test studies
4.2		**How do different methods of access surveillance compare for predicting access clotting?**
4.3		**How should one act on abnormal test results to prevent access clotting?**
	Population	HD patient with functional AVFs or AVGs
	Predictor/Intervention	Periodic access surveillance by physical exam or other methods which measure access flow Static pressures; Dynamic pressures; Recirculation; Hemodilution parameters
	Outcomes	Maintenance of function; Maintenance of patency; or access survival Exclude studies only reporting blood flow

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Table 4. Literature Search and Review by Topic

Guideline Topic	Citations Screened	Articles Retrieved	Articles Added by Experts	Articles Data-Extracted*	Articles Included in Summary Tables*
Hemodialysis	2,512	223	14	87	23
1			0	31	0
2			0	5	2
3			0	19	11
4			0	27	10
5			0	7	1
Peritoneal Dialysis	2,380	293	7	104	37
1			0	28	17
2			0	21	4
3			0	12	4
4			0	26	1
5.1			0	17	9
5.2			0	8	0
Vascular Access	2,892	113	5	58	24
1			0	10	0
2.1			0	2	0
2.2			0	4	3
3.1			0	6	2
3.2			0	3	3
4.1			0	10	9
4.2			2	17	4
4.3			3	7	6

*Columns do not add up because some studies were data-extracted for more than 1 topic and used in more than 1 Summary Table.

Sample is representative of a relevant sub-group of the target population. For example, sample is only representative of people with virgin arteriovenous fistulas, or only a specific relevant subgroup, such as elderly individuals or incident dialysis patients.

Sample is representative of a narrow subgroup of patients only, and not well generalizable to other subgroups. For example, the study includes only a small number of patients or patients with a rare disease or virgin fistulas with no access dysfunction. Studies of such narrow subgroups may be extremely valuable for demonstrating exceptions to the rule.

Results

The type of results available in each study is determined by the study design, the purpose of the study, and the question(s) being asked. The Work Group decided on the eligibility criteria and outcomes of interest (see Tables 1-3).

Diagnostic Test Studies

For studies of diagnostic tests, sensitivity and specificity data or area under the curve were included when reported. When necessary, sensitivity and specificity data were calculated from the reported data. Diagnostic tests were evaluated according to a hierarchy

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of diagnostic tests.* Each test was assessed according to diagnostic technical capacity, accuracy, diagnostic and therapeutic impact, and patient outcome. This ultimately affected the overall strength of a recommendation regarding a diagnostic test.

Methodological Quality

Methodological quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of types of design were evaluated, a 3-level classification of study quality was devised:

- ● Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; clear description of the population and setting; clear description of an appropriate reference standard; proper measurement techniques; appropriate statistical and analytical methods; no reporting errors; and no obvious bias. Not retrospective studies or case series.
- ◉ Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria in the category above. It has some deficiencies but none likely to cause major bias.
- ○ Significant bias that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting.

Summarizing Reviews and Selected Original Articles

Work Group members had wide latitude in summarizing reviews and selected original articles for topics that were determined not to require a systemic review of the literature.

Guideline Format

The format for each guideline chapter is outlined in Table 5. Each guideline contains 1 or more specific "guideline statements" that represent recommendations to the target audience. Each guideline contains background information, which is generally sufficient to interpret the guideline. The rationale for each guideline describes the evidence upon which each guideline recommendation is based. The guideline concludes with a discussion of limitations of the evidence review and a brief discussion of clinical applications, and implementation issues regarding the topic. Research recommendations for each guideline update are summarized in a separate section at the end of each guideline update.

Rating the Strength of Recommendations

After literature review, the experts decided which recommendations were supported by evidence and which were supported by consensus of Work Group opinion. Evidence-based guideline recommendations were graded as strong (A) or moderate (B). Recommendations based on weak evidence (C) and/or consensus of expert opinion were labeled as Clinical Practice Recommendations (CPRs). An "A" rating indicates "it is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is

*Fineberg HV, Bauman R, Sosman M: Computerized cranial tomography. Effect on diagnostic and therapeutic plans. JAMA 238:224-227, 1977

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Table 5. Format for Guidelines

Introductory Statement

Guideline or CPR Statement 1

Guideline or CPR Statement 2

BACKGROUND

RATIONALE

Definitions (if appropriate)

Rationale statement 1

Supporting text and tables

Rationale statement 2

Supporting text and tables

LIMITATIONS

IMPLEMENTATION ISSUES

Research Recommendations are presented in a separate chapter.

strong evidence that the practice improves health outcomes, and benefits substantially outweigh harm." The "B" rating indicates "it is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes." A "CPR" rating indicates "it is recommended that clinicians consider following the guideline for eligible patients. This recommendation is predominantly based on consensus of opinions of the Work Group and reviewers that the practice might improve health outcomes." (See Table 6).

The strength of each guideline recommendation is based on the quality of the supporting evidence as well as additional considerations. Additional considerations, such as cost, feasibility, and incremental benefit were implicitly considered. The quality of evidence was not explicitly graded. It was implicitly assessed according to the criteria outlined in Table 7, and considered: i) the methodological quality of the studies; ii) whether

Table 6. Rating the Strength of Guideline Recommendations

Grade	Recommendation
A	It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes.
B	It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes.
CPR	It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence or on the opinions of the Work Group and reviewers that the practice might improve health outcomes.

Health outcomes are health-related events, conditions, or symptoms that can be perceived by individuals to have an important effect on their lives. Improving health outcomes implies that benefits outweigh any adverse effects.

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Table 7. Rating the Quality of Evidence

Outcome	Population	Methodological Quality: Well designed and analyzed (little, if any, potential bias)	Some problems in design and/or analysis (some potential bias)	Poorly designed and/or analyzed (large potential bias)
Health outcome(s)	Target population	Strong[1]	Moderately strong[2]	Weak[3]
Health outcome(s)	Other than the target population	Moderately strong[4]	Moderately strong[5]	Weak[6]
Surrogate measure for health outcome(s)	Target population	Moderately strong[7]	Weak[8]	Weak[9]
Surrogate measure for health outcome(s)	Other than the target population	Weak[10]	Weak[11]	Weak[12]

Strong: Evidence includes results from well-designed, well-conducted studies/studies in the target population that directly assess effects on health outcomes.

Moderately strong: Evidence is sufficient to determine effects on health outcomes in the target population, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; OR evidence is from a population other than the target population, but from well-designed, well-conducted studies; OR evidence is from studies with some problems in design and/or analysis; OR evidence is from well-designed, well-conducted studies on surrogate endpoints for efficacy and/or safety in the target population.

Weak: Evidence is insufficient to assess the effects on net health outcomes because it is from studies with some problems in design and/or analysis on surrogate endpoints for efficacy and/or safety in the target population; OR the outcome is only for surrogate measures in a population other than the target population; OR the evidence is from studies that are poorly designed and/or analyzed.

or not the studies were carried out in the target population, ie, patients on dialysis, or in other populations; and iii) whether the studies examined health outcomes directly, or examined surrogate measures for those outcomes, eg, blood flow instead of access survival.

Limitations of Approach

While the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched, and searches were limited to English language publications. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain experts that were missed by the literature search were included in the review.

Because of resource limitations and other practical considerations, there were several deviations from the original protocol for several of the update topics. These primarily resulted in nephrologists in the Evidence Review Team, rather than Work Group members, performing the primary article screening and the data extraction for articles included in several Summary Tables. However, all articles that met criteria for all topics, all completed data extraction forms, and all Summary Tables were distributed to relevant Work Group members for critical review and incorporation into guidelines.

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HEMODIALYSIS ADEQUACY, UPDATE 2006

Ovid MEDLINE, Ovid MEDLINE Daily Update, Ovid MEDLINE In-Process

Search from 1/1/97 through 6/22/04

#	Search History	Results
1	exp Renal Dialysis/	13447
2	HD.mp.	10309
3	hemodialysis.mp.	2037
4	or/1-3	21546
5	equilibrat$.mp.	1478
6	post.mp.	19057
7	urea dialysance.mp.	28
8	urea reduct$.mp.	570
9	Kt.mp.	11092
10	urea kinetic$.mp.	336
11	dialysis adequacy.mp.	256
12	recirculation.mp.	1316
13	clearance.mp.	27570
14	8 or 9	2306
15	"dialysis dose".af.	259
16	"dialyzer membrane".af.	77
17	"dialyzer reuse".af.	42
18	clearance.af.	13613
19	pump.af.	16174
20	"residual renal function".af.	427
21	cellulose.af.	7367
22	synthetic.af.	45739
23	or/5-22	138437
24	4 and 23	3474
25	limit 24 to (human and English language and yr="1997-2004") [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	2747
26	limit 25 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index) [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	235
27	25 not 26	2512
28	limit 27 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	319
29	27 not 28	2193

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Ovid MEDLINE, Ovid MEDLINE Daily Update, Ovid MEDLINE In-Process
Search from 1/1/97 through 10/27/04 (search from 6/22/04 with "Artificial Kidney" added)

#	Search History	Results
1	exp Renal Dialysis/	20652
2	HD.mp.	10818
3	hemodialysis.mp.	2835
4	"Kidney, Artificial"/	235
5	or/1-4	23761
6	qualification$.mp.	1535
7	post.mp.	15709
8	urea distribution.mp.	29
9	urea reduction$.mp.	184
10	flux.mp.	12080
11	urea kinetic$.mp.	235
12	(dialysis adequacy).mp.	314
13	recirculation.mp.	1383
14	clearance.mp.	28747
15	kt.af.	2911
16	"dialysis dose".af.	321
17	"dialyzer membrane".af.	61
18	"dialyzer mass".af.	44
19	contribution.af.	14164
20	pump.af.	19882
21	"residual renal function".af.	442
22	conc.af.	7628
23	synthesis.af.	478275
24	or/6-23	1437366
25	5 and 24	3842
26	(2004107$ or 2004205 or 2004306 or 2004103 or 2004062$ or 2004052$ or 2004062$ or 2004062$ or 2004062$ or 2004062$ or 2004062$ or 2004062$ or 2004062$).ed.	206979
27	25 not 26	3467
28	limit 27 to (humans and English language and yr="1997-2004") [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	2755
29	limit 28 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	237
30	28 not 29	2518
31	limit 30 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	324
32	30 not 31	2194

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PERITONEAL DIALYSIS ADEQUACY, UPDATE 2006

Ovid MEDLINE, Ovid MEDLINE Daily Update, Ovid MEDLINE In-Process. Search from 1/1/97 through 5/28/04

#	Search History	Results
1	exp PD and PD.mp	13615
2	exp ultrafiltration/ and ultrafiltration.mp.	6891
3	or/1-2	20307
4	clearance.mp.	75094
5	exp urea/ or urea.mp.	68704
6	fluid removal.mp.	373
7	sodium removal.mp.	179
8	exp dialysis solutions/ or dialysis solution.mp.	3208
9	kt/adequacy.mp.	195
10	peritoneal membrane.mp. [mp=ti, ot, ab, nm, sh]	654
11	or/4-10	154459
12	limit 11 to yr=1999-2004	90187
13	residual renal function.mp.	519
14	peritoneal equilibration test.mp.	283
15	or/13-14	669
16	limit 15 to yr=2000-2004	344
17	3 and 12	2036
18	3 and 16	222
19	17 or 18	2249
20	limit 19 to (human and English language) [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	2488
21	limit 20 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index) [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	223
22	20 not 21	2275
23	limit 21 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	26

VASCULAR ACCESS, UPDATE 2006

Search #1. Ovid MEDLINE, Ovid MEDLINE Daily Update, Ovid MEDLINE In-Process. Search from 1/1/97 through 5/5/04

#	Search History	Results
1	exp Renal Dialysis/	13138
2	HD.mp.	10126
3	exp Kidney Diseases/ or exp Kidney Failure, Chronic/	58052
4	exp Catheters, Indwelling/	3871
5	exp Catheterization, Central Venous/	3338
6	exp Vascular Fistula/	2360
7	exp Arteriovenous Fistula/	1537
8	vascular access.mp	1389
9	fistula.mp.	10010
10	catheter$.tw.	34860
11	or/1-3	77948
12	or/4-10	112219
13	11 and 12	3513
14	limit 13 to human [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	3078
15	limit 14 to English language	2914
16	limit 15 to yr=1997-2004	2520
17	limit 16 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index) [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	694
18	16 not 17	1826
19	limit 18 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	338
20	18 not 19	1588

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VASCULAR ACCESS, UPDATE 2006 PEDIATRIC SEARCH[a]

Ovid MEDLINE <1996 to July Week 3 2004>

Search from 1/1/97 through 7/28/04

#	Search History	Results
1	exp Renal Dialysis/	19635
2	HD.mp.	9798
3	exp Kidney Diseases/ or exp Kidney Failure, Chronic/	78202
4	exp Catheters, Indwelling/	3963
5	exp Catheterization, Central Venous/	3437
6	exp Vascular Patency/	3463
7	exp Arteriovenous Fistula/	1678
8	vascular access.mp.	1352
9	fistula.mp.	19892
10	catheter$.tw.	34622
11	or/1-3	78634
12	or/4-10	47279
13	11 and 12	3549
14	limit 13 to human	3458
15	limit 14 to English language	2038
16	limit 15 to yr="1997-2004"	2006
17	limit 16 to (addresses or bibliography or biography or case reports or comment or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or "lectures" or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	737
18	16 not 17	1269
19	limit 18 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	351
20	18 not 19	1573
21	limit 20 to ("infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")	292
22	20 not 21	1385
23	limit 22 to ("all adult (19 plus years)" or "newborn infant (birth to 1 month)")	918
24	20 not 23	662
25	20 not (21 or 23)	368

a. This search is a subset of search #1

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VASCULAR ACCESS, UPDATE 2006 SEARCH #2

Ovid MEDLINE <1966 to August Week 2 2004>

Search from 1/1/97 through 8/19/2004 (original search date 5/5/04 with terms "shunt" and "graft" added)

#	Search History	Results
1	exp Renal Dialysis/	61537
2	HD.mp.	28603
3	exp Kidney Diseases/ or exp Kidney Failure, Chronic/	269127
4	exp Catheters, Indwelling/	10418
5	exp Catheterization, Central Venous/	6308
6	exp Vascular Fistula/	8030
7	exp Arteriovenous Fistula/	6971
8	vascular access.mp.	3854
9	fistula.mp.	24166
10	catheter$.tw.	84368
11	or/1-3	269156
12	or/4-10	1,37208
13	11 and 12	6946
14	limit 13 to human	6464
15	limit 14 to English language	6089
16	limit 15 to yr="1997-2004"	2741
17	limit 16 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	736
18	16 not 17	2005
19	limit 18 to (guideline or meta analysis or practice guideline or review or review, academic or review, tutorial or review, multicase or review of reported cases or review, tutorial)	372
20	18 not 19	1633
21	follow-up studies/	287082
22	(follow-up or follow-up).tw.	307877
23	exp Case-Control Studies/	261329
24	(case adj3 control).tw.	39853
25	exp Longitudinal Studies/	458692
26	longitudinal.tw.	56837
27	exp Cohort Studies/	501768
28	cohort.tw.	54384
29	(random$ or rct).tw.	295585
30	exp Randomized Controlled Trials/	33565
31	exp random allocation/	54582
32	exp Double-Blind Method/	74233
33	exp Single-Blind Method/	8332
34	randomized controlled trial.pt.	193490
35	clinical trial.pt.	369032
36	(clin$ adj trial$).tw.	80694
37	((singl$ or doubl$ or treb$ or trip$) adj (blind$ or mask$)).tw.	75835
38	exp placebos/	23235
39	placebo$.tw.	85529
40	exp Research Design/	183137
41	exp Evaluation Studies/	495116
42	exp Prospective Studies/	175636
43	exp Comparative Study/	1163862
44	or/21-43	2574658
45	20 and 44	1046
46	20 not 45	587
47	exp arteriovenous shunt, surgical/	5618
48	(arteriovenous adj5 graft$).tw	648

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Nephrol Dial Transplant (2004) 19: 100–107
DOI: 10.1093/ndt/gfg418

Nephrology Dialysis Transplantation

Original Article

Haemodialysis prescription, adherence and nutritional indicators in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Abstract

Background. The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a prospective, observational study designed to evaluate practice patterns in random samples of haemodialysis facilities and patients across three continents. Participating countries include France, Germany, Italy, Spain and the UK (Euro-DOPPS), Japan and the USA. DOPPS data collection has used the same questionnaires and protocols across all participating countries to assess components of dialysis therapy and outcomes. This study focuses on dialysis prescription, adherence and nutrition among the Euro-DOPPS countries.

Methods. In each Euro-DOPPS country, patients were selected randomly from 20–21 representative facilities. Simple means and frequencies were calculated to compare relevant data elements to gain insights into differences in therapeutic aspects among nationally representative patients. Participants entering the study within 90 days of beginning dialysis therapy were excluded from these analyses.

Results. Among the five countries, mean delivered dose as measured by normalized urea clearance (Kt/V) varied from 1.28 to 1.50 and was accompanied by differences in dialysis prescription components, including blood flow rates, treatment times, and dialyser membrane and flux characteristics. By country, a nearly 2-fold difference was observed in indicators of patient adherence and management (skipping and shortening dialysis, hyperkalaemia, hyperphosphataemia and high interdialytic weight gain). Indicators of malnutrition varied substantially.

Conclusions. This study demonstrates differences in the management of haemodialysis patients across Euro-DOPPS and offers opportunities for improving dialysis dose, adherence and nutrition. Correlation of differences in practice patterns at the dialysis unit level with patient outcomes will offer new insights into improving dialysis therapy.

Keywords: adherence; dialysis dose; Europe; haemodialysis; nutritional parameters; outcomes

Introduction

A study of survival rates among haemodialysis patients in Europe, Japan and the USA in the 1980s showed large differences among these regions [1]. This study, however, was based on registry data, which had not been collected in a standardized way across countries and did not allow for comparisons in relation to variations in dialysis prescription and patient adherence.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) evaluates several components of facility practice and patient outcomes using nationally representative samples of haemodialysis patients from seven countries (France, Germany, Italy, Japan, Spain,

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the UK and the USA). Identical questionnaires and protocols have been used to evaluate patient characteristics, a variety of practice patterns and patient outcomes [2,3]. Previous studies have shown that the relative risk of mortality is lower with three treatment characteristics: higher dialysis dose [4–6], improved patient adherence to therapy [7] and better nutritional status indicators [8]. These studies set the stage for the DOPPS and its primary aim of identifying cross-national differences in dialysis practice patterns and correlating these differences to variations in patient outcomes. The present study describes and evaluates the differences among the five European DOPPS countries (Euro-DOPPS) in three domains: (i) haemodialysis prescription; (ii) patient adherence; and (iii) nutritional indicators.

Subjects and methods

Data source

At study start, the DOPPS protocol was tested in a random sample of US patients and facilities, and study materials for Euro-DOPPS countries were professionally translated. In each Euro-DOPPS country, 20 haemodialysis facilities were selected randomly for study participation; the need for a replacement unit brought Germany's total to 21. Facilities were stratified by geographic region and facility type [France stratified by general, private, university and association facilities; Germany by clinics (medical centres), non-profit freestanding and private practice units; Italy by public and private units; Spain by academic and non-academic units; and the UK by centre and satellite units]. For efficiency, dialysis units with <25 patients were excluded, a decision that ruled out fewer than 5% of haemodialysis patients in the Euro-DOPPS countries.

Within each facility, 20–40 patients were selected randomly from a census of prevalent patients for detailed longitudinal follow-up, depending on the total number of patients in each unit. Patients who departed (due to transplantation, transferring to another unit or death) were replaced with randomly selected patients entering the dialysis facility during that interval. Euro-DOPPS data collection occurred between June 1998 and November 2000, with follow-up data collected every 4 months. The study was approved by appropriate review boards in each country. Appropriate patient consent was obtained at all study sites; units and patients remained anonymous to the investigators. A more detailed explanation of the study design and analytical methods for DOPPS have been published elsewhere [2].

Sample used for analysis

There were 11 422 total patients in the 101 randomly selected units that participated in Euro-DOPPS. Information was collected on age, race, gender, whether diabetes was the primary cause of end-stage renal disease (ESRD), date of death, date and reason for patient entry and departure from the facility. Detailed patient information was collected from a random sample of 4591 patients from the 11 422 patients treated in the facilities during the study. Detailed data contained information on topics such as co-morbidities, laboratory values, quality of life variables, medications, hospitalization history and vascular access history.

Out of the 4591 sample patients, 3039 patients who were enrolled in the study at least 90 days after their first-ever dialysis treatment were used in this analysis; 1552 patients who did not meet this criterion were excluded. Patients entering the study within 90 days of their first-ever dialysis treatment were removed because such patients are known to differ from patients in a steady state of haemodialysis treatment. In the dialysis dose/prescription analyses, only patients who had been on dialysis >1 year and received three times weekly dialysis were used in order to minimize the effect of residual renal function on these statistics ($n=2498$).

Statistical analysis and formulae

Simple means were calculated by country for the characteristics of interest. Also, an overall unweighted mean was calculated for each measurement. Statistical comparisons were made between individual countries and the overall Euro-DOPPS mean using linear regressions for continuous responses and logistic regressions for dichotomous responses. Linear regression was used to examine the trends in Kt/V over time. Each patient's first dose measurement (after being on dialysis at least 1 year) was modelled against the calendar year in which that measurement occurred. Differences in trends between countries were examined using interaction terms within this model.

The effects of facility clustering on standard error estimates were addressed in these analyses using the generalized estimating equation procedure specifying facility-level clustering and an exchangeable correlation matrix [9]. This method of analysis takes into account the fact that patients from the same facility may be more similar to each other than they are to patients from another facility. All analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

'Prescribed' dialysis dose was calculated from patient volume, dialyser characteristics, prescribed blood flow rate and treatment time. 'Delivered' dialysis dose was measured using the single- and double-pool methods for calculating Kt/V [10]. Pre- and post-dialysis blood urea or urea nitrogen (BUN) measurements were used for Kt/V calculations, and the post-dialytic BUN or urea was standardized according to the facility's reported timing of post-dialysis blood sampling. Patients in facilities that drew blood immediately at the end of a dialysis session received the full Daugirdas adjustment for double-pool dose. Patients in facilities that waited 30 min received no adjustment for double-pool dose, as the rebound was presumed to have occurred within 30 min. Patients in facilities that waited between 0 and 30 min received a fraction of the Daugirdas adjustment for double-pool dose depending on facility-reported blood draw times and assuming that the rebound effect was fastest immediately at the end of dialysis and tapered off at 30 min afterward.

The patient measures of non-adherence used in this study were skipping of more than one dialysis session in 1 month, shortening a dialysis session by >10 min in 1 month, serum potassium concentration of >6.0 mEq/l, phosphate level of >7.5 mg/dl or interdialytic weight gain (IDWG) $>5.7\%$ of body weight (the last cut-off was based on a >4 kg IDWG in a 70 kg patient). These definitions are identical to those used in a prior publication from a US Renal Data System

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(USRDS) special study [7]. A session missed because of hospitalization was not considered non-adherence. IDWG was defined by the amount of weight removed during a haemodialysis session and is presented as the percentage of body weight removed. The prevalence of each adherence measure was calculated for the initial round of patients at time of entry into the study. Skipping and shortening status were evaluated for the 30 days prior to enrolment into the DOPPS. IDWG was calculated from the most recent haemodialysis treatment before enrolment, and potassium and phosphorus measurements were those obtained on or before the enrolment date. The non-adherence measures of IDWG, potassium and phosphate were adjusted for day of the week of the blood draw. All patients were adjusted to a Wednesday blood draw value to ensure comparability.

To assess nutritional status, a number of laboratory indicators were investigated, including pre-dialysis BUN, serum albumin, serum creatinine, serum potassium, serum phosphorus, weight, IDWG, body mass index (BMI), modified subjective global assessment (mSGA) and normalized protein catabolic rate (nPCR or nitrogen appearance rate). Serum albumin was adjusted for the method of measurement (bromo-cresol green, bromo-cresol purple or other method). The mSGA [11] was used to gather subjective and objective aspects of patient medical history and physical examination. Data captured included weight loss and physical appearance, appetite, nausea, energy level and disease burden. The nPCR was determined using the two-point model of urea kinetics published by Depner and Daugirdas [12]: $\mathrm{nPCR}_{(g/kg/day)} = C_0/(a + bKt/V + c/[Kt/V]) + 0.0168$, where C_0 is the pre-dialysis BUN in mg/dl and Kt/V is the single-pool estimate of dialysis dose. For patients who received dialysis three times weekly, appropriate coefficients (a, b, c) were used, depending on whether laboratory measurements were obtained at the beginning, middle or end of the week.

Results

Table 1 shows demographic factors and patient modalities by country for haemodialysis patients who had been on dialysis >90 days upon entering the DOPPS. The overall average age was 59.5 years, with Italy displaying the highest mean age (61.3 years) and the UK the lowest average age (56.6 years). In the UK, 62% of patients were male compared with 57% in each of the four other Euro-DOPPS countries. The size of facilities, as defined by the mean number of treated haemodialysis patients, was similar across countries, with the median size varying from 50 patients/facility in Spain to 59 patients/facility in France. The difference between the country mean and median indicates the presence of a skewed distribution, with some very large dialysis units in each country, particularly in Italy, where this difference was the greatest (Table 1).

Table 2 displays patient-level characteristics of dialysis dose. The delivered dialysis dose, assessed by single-pool Kt/V and double-pool eKt/V from measurements of pre- and post-dialysis BUN concentrations, averaged 1.37 and 1.24, respectively, in Euro-DOPPS overall. However, there was considerable country variation, with single-pool Kt/V ranging from 1.28 in Germany to 1.50 in France. Mean double-pool delivered dose was 6–19% lower than the prescribed dialysis dose in the five countries. Considerable country variation was observed in the components of prescribed dialysis dose. For example, mean haemodialysis treatment time varied from 217 min in Spain to 249 min in France and Germany; the mean blood flow rate ranged from 248 ml/min in Germany to 320 ml/min in Spain; and mean patient volume varied from 36.8 to 40.91 across the five Euro-DOPPS countries.

Dialysers with the largest surface area and highest efficiency, according to the reported overall mass transfer coefficient (KoA), were used in Spain (Table 2). Synthetic membranes accounted for 41–74% of dialysers by country. High-flux dialysers were used predominantly in France (62%); these dialysers were used least frequently in the UK (20%). These findings indicate substantial variations by country regarding different components of the prescribed dose. Even larger variation in components of prescribed dose was seen when comparing across all facilities in Euro-DOPPS.

A time-trend analysis of changes in delivered dialysis dose in Euro-DOPPS during the data collection time interval from 1998 to 2000 indicated a small, but statistically significant, decline in delivered dialysis

Table 1. Demographics, modalities of care and facility size

Facility characteristics	Country					All Euro-DOPPS
	France	Germany	Italy	Spain	UK	
Sample size						
Facilities (*n*)	20	21	20	20	20	101
Patients (*n*)	672	571	600	576	620	3039
Age (years)	59.3	60.5	61.3	61.0	56.6†	59.5
Male (%)	57	57	57	57	62	58
Facility size						
Mean no. of HD patients	62	61	65	53	61	61
Median no. of HD patients	59	56	54	50	58	55

Patients entering the study within 90 days of their first dialysis treatment were excluded from this analysis. Dialysis units with fewer than 25 patients were excluded.
†$P < 0.01$ *vs* All Euro-DOPPS, accounting for facility clustering.

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Table 2. Delivered dialysis dose and dialysis prescription

Measure	Country					All Euro-DOPPS
	France	Germany	Italy	Spain	UK	
Delivered dose (SP Kt/V)	1.51‡	1.30*	1.32	1.32	1.38	1.38
% < 1.2 (SP Kt/V)	16‡	40*	34	35	28	30
Delivered dose (DP eKt/V)	1.36‡	1.19†	1.22	1.20†	1.23	1.25
% patients with either prescribed dose or components of dose measured	96*	91	87	96†	90	92
Prescribed dose	1.68*	1.31*	1.46	1.46	1.23*	1.38
Duration of HD treatment (min)	249†	251†	221†	216‡	230	234
Blood flow rate (ml/min)	292	251‡	307	322†	311	296
Patient volume (l)	37.8	40.7‡	37.0†	36.4‡	39.4†	38.2
Dialyser KoA (ml/min)	734	748	715*	861†	744	760
Dialyser surface area (m^2)	1.45†	1.54	1.50	1.72†	1.62	1.56
Synthetic membrane (%)	64	69	42†	53	71	59
High-flux membrane (%)	60†	54*	28*	49	19‡	43

Patient dialysis dose was taken from the first haemodialysis treatment measured in the DOPPS after the first year on dialysis. Patients not on a thrice-weekly haemodialysis schedule were excluded from this analysis. SP, single pool; DP, double pool; HD, haemodialysis.
*$P < 0.05$; †$P < 0.01$; ‡$P < 0.0001$ *vs* All Euro-DOPPS, accounting for facility clustering.

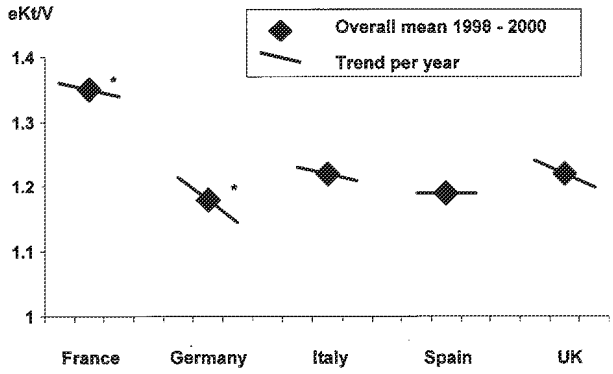

Fig. 1. Mean eKt/V (double-pool) in Euro-DOPPS countries and trend per year. *Indicates that the country mean was significantly different from overall average eKt/V. Trends were statistically significantly different ($P < 0.05$) between: Germany and France, Germany and Spain, and Spain and the UK. Overall average slope was significantly negative ($P < 0.001$).

dose (Figure 1). In Euro-DOPPS, the overall trend in single-pool Kt/V was a 0.03 decline per year. The decreasing trend in Kt/V was seen in each country except Spain. Various dialysis-related factors were evaluated to understand the reason for this declining trend in delivered dose in Euro-DOPPS, including changes in total body water, post-dialysis weight and blood flow rates, and trends in percentage of patients who skipped or shortened a haemodialysis session per month. The results indicated that the decrease in dose (ranging from 0 eKt/V per year in Spain to −0.07 eKt/V per year in Germany) was primarily because of an increase in average patient weight and a decrease in blood flow rate during the 2 years of the study. The average patient weight increased by 1.8 kg/year in Euro-DOPPS (range of increase: 0.86 kg/year in Italy to 2.79 kg/year in the UK). The average blood flow rate decreased by 4.4 ml/min/year in Euro-DOPPS (range of average decrease: −1.7 ml/min/year in Italy to −7.4 ml/min/year in Germany).

When patients skip dialysis sessions, monthly delivered dialysis dose is lower than the prescribed dose. In European dialysis centres, however, this occurred very rarely (<1% per month, Table 3) compared with reports for the USA [7]. Shortening of sessions by 10 min or more at least once within a 30-day period occurred more frequently than sessions being skipped. The Euro-DOPPS average for shortened sessions was 9%, ranging from 12.6% in the UK to ~7% in Spain and France (Table 3). Several other parameters may suggest problems with adherence and/or treatment issues. Overall, almost 20% of patients had hyperkalaemia of ≥6.0 mmol/l. This percentage varied from 10% in the UK to almost 30% in Italy. The pattern for hyperphosphataemia by country was different, with an average of 11.7% of patients having levels >7.5 mg/dl (2.42 mmol/l). This condition was most frequent in Germany (22%) and least frequent in Italy (4%). More detailed data by country are shown in Table 3. Intradialytic weight loss of >5.7% of dry weight is equivalent to an IDWG of >4 kg for a 70 kg patient. Relatively high IDWG values were observed in Italy and France, with the lowest IDWG values in the UK and Germany.

Analyses of mSGA data showed that 3.8% of patients were assessed with a cachetic or severely malnourished score, ranging from 2.3% in Italy to 6.5% in the UK (Table 4). Moderate or severe mSGA scores were indicated in 15% of patients, being slightly lower in Spain (11.2%) and somewhat higher in France (18%). Data on mean BMI showed only small variation and did not appear to correspond to the mSGA.

The average pre-dialysis serum albumin, a nutritional indicator and inflammatory marker, ranged from 3.73 g/dl in the UK to 4.14 g/dl in Germany (Table 4). The relatively high average albumin level in Germany may have resulted, in part, from Germany's practice of measuring serum albumin with a laboratory

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Table 3. Adherence and treatment measures

Measure	Country					All Euro-DOPPS
	France	Germany	Italy	Spain	UK	
% Patients shortened session by ≥10 min in past month	7.3	9.5	8.8	6.6	12.6	9.0
% Patients skipped ≥1 session/month	0.3	0.9	0.5	0.5	0.8	0.6
Serum potassium >6.0 mEq/l (%)	10.9†	15.4	28.0‡	27.3‡	9.8‡	18.0
Serum phosphorus >2.42 mmol/l (or >7.5 mg/dl) (%)	9.4	22.4‡	3.8‡	12.2	11.6	11.7
Serum phosphorus >2.10 mmol/l (or >6.5 mg/dl) (%)	21.3	38.5‡	15.5‡	22.6	21.9	23.8
IDWG >5.7% body weight (%)	14.3†	5.6	17.7‡	7.5	3.4†	9.8

Patients entering the study within 90 days of their first dialysis treatment were excluded from this analysis. IDWG, interdialytic weight gain
†$P < 0.01$; ‡$P < 0.0001$ *vs* All Euro-DOPPS, accounting for facility clustering.

Table 4. Nutritional Indicators

Measure	Country					All Euro-DOPPS
	France	Germany	Italy	Spain	UK	
Pre-BUN (mg/dl)	73.1*	66.6†	75.7†	72.1	64.8†	70.8
Pre-dialysis albumin (g/dl)	3.87	4.17†	3.98	3.98	3.72‡	3.92
Pre-dialysis serum creatinine (mg/dl)	9.5	8.7*	9.8†	9.1	9.2	9.3
Pre-dialysis serum potassium (mEq/l)	5.0‡	5.3	5.5‡	5.5†	5.0‡	5.3
Pre-dialysis serum phosphorus (mg/dl)	5.3*	6.5‡	5.0‡	5.4	5.6	5.5
nPCR (g/kg/day)	1.12*	0.97*	1.14†	1.09	1.03†	1.09
Weight (kg)	63.6†	69.7‡	63.9†	63.5‡	68.1†	65.6
IDWG (%)	3.9*	3.0†	4.2‡	3.2	2.8‡	3.5
BMI (kg/m^2)	23.2†	24.5†	23.5	23.9	24.2	23.8
mSGA score (%)						
Moderately malnourished	18.0	14.1	16.1	11.2*	15.4	15.1
Severely malnourished	4.5	2.6	2.3	3.2	6.5†	3.8

Patients entering the study within 90 days of their first dialysis treatment were excluded from this analysis. In Germany, albumin commonly is measured using total protein and serum protein electrophoresis, which may overestimate albumin compared with the direct method. BUN, blood urea nitrogen; nPCR, normalized protein catabolic rate; IDWG, interdialytic weight gain; BMI, body mass index; mSGA, subjective global assessment, modified to adapt to available DOPPS data.
*$P < 0.05$; †$P < 0.01$; ‡$P < 0.0001$ *vs* All Euro-DOPPS, accounting for facility clustering.

method relying on serum protein electrophoresis. Serum creatinine serves as a marker of muscle mass and dialysis dose, and its mean value ranged from 8.7 mg/dl (0.77 mmol/l) in Germany to 9.8 mg/dl (0.87 mmol/l) in Italy. The average BUN varied by country from 64.8 mg/dl to 75.7 mg/dl and showed little correlation to serum creatinine. Although BUN and creatinine both are dependent on dialysis dose, creatinine is probably a stronger indicator of muscle mass than of dialysis dose. The average nPCR was 1.09 g/kg, with lower values in Germany and the UK (0.97 and 1.03 g/kg, respectively) and relatively higher values in Italy and France (1.14 and 1.12 g/kg, respectively).

The average dialysis dose by BMI categories is presented in Figure 2. The relationships between BMI and prescribed Kt/V, single-pool Kt/V and double-pool Kt/V were similar, each showing that patients with the highest BMI received the lowest dialysis dose. The correlation between BMI and double-pool Kt/V was modest, but statistically significant (generalized $r = 0.3$, $P = 0.0003$ after accounting for facility clustering) [13].

Considerable variation in monitoring nutrition was apparent across countries. Overall, 62% of Euro-DOPPS units did not measure nPCR, ranging from 20% of units in Spain to 90% in Germany (Table 5). Study coordinators also reported highly variable use of dietitians, ranging from 20% in Spain to 85% in the UK. These data were compared with reports from the patient questionnaire in which patients were asked if they had been counselled by a dietitian in the 6 months prior to study enrolment. Here again, wide variation was observed, spanning from 7% in Italy to 75% in the UK.

Finally, caloric oral supplements were prescribed for between 1 and 14% of patients,, with the lowest percentages for Spanish and German patients (1 and 2%, respectively) and highest percentages for patients in the UK (14%).

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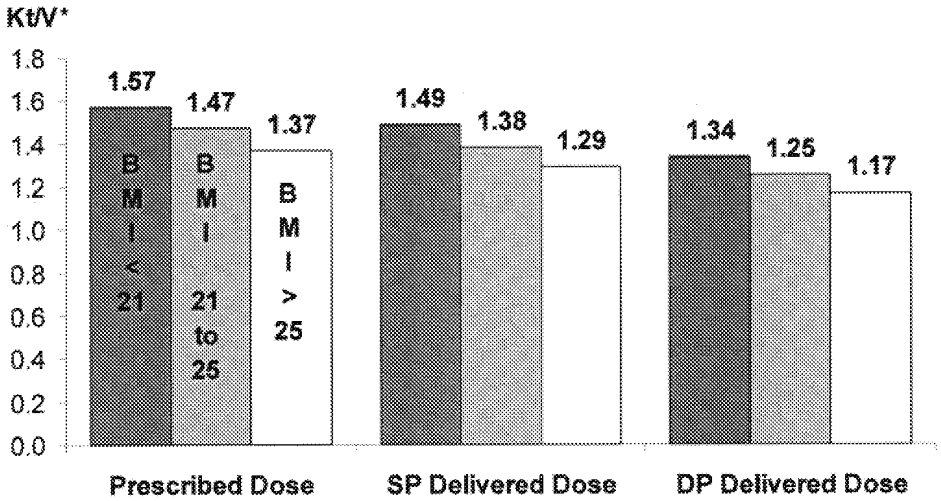

Fig. 2. Three measures of dialysis dose by patient body mass index. Patients entering the study within 90 days of their first dialysis treatment were excluded. BMI, body mass index. *Adjusted for the time of the blood draw for post-dialysis BUN.

Table 5. Nutrition practices

Facility nutrition practices	Country					All Euro-DOPPS
	France	Germany	Italy	Spain	UK	
Sample size (*n*, facilities)	20	21	20	20	20	101
Renal dietitian available (%)	50	29	25	20*	85†	43
Patients reported having seen dietitian in past 6 months (%)	33	19‡	7‡	15‡	75‡	29
nPCR not measured (%)	80	90†	60	20‡	60	62
Oral supplements (%)	8	3*	8	6	19‡	10

Practices are as reported by the study coordinators in the dialysis units. nPCR, normalized protein catabolic rate.
*$P < 0.05$; †$P < 0.01$; ‡$P < 0.0001$ *vs* All Euro-DOPPS.

Discussion

Dialysis units in the Euro-DOPPS countries

The haemodialysis units participating in Euro-DOPPS were randomly selected to be representative of the different types of haemodialysis units and geographic regions within each country, with the caveat that small units treating <25 chronic haemodialysis patients were excluded. The average facility size was nearly the same in all countries, after excluding centres with <25 prevalent patients. Since the random selection of facilities had been stratified by type of dialysis unit in order to be representative of all facilities in each country, the observed patterns of types of facilities reflect the distribution in each country.

Age

Observed differences in the mean age of the prevalent sample suggest that several things may be occurring: variation in the selection of patients accepted for haemodialysis therapy, differential loss to transplantation and possibly differential mortality by age group. In the UK, the mean patient age was lower (57 years) and the proportion of males higher (62%, Table 1). Efforts are still needed to distinguish to what extent the finding of a younger mean age in the UK may, in part, be a reflection of limited acceptance rates for the oldest patients, higher levels of peritoneal dialysis and a relatively high dialysis mortality rate (18.0% in 1999 as reported by the UK Renal Registry) [14]. Despite trends toward accepting older patients in the UK, the effects of prior preferential acceptance of younger patients persist in the age distributions of a current prevalent sample. An age increase of 4.2 years would be expected to be associated with a 10–20% higher mortality risk [15]. The age differences across the Euro-DOPPS countries are sufficiently large to account for substantial differences in mortality.

Dialysis prescription

The dialysis dose, measured from pre- and post-dialysis urea or BUN or calculated according to Kt/V or eKt/V, showed variation by country. Since delivered dose was not measured in approximately one-quarter of German patients, 'prescribed' Kt/V was also used for comparisons across all five countries. Ranking of dose by country was similar for both

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delivered and prescribed Kt/V. It is of interest, however, that dose was achieved by different means, including choice of dialyser (surface area, type of membrane and flux) and blood flow. Recent studies have demonstrated that use of high-flux synthetic membranes is associated with lower mortality risk at the same Kt/V [16]. Similarly, delivering the same dialysis dose by higher blood flow rates was associated with lower mortality [17]. This correlation has been observed consistently in Euro-DOPPS, as well as in US-DOPPS and Japan-DOPPS. Thus, a higher dose may be delivered through higher blood flow rates at no apparent disadvantage in terms of patient survival.

Mean treatment times varied across the Euro-DOPPS countries by 32 min, from 249 min per session in France to 217 min in Spain (Table 2). Previous studies show contradictory results for treatment time and mortality risk at the same Kt/V [18,19].

The HEMO study did not show a reduction in mortality risk with high dialysis doses or high flux in a randomized design [20]. The confidence intervals of these negative findings agree with the null hypothesis of no effect and also agree with the prior findings of some benefit with higher dose and high flux. The HEMO study did not evaluate low dose ($<$ Kt/V 1.2). Therefore, the findings that 30% of Euro-DOPPS patients receive doses of <1.2 Kt/V appear of serious concern, as they are likely to be associated with increased risk of mortality.

The finding of a lower dialysis dose for patients with higher BMI confirms similar results from the USA [5,21]. It indicates that dialysis dose is prescribed with only partial consideration of patient size. This finding suggests that prescription by time is more common than by a target Kt/V. Since studies have clearly shown lower mortality risk with larger BMI and higher dialysis dose [5,22,23], greater consideration of body size for dialysis prescription and greater focus on improved nutrition appear advisable. Previous DOPPS findings have shown that during the same study period, body weights increased while average blood flow rates decreased, suggesting that patient nutritional status is improving with time but is not accompanied by a corresponding increase in the dialysis prescription [24].

Measures of adherence and nutritional status

Measures of adherence with the dialysis schedule show that shortening dialysis treatment occurred among 9% of patients (Table 3). Skipping dialysis sessions was very rare, and both types of poor adherence were recorded less frequently in Euro-DOPPS than in the USA [7]. Adherence to dietary restrictions was only indirectly measured by the incidence of high levels of potassium, phosphorus and fluid intake, as these are also modified by adjustments to aspects of dialysis treatment such as treatment time, dialysis membrane and dialysate composition. Furthermore, the potassium content of the normal diet in each country will also influence the value of hyperkalaemia as a measure of dietary adherence. As factors such as hyperkalaemia, large IDWG and hyperphosphataemia (>6.5 mg/dl, 2.1 mmol/l) are associated with mortality risk [7,25], further analysis by country, facility, regional diet and practice pattern are needed to identify ways to reduce the frequency of these problems. Furthermore, although a large IDWG is associated with higher mortality risk, the possibility still requiring further investigation is to examine for certain haemodialysis patients whether a moderate IDWG serves as a positive marker of nutritional intake rather than lack of adherence. For example, is a diet that maintains a good nutritional status associated with higher intake of liquids and, consequently, moderate IDWG?

Nutritional management appears to vary substantially among the Euro-DOPPS countries, when looking by country at such elements as the mSGA, nPCR, BMI and input from a dietitian. The DOPPS has already evaluated in detail the association between a low BMI and increased mortality risk in haemodialysis patients [8,11]. Since nutritional status is quite strongly associated with mortality risk [8,11], further study is needed to evaluate best practices, including the role of advice from dietitians and the use of dietary supplementation, which are shown to vary widely [26]. The reported association of dialysis dose with dietary protein intake [27] and patient albumin levels [28] also deserves further study.

Possible limitations of this study include noise due to use of different laboratories and potential misclassification or underascertainment of co-morbid conditions. Non-significant findings may suffer from noise and possible misclassification. However, significant findings might be more striking if there was less noise or less misclassification.

This study and two companion papers reviewing mortality and anaemia in the Euro-DOPPS countries [29,30] seek to present a comprehensive overview of the haemodialysis and anaemia practices and outcomes for the European study population. In the present study, the DOPPS provides international comparisons of haemodialysis therapy, adherence and nutrition among five large European countries with new descriptive information on differences in patient management. These data also indicate opportunities for improvements in patient care, through avoidance of low prescribed dialysis dose, counselling for better adherence and effective dietary instruction. Since dialysis dose, adherence and nutritional status have been associated with mortality, these DOPPS results provide an important base of information for promoting changes in haemodialysis practices that will probably lead to improvements in patient outcomes.

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Nephrology Dialysis Transplantation

EBPG on Vascular Access

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1. Patient referral

Guideline 1.1. An early plan for venous preservation should be a substantial part of pre-dialysis care and education in any chronic kidney disease (CKD) patient regardless the choice of treatment modality (Evidence level IV).

Guideline 1.2. Every chronic renal failure patient, who have opted for haemodialysis, should start dialysis with a functioning vascular access (Evidence level III).

Guideline 1.3. Potential chronic haemodialysis (HD) patients should be ideally referred to the nephrologist and/or surgeon for preparing vascular access when they reach the stage 4 of their CKD (glomerular filtration rate <30 ml/min/1.73 m^2) or earlier in case of rapidly progressive nephropathy or specific clinical conditions such as diabetes or severe peripheral vascular disease (Evidence level III).

Rationale

Early referral of CKD patients to the nephrologist and/or vascular surgeon is strongly recommended. This is to start a policy to preserve access sites and to allow adequate time for planning, creation and maturation of the vascular access. The planning stage involves examination and pre-operative vascular mapping. An autogenous fistula requires at least 6 weeks for maturation before it can be used. Additional time may be required for interventional or surgical revisions to enhance maturation. For these reasons, it is recommended that the fistula is created at least 2–3 months before the earliest likely date for starting haemodialysis. Prosthetic graft AVFs do not need a maturation period and can be cannulated 2–3 weeks after implantation. However, prosthetic graft AVFs are not recommended as primary vascular access. This approach is recommended to minimize the use of catheters and to reduce catheter-related morbidity and need for hospitalization. Early referral to the nephrologist is also required for psychological preparation for dialysis, discussion of all options for dialysis modality, interventions to delay progression of renal damage and to correct the hypertension, anaemia and metabolic effects of renal failure [1–5].

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Recommendations for future research

Streamlining of early patient referral and organization of predialysis care are major subjects for research. A policy of venous preservation should be educated and implemented.

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2. Pre-operative evaluation

Guideline 2.1. Clinical evaluation and non-invasive ultrasonography of upper extremity arteries and veins should be performed before vascular access creation (Evidence level II).

Guideline 2.2. Central vein imaging is indicated in patients with a history of previous central vein catheters (Evidence level IV).

Rationale

There is a significant failure rate for autogenous arteriovenous fistulae (AVFs), estimated at 0.2 events per patient/year. For graft AVF, this increases to 0.8–1.0 events per patient/year. In a recent meta-analysis, the primary failure rate for autogenous wrist AVF was 15.3%. Primary and secondary 1-year patency rates were 62.5 and 66.0% [1]. Nowadays, the chronic dialysis population is becoming elderly and is increasingly likely to have diabetes, peripheral arterial obstructive disease (PAOD) or coronary artery disease. Many of these patients have poor vessels for construction of autogenous fistulae and this may be the major reason for the high primary failure and moderate long-term patency.

Physical examination

Careful selection of suitable vessels based on objective evaluation, is required for successful creation of a functioning AVF. Physical examination is used for pre-operative assessment and access planning. This includes assessment of the distal arterial pulse and the presence, diameter and course of the superficial fore- and upper arm veins. Physical examination may be difficult in obese patients and depends on the experience of the examiner.

Ultrasonography

Pre-operative vessel assessment with ultrasonography enhances the success of creation and the outcome of autogenous AVF. In a randomized trial, the primary AVF failure rate was 25% when pre-operative assessment depended on physical examination alone, compared with 6% ($P=0.002$) when ultrasonography was used [2]. In the study performed by Silva *et al.* [3] strategies for vascular access creation were based on pre-operative duplex scanning. Patients with a radial artery diameter of $\geq$2 mm and a cephalic vein diameter of $\geq$2.5 mm received radial-cephalic AVFs (RCAVF). Grafts were used in patients with insufficient radial arteries or cephalic veins and in those with outflow vein in the elbow with a diameter of $\geq$4 mm. The percentage of RCAVF creation increased from 14% to 63%, while the early failure rate decreased from 36% to 8% [3]. In other studies, the fistula rate increased from 17–35% to 58–85% [4–7]. All studies were performed in American dialysis facilities with their historical low autogenous fistula creation rate in past years.

One study showed that the functional maturation rate of AVFs decreased from 73% to 57% as the autogenous fistula creation rate increased from 61% to 73% after the implementation of pre-operative duplex scanning [8]. This outcome suggests that other selection criteria based on findings at pre-operative imaging are needed to further refine and optimize arteriovenous access surgery. Pre-operative ultrasound screening is especially useful in obese patients. AVF rates were similar in 50 patients with body mass index (BMI) >27 kg/m^2 compared with 130 patients with lower BMI when pre-operative vein mapping was employed [9].

Arterial imaging

Radial artery diameter predicts the outcome (failure or dysmaturation) of RCAVF and influences the strategy for vascular access creation. Wong *et al.* [10] observed either thrombosis or failure to maturation in all RCAVFs created in patients with a radial artery diameter of <1.6 mm. In another study, successful RCAVFs had a pre-operatively measured radial artery diameter of 2.7 mm *vs* 1.9 mm in failed RCAVFs [11]. Malovrh discriminated between RCAVFs created with radial arteries, with a diameter >1.5 mm *vs* $\leq$1.5 mm. Immediate patency rate in the >1.5 mm group was 92 *vs* 45% in the $\leq$1.5 mm group, while the patency rates after 12 weeks were 83% *vs* 36%, respectively [12]. The predictive value of the radial artery peak systolic velocity (PSV) and resistance index (RI), calculated from pre-operative ultrasonographic parameters, is uncertain [10,13,14]. However, Malovrh showed a significant correlation between radial artery RI (0.50 *vs* 0.70), diameter (0.294 *vs* 0.171 cm), and flow (90 *vs* 33 ml/min) during pre-operative hyperaemia testing and the outcome of AVF creation [15].

Venous imaging

Vein diameters of <1.6 mm have been associated with AVF failure [10], while good patency rates were obtained in patients with RCAVFs where the diameter of the cephalic vein at the wrist was >2–2.6 mm or upper arm veins >3 mm) [16]. The cephalic vein diameter increase after application of a proximal tourniquet is an important predictor of success. In a group of successfully created AV fistulae, the vein diameter increased by 48%, while vein diameter only increased by 11.8% in the group of failed AV fistulae [15].

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Table 1. Vessel diameters for successful RCAVF creation

Author	Radial artery (mm)	Cephalic vein (mm)
Wong *et al.* [10]	1.6	1.6
Malovrh [12]	1.5	1.6
Silva *et al.* [3]	2.0	2.5
Ascher *et al.* [21]	–	2.5

Arterial and venous vessel selection

From the available literature (Table 1) a minimal diameter of the anastomosed vessels (radial artery and cephalic vein) of 2.0 mm is advisable for the creation of successful RCAVFs. Critical minimal diameters of cubital and/or upper arm vessels for the creation of successful elbow/upper arm fistula creation are not established.

Venous preservation with additional handgrip exercise may enhance the quality and diameters of arteries and veins for fistula creation [17].

Venography and magnetic resonance angiography

Conventional iodine venography may cause permanent deterioration in renal function in patients with severe renal damage. It is, therefore, not suitable for patients who are preparing for dialysis or for dialysis patients with some residual renal function. Gadolinium is a safe alternative to iodine venography with acceptable inter-observer correlation regarding imaging quality ($\kappa = 0.62$) and strategy planning ($\kappa = 0.64$) [18]. CO_2 angio/venography can also be employed, because of its low risk of renal function deterioration.

Magnetic resonance angiography (MRA), with either time-of-flight (TOF) or contrast-enhanced (Gadolinium) technique (CE-MRA) has been rarely used for access planning. CE-MRA results in a good visualization of arm veins. Diameter measurements were closely correlated overall ($r = 0.91$) and on a vein-to-vein basis ($r = 0.84$–0.98) compared with conventional venography [19]. Studies on the diagnostic accuracy of preoperative MRA *vs* duplex scanning, however, are lacking. Central vein imaging can be accurately performed by CE-MRA [20]. Alternatively, MRA has the potential for imaging of both arterial and venous vessels.

Recommendations for future research

Detection of significant pre-operative parameters for successful fistula creation and maturation remains a major issue for further investigation. Newer imaging techniques with high-resolution quality should be further developed.

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3. Strategies for access creation

Guideline 3.1. The access should provide sufficient blood flow to perform adequate haemodialysis (Evidence level II).

Guideline 3.2. Autogenous arteriovenous fistulae should be preferred over AV grafts and AV grafts should be preferred over catheters (Evidence level III).

Guideline 3.3. The upper extremity arteriovenous fistula should be the preferred access and should be placed as distal as possible (Evidence level III).

Guideline 3.4. Fistula maturation should be monitored to allow pre-emptive intervention if needed (Evidence level III).

Rationale

For decades there have been remarkable differences in strategy for access creation between Europe and the USA. In Europe, the majority of new and incident patients receive autogenous arteriovenous fistulae (AVF), in the USA prosthetic graft placement remains the access of choice in most of the dialysis facilities (AVF 80 *vs* 24%; graft 16 *vs* 70%). The reason for this marked difference is not clear, although patient comorbidity seems to be more pronounced in USA and this could influence the strategy for access creation. Data from DOPPS (Dialysis Outcome and Practice Pattern Study) showed that rates of diabetes mellitus (46 *vs* 22%), peripheral arterial obstructive disease (PAOD) (23 *vs* 19%), coronary artery sclerosis (37 *vs* 25%) and obesity are significantly higher in the American dialysis population [1,2]. It is estimated that an AVF needs 0.2 interventions per patient/year compared with 1.0 intervention per patient/year for prosthetic graft fistulae for access salvage. In addition, long-term primary access survival (patency rate) differs significantly, ranging from 90% to 85% for AVF and from 60% to 40% for graft at one and 2 year of follow up [3]. With intensive access monitoring and surveillance, the secondary survival of grafts may rise due to a pre-emptive stenosis repair policy. The patency rate for grafts may be comparable with AVFs, ranging from 90% to 70% at 1 and 2 years of follow-up, respectively.

Ifudu *et al.* [4] stated that grafts do not permit the delivery of better haemodialysis than autogenous arteriovenous fistulae. They analysed 214 patients over a period of 1 month by urea reduction ratio; serum albumin concentration was used as a secondary outcome measure of dialysis adequacy [4].

Primary choice for vascular access

Autogenous AVF creation

Radial-cephalic AVF. The wrist radial-cephalic (RC) AVF is the first option for access creation. When the RCAVF matures adequately, it may function for years with a minimum of complications, revisions and interventions. The high early thrombosis/non-maturation percentage is the major disadvantage of this access and is usually influenced by patient factors like age, diabetes mellitus and the presence of cardio-vascular disease. Early failure rates range from 5% to 30% [5,6] and long-term patency from 65–90 to 60–80% at one and 2 years of follow-up, respectively. The incidence of thrombosis (0.2 events per patient/year) and infection (2%) is low.

Proximal forearm AVF. When a wrist RCVF is impossible due to poor vessels a more proximally located anastomosis from the mid-forearm to the elbow between the radial artery and cephalic vein may be employed.

Brachial-cubital/cephalic/basilic AVF. When peripheral vessels are too tiny and diseased for the creation of an RCAVF, more proximal fistulae are indicated at the elbow and upper-arm region. These AVFs (brachial-cubital = Gracz; brachial-cephalic and brachial-basilic) generate a high blood flow which is favourable for high-efficiency dialysis. The incidence of thrombotic and infectious complications is low and long-term outcome is usually good [7–17]. The major disadvantages of these high-flow AVFs are the risk of distal hypoperfusion, which may lead to symptomatic hand ischaemia, and high-output cardiac failure, particularly in patients with coronary artery disease and/or cardiac failure [18].

Early access failure and interventions

The success rate for AVFs should be enhanced by pre-operative vessel assessment (see Guideline 2), perioperative vasodilatation [19] and post-operative monitoring of maturation. Access blood flow measurement by Doppler ultrasound at day 1 and 7 after operation is indicative of successful maturation. AVFs with initial blood flow rates of <400 ml/min fail to mature in the majority of cases [20,21]. Increased post-operative blood flow through the AVF with high shear stress on the vessel wall initiate the process of vessel adaptation (remodelling) resulting in vessel dilatation and further flow increase. Inability of vessel adaptation is usually due to the presence of significant stenoses or small arterial inflow vessels. Diagnostic angiography or ultrasound evaluation is indicated when there is failure of maturation. Percutaneous intervention (PTA) is indicated for any stenosis, and

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when not successful surgical revision can be considered [22–24].

The use of non-penetrating vascular clips for arteriovenous anastomosis may cause less endothelial cell damage and reduce the smooth muscle cell proliferation which leads to intimal hyperplasia (IH) [25–27].

Patient variables and outcome of vascular access

Several studies have shown that patient variables may have an important impact on the choice and outcome of vascular access. Age may have an influence on post-operative blood flow in newly created autogenous fistulae, which results in a slightly higher failure rate compared with young patients (18.9 *vs* 13.6%) [28]. However, the combination of age and diabetes does have an impact on fistula outcome with significantly higher failure rates (28.6%). Large European, Australian and American population-based studies have shown an increased percentage of grafts in elderly patients. In Europe, the use of grafts increased from 5% in patients <45 years to 8.8% in patients >75 years of age [29,30]. In Australia and USA, significant odds ratios were calculated indicating age as a predictive factor for graft use in incident and prevalent patients. In addition, grafts were associated with poor outcome in terms of primary failure and with a higher incidence of revisions compared with fistulae [31–34]. On the other hand, grafts may do well in the higher age group over 70 years. Staramos *et al.* [35] showed better patency at 2 and 3 year for prosthetic grafts compared with fistulae. This difference can be explained by the high number of dropouts due to early failure of the fistulae (24 *vs* 11%).

Women usually have smaller arteries and veins and, therefore, may do worse compared with men. And this may be the reason for poorer maturation and survival rates of vascular access. However, the literature remains contradictory. Caplin *et al.* [36] showed that arterial and venous diameters were not significantly different between men and women and functioning fistulae were created in 72% of the female and 77% of the male patients. In a meta-analysis of RCAVFs, women had similar maturation and 1-year patency rates as men. It is possible that pre-operative vessel selection for AV anastomosis influenced the outcome of access creation, irrespective of gender [5].

Other studies showed that female gender was associated with an increased use of grafts and a higher number of access revisions [30,32,34,37–40]. In the HEMO study, Allon *et al.* [41] found female gender, PAOD, black race, body mass index (BMI) and older age, significant predictor variables for the chance on fistula use. In addition, they found remarkable differences in the percentage of fistulae used in the different dialysis facilities (ranging from 4% to 77%).

Influence of comorbidity on vascular access creation and outcome

During the past decade there has been a shift in the aetiology of end-stage renal failure. Diabetes mellitus and arteriosclerosis are now the most important causes for dialysis treatment. The presence of diabetes and concomitant arteriosclerosis may have an additional negative impact on the chance of successful access creation [38]. These patients usually have poor, thickened and calcified arteries with proximal and/or distal vessel obstruction [42]. Access creation is more difficult, and the risk of symptomatic ischaemia of the upper and lower extremity due to access-induced steal syndrome is significant (see Guideline 9). Many studies report a correlation between the use of prosthetic graft AVF and the prevalence of diabetes in their population. The probability of graft thrombosis is significantly higher in diabetic patients, which results in decreased graft survival [43]. On the other hand, autogenous fistula creation can certainly be successful in patients with diabetes. Similar percentages of primary fistula creation with the use of comparable vessel diameters in non-diabetic and diabetic patients have been reported but more vessel calcifications were detected in diabetics [44]. Excellent results of primary fistula creation even in diabetics have been described by Konner *et al.* [17]. Three types of fistulae were created and none of the patients needed grafts. RCAVFs were created in 62 and 23% of patients (non-diabetics *vs* diabetics), while more proximal forearm and elbow AVFs were needed in diabetics (77%). Primary access survival was similar, however, secondary survival was better in non-diabetics at 2 years of follow-up. Ischaemia occurred significantly more frequently in the diabetic group (7 *vs* 0.6 events per 100 patient/years).

Homocysteine levels do not have any influence on vascular access failure [45], while elevated lipoprotein among black dialysis patients may be a risk factor for access complications [46]. Chou *et al.* [47] identified in a retrospective analysis CRP as an independent predictor for AV fistula thrombosis. The association between specific drug use and access failure was investigated in the DOPPS study. Treatment with calcium channel blockers, aspirin and angiotensin-converting enzyme inhibitors resulted in improved graft and fistula patency [48].

Non-patient variables and success of fistula creation

Late referral and starting dialysis treatment with a central venous catheter reduce the chance of successful autogenous fistula creation [49–51]. Experience and dedication of the physician performing vascular access surgery have a considerable influence on outcome. Prischl *et al.* [52] showed that the experience of the operating surgeon was the major determinant for the patency of RC fistulae. Some nephrologists create vascular access themselves and

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it has been shown that this approach may result in a higher number of functioning fistulae [53,54].

Vascular access morbidity, hospitalization and mortality

The probability of any access-related hospitalization is greater for patients with grafts than for those with fistulae. Reasons include thrombosis, infection and septicaemia [55–58]. In diabetic patients, the mortality rate is higher for those with grafts or central venous catheters, compared with those with autogenous AVF. In particular, there were more infection-related deaths in both diabetic and non-diabetic patients with central venous catheters compared with those with AVF. AV shunting may increase cardiac risk and death, however, this hypothesis could not been proven in a large patient group [59]. On the other hand, left ventricular hypertrophy does occur in patients with vascular access [60] and may be normalized after access closure in patients with functioning renal transplants [61].

Second choice for vascular access

Upper extremity non-autogenous vascular access

When autogenous AVF creation is impossible or the fistula has failed, one may decide to implant grafts as a vascular access conduit. Greater saphenous vein translocation or homologous saphenous vein implants have been used for some time with moderate results [62]. Nowadays bovine mesenteric vein (Procol®) or ureter (Synergraft®) are popular materials as an alternative access conduit, with acceptable patency and low infection rates [63]. Prosthetic grafts are available as polyurethane (Vectra®) [64], poly-ester (Dacron) and poly-tetrafluoroethylene (Goretex®; Impra®) material. Short-term functional patency is usually good, but stenosis formation (mostly at the graft-vein anastomoses) will lead to thrombotic occlusion within 12 to 24 months. The primary patency rate of prosthetic graft AVFs vary from 60% to 80% and from 30% to 40% at 1 and 2 years of follow-up. Secondary patency ranges from 70% to 90% and from 50% to 70% at 1 and 2 years, respectively [65–69]. Intimal hyperplasia (IH) with smooth muscle migration and proliferation and matrix deposition is the major cause for stenosis formation and thrombosis. The aetiology of IH is unknown, however, high shear stress will denudate the endothelial layer, resulting in platelet adhesion and initiation of a cascade of proteins that stimulate the smooth muscle cells to proliferate and migrate [70–74].

Grafts may have similar outcomes compared with fistulae, in elderly patients in particular. Staramos *et al.* [35] showed good results of graft implantation in very old patients. They argued that this patient group has a very limited life expectancy and early cannulation may be considered with the advantage of avoiding central venous catheters. Also the risk on non-maturation is low as compared with autogenous fistulae.

Measures to improve graft patency

Numerous experimental and clinical studies have been employed to outline the influence of type of graft and graft design on graft patency. Modulating the geometry of the arterial inlet and/or venous outlet of the graft could possibly have a beneficial effect on IH. Clinical studies using tapered (at the arterial side of the graft) grafts did not show better patency rates nor did cuff implantation at the venous anastomosis. However, primary patency did improve with the use of a cuff-shaped prosthesis (Venaflo®) [75–79]. Compliant grafts could probably influence IH by the better matching of the stiff prosthesis with the compliant vein at the anastomotic site. However, in clinical studies this feature was not proven [80].

Anticoagulants and graft patency

The use of warfarin or aspirin on graft survival has been studied [81–83]. In a randomized controlled trial, time-to-graft failure was not significantly different in the treatment group receiving warfarin compared with controls. However, major bleeding occurred in 10% of patients in the warfarin group compared with none in the control group [84]. In the DOPPS study, patients that used anticoagulants such as warfarin, showed even worse graft survival [48]. In another study, aspirin and dipyridamole (Persantin®) administration was compared with a placebo group. Only dipyridamole showed a beneficial effect on thrombosis with a relative risk of 0.35 ($P=0.02$) [85]. Kaufman *et al.* [86] showed no effect of aspirin and clopidogrel (Plavix®) on graft thrombosis and in their randomized study the risk of bleeding complications was substantial.

A Cochrane database study showed good results of ticlopidine on AVF and graft patency in a total number of 312 patients [87]. The administration of pentoxifylline does not improve graft patency [88].

Radiation and graft patency

External beam radiation and intravascular brachytherapy have been administered to prosthetic graft AVFs to inhibit smooth muscle cells to proliferate at the venous anastomosis [89]. In animal studies, beneficial effects could be demonstrated, however, in patient groups no improvement in graft patency was shown and the risk of adverse effects such as infection increased [90]. Randomized studies could not show any advantage of external radiation on graft patency rates [91,92].

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Lower extremity autogenous and non-autogenous vascular access

Probably the only indication for lower extremity vascular access is bilateral central venous or caval vein obstruction, which endangers the outflow of upper extremity AVF. Saphenous or superficial femoral vein transposition are primary options for thigh AVF with a relatively high risk on ischaemia (see Guideline 9). Clinical follow-up and primary flow reduction by tapering of the anastomosis are indicated to prevent ischaemia [93,94]. Prosthetic graft implantation in the thigh has a high risk of infection and septicaemia [95–97].

Third choice for vascular access

Central venous catheter

There may be a few indications for permanent tunnelled central venous catheters as an (primary) option for vascular access. Patients with severe access-induced upper extremity ischaemia or cardiac failure may be candidates for catheters. Life expectancy for these patients is likely to be poor and the need for vascular access limited to some months. The same holds true for patients with disseminated cancers.

Recommendations for future research

Despite the rationale of creating autogenous fistulae for vascular access, research into the development of new non-thrombotic grafts and the prevention of IH remains of utmost importance.

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4. Role of nurses and staff in access management

Guideline 4.1. Nurses and medical staff should be involved in vein preservation and monitoring of the vascular access. Every patient with chronic kidney disease should have a declared plan for preserving the vascular access and potential access sites (Evidence level IV).

Guideline 4.2. Any staff involved in handling vascular access or cannulating veins in renal patients should be adequately trained and be in a continuous training scheme for access management (Evidence level IV).

Guideline 4.3. An autogenous fistula should be cannulated when adequate maturation has occurred (Evidence level III).

Guideline 4.4. The rope ladder technique should be used for cannulation of grafts (Evidence level III).

Rationale

A substantial part of the pre-dialysis care is the preservation of veins in both arms, favouring the use of the veins of the dorsum of the hand for blood sampling, infusions and transfusions [1]. After placement of the initial vascular access, preferably an autogenous AVF, the correct needling technique has a favourable influence on maturation and fistula lifespan. Nurses play a pivotal role in the care for vascular access: they see the patient every dialysis, perform cannulation and assess function of the vascular access [2]. The vascular access should be checked before each cannulation by inspection and palpation. Nurses train patients and partners to perform home haemodialysis. This includes teaching about vascular access and (self-) cannulation [3].

Nurses generally have more practical experience and skills for cannulating and managing vascular access than physicians. Written protocols for cannulation, handling central venous catheters and physical examination of the vascular access prior to cannulation should be provided. The nephrologist bears ultimate responsibility to ensure adequate standards and training in the delivery of care for the vascular access. While this care is almost always delivered by others, the nephrologist should be involved in the training and monitoring of standards. Training courses in vascular access have been initiated for residents, vascular surgeons and nephrologists in the Netherlands and for nurses in France and Turkey [4]. Examinations and qualifications should be mandatory in the future. Societies like the EDNA/ERCA and the European Vascular Access Society or other dedicated initiatives should implement new structural approaches in the care for vascular access.

Technique and Timing of cannulation

While few scientific data concerning access handling and the outcome of specific cannulation techniques have been reported, the rope ladder technique is advised for the cannulation of AV grafts [5], to avoid graft disintegration and the formation of pseudo-aneurysms. In autogenous fistulae, particularly those with only a short vein segment available for needling, the buttonhole method is preferred over area puncture. The timing of access cannulation has been reported from the DOPPS study [6]. For grafts, first cannulation occurred within 2–4 weeks at 62% of USA, 61% of European and 42% of Japanese facilities. For fistulae, first cannulation occurred <2 months after placement in 36% of USA, 79% of European and 98% of Japanese facilities. Earlier cannulation of a newly placed fistula may be associated with impaired AVF survival. Cannulation after <2 weeks should be avoided while usually the minimum maturation period should be ideally >4 weeks. Adequate fistula flow (>600 cc/min) and diameter (>5 mm) measured by ultrasonography can improve the documentation of matured fistulas [7–9].

Recommendations for future research

Studies on cannulation complications and techniques are needed.

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5. Surveillance of vascular access

Guideline 5.1. Prior to any cannulation, autogenous arteriovenous fistulae and grafts should be assessed by physical examination (Evidence level IV).

Guideline 5.2. Objective monitoring of access function should be performed at a regular base by measuring access flow (Evidence level II).

Rationale

It is necessary to evaluate the vascular access clinically prior to any cannulation, both in autogenous AV fistulae and AV grafts. Inspection may reveal swelling, infection, haematoma, aneurysm or stenoses. Palpation evaluates the characteristic thrill and the intravascular pressure as it may differ between a pre- and a post-stenotic vessel segment. Post-stenotic collapse of the vein after elevation of the arm above the heart is proof of the haemodynamic relevance of a stenosis in autogenous AV fistulae. Auscultation is indicated if a stenosis is suspected and a high-pitched bruit can be heard in the presence of a stenosis. Clinical evaluation for the monitoring of prosthetic grafts may be difficult because of their rigidity, however, has been reported reliable to indicate flow changes [1]. Usually, no dilatation is observed, except in case of cannulation-related pseudo-aneurysm formation. Any suspicion of complications arising from the clinical examination should be confirmed by objective measurements. There are a wide variety of functional and anatomic imaging techniques such as access flow measurement, ultrasonography and angiography, each with their own applicability and accuracy rates. The goal of these measurements is the early diagnosis of AV fistula or AV graft dysfunction, aiming at a pre-emptive correction by interventional techniques [2] (See Guideline 7). These measurements require technical equipment and can never substitute for physical examination. Modern dialysis machines always provide venous and arterial pressures which can be used to monitor access function. Numerous dialysis facilities exclusively rely on this type of monitoring, although standardization and comparability is lacking as the pressures are influenced by blood flow, needle diameter and cannulation site. Today, we know that these parameters have a poor predictive value compared with access flow measurements [3]. With the introduction of prosthetic graft materials and their well-known high complication rate, more sophisticated methods came into use such as dynamic and static venous pressure measurements [4,5]. Static intra-access pressure ratio (static venous pressure in relation to mean arterial pressure) as introduced by Besarab [6] offers some advantage over dynamic pressure [7]. Smits *et al.* [8] reported that standardized monitoring of either venous pressure, access flow or the combination of both with subsequent corrective intervention can reduce thrombosis rate in grafts. Recently, Spergel *et al.* [3] concluded in a preliminary report that all types of pressure measurements should be abandoned in favour of access flow measurements.

Various techniques to measure access flow have been described:

Duplex ultrasound, Ultrasound flow dilution (Transonic®), Crit-Line III, Crit-Line III TQA, Variable flow Doppler, In graft Velocitymetry, Blood Velocity Meter and Glucose Pump Test. There is no clear preference for any one of these techniques [7].

In summary, access flow measurement is an accurate predictor of fistula/graft dysfunction, which may result in access thrombosis. An access flow <600 ml/min in AV grafts [8–10] respectively, a reduction of flow $>20\%$ per month [9] or <300 ml/min in forearm AV fistulae is an indication for pre-emptive intervention [11]. For upper arm fistulas these flow data are lacking. Monthly flow measurements for grafts and three monthly for fistulae are recommended. Monitoring and surveillance with subsequently pre-emptive radiological or surgical intervention reduce the rate of thrombotic events in AV grafts as well as in AV fistulae, thus substantially decreasing patient morbidity, hospital admissions and costs of healthcare delivery [12–14]. Access monitoring programmes should be included as an integral part of routine dialysis care [13].

Recommendations for further research

Improvement of monitoring methods to accurately detect failing vascular access remains an important issue for research.

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6. Diagnosis of stenoses in AV fistulae and AV grafts

Guideline 6.1. If a haemodynamically significant stenosis is suspected by physical examination and/or flow measurement, imaging should be performed as soon as possible (Evidence level III).

Guideline 6.2. Pre-emptive intervention should be performed percutaneously or surgically without further delay and imaging should be performed immediately before the intervention (Evidence level II).

Guideline 6.3. If the complete arterial inflow and venous outflow vessels need to be visualized, magnetic resonance angiography (MRA) should be performed (Evidence level III).

Rationale

Clinical examination should remain the key method for the diagnosis of stenosis in autogenous arteriovenous fistulae and AV grafts [1]. However, the decision on whether clinical examination alone is sufficient or additional imaging examination must be performed before treatment, depends on local customs and practice. In cases of percutaneous treatment of stenoses, pre-, intra- and post-operative angiography must be conducted. When surgical revision is carried out, on-table angiography after completion should also be conducted when available. Angiography entirely for diagnostic purposes, without concommitant treatment should be avoided. Once thrombosis has occurred, surgical or interventional radiological clot removal is necessary to allow haemodialysis through the vascular access without the need for central venous catheter insertion. Correction of the underlying stenosis is an integral part of any declotting procedure.

Diagnosis of stenosis

Duplex ultrasonography

Whenever stenosis is suspected, duplex ultrasonography can be performed to locate and to quantify the degree of diameter reduction due to the stenosis [2–5]. Duplex ultrasonography in the hand of an experienced clinician or vascular technician is an adequate diagnostic tool except for hand arteries and central veins [6] and can be helpful in defining thrombus extent. Angiography is not necessary if duplex indicates a stenosis at the arteriovenous anastomosis in forearm fistulae, which usually are only amenable to surgical revision by proximal re-anastomosis. Duplex examination is especially valuable in detecting stenoses and to perform flow measurements in non-maturing AV fistulae in which iodine injection should be avoided, because of the risk of renal function deterioration. Recently, duplex was suggested as the initial imaging modality of dysfunctional fistulae, but complete access should be depicted at DSA and angioplasty to detect all significant stenoses eligible for intervention. Magnetic resonance angiography (MRA) should be considered only if DSA is inconclusive [7].

Angiography

Diagnostic angiography with iodinated contrast agents without subsequent dilatation or surgical revision is not advised. However, angiography is typically performed before, during and after dilatation or percutaneous thrombolysis and after surgical thrombectomy in order to guide the treatment and depict inflow as well as residual stenoses and/or clots or central venous obstruction [8]. To avoid impairment of residual renal function, gadolinium-enhanced digital subtraction angiography may be an alternative. Le Blanche *et al.* [9] found no impairment of renal function using gadolinium in their patient collective. They concluded, that gadolinium-enhanced digital subtraction angiography is an effective and safe method to assess the cause for malfunctioning AVFs. It can also be used to plan and perform percutaneous transluminal angioplasty. As an alternative, diluted iodine may be used, with a low risk of further renal function detoriation. Arterial inflow stenosis may be missed by diagnostic angiography. By introduction of a catheter through the access up into the arterial tree, also the subclavian and brachial arteries can be imaged [10].

Magnetic resonance angiography

MRA has been reported to be an useful, safe and practical imaging modality in complex fistulae with fewer complications and side-effects compared with fistulography [11]. It allows non-invasive evaluation of the arterial and venous system in one examination [12]. If MRA is performed as an alternative, it should be employed with contrast-enhanced (Gadolinium) technique (CE-MRA), since the latter shows a good visualization of arm veins with diameter measurements closely correlating with conventional venography [9]. In one study, MRA depicted all 13 stenoses and two false-positive findings, resulting in a sensitivity of 100% and a specificity of 94% for the arterial and venous tree [13]. Froger *et al.* found a sensitivity, specificity and positive and negative predictive value of MRA in the detection of stenosed vessel segments of 97, 99, 96 and 99%, respectively [14]. When central

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venous obstruction is suspected, angiography of the complete venous outflow system up to the right atrium is mandatory. MRA of the central veins is accurate and even superior to contrast venography, which may fail to show all patent thoracic vessels [15,16]. However, it is an elaborate procedure, and therefore not possible in every hospital. Also, an additional intervention is not possible at the same time [17].

Recommendations for further research

New imaging modalities may be applied for a more accurate diagnosis of access stenosis.

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7. Treatment of stenosis and thrombosis in AV fistulae and AV grafts

Guideline 7.1. For venous outflow stenosis percutaneous transluminal angioplasty (PTA) is the first treatment option (Evidence level III).

Guideline 7.2. Thrombosed autogenous and graft fistulae should be treated either by interventional radiology or surgery. Individual centres should review their results and select the modality that produces the best results for that centre (Evidence level III).

Management of autogenous AV fistula stenosis

Relevant stenosis

Stenoses should be treated if the diameter is reduced by >50% and is accompanied with a reduction in access flow or in measured dialysis dose. Other indications for stenosis treatment are difficulties in cannulation, painful arm oedema, prolonged bleeding time after cannulation or after removal of the cannulae (due to high venous pressure) and handischaemia due to arterial inflow or distal stenoses. A stenotic lesion, due to intimal hyperplasia, is the most common cause for low access flow. In RCAV fistulae, 55–75% of these stenoses are located close to the AV anastomosis and 25% in the venous outflow tract [1,2]. In brachial-cephalic and/or basilic AV fistulae, the typical location (55%) is at the junction of the cephalic with the subclavian vein and the basilic with the axillary vein, respectively [1]. An arterial inflow stenosis >2 cm from the anastomosis is uncommon, but may endanger the flow in the AV fistula.

Stenosis of the anastomotic area

Surgical treatment is indicated in stenoses of the anastomotic area located in the lower forearm. Alternatively, PTA is possible although its results are likely to be less long-lasting. Primary interventional treatment is indicated in stenoses of the anastomotic area located in the upper forearm and in the upper arm. Surgery should be considered in cases of early or repeated recurrences of the lesions. Dilatation or surgical revision of anastomotic stenoses in upper arm fistulae can cause steal syndrome and access-induced hand ischaemia. Careful dilatation up to 5 or 6 mm initially is recommended. Dilatation to >6 mm is rarely indicated.

Venous outflow stenosis

PTA is the first treatment option in the outflow veins (cephalic/basilic) [3]. Junctional stenoses, of the superficial veins with the deep venous system, can also be treated by PTA. If a stent is placed in the final arch of the cephalic vein, it must not protrude into the subclavian vein where it could induce stenosis and preclude future use of the distal (basilic, brachial and axillary) veins [4].

Balloon angioplasty

In order to visualize the stenoses, angiography is performed by retrograde puncture of the brachial artery, in case of anastomotic problems, or by direct antegrade puncture of the vein above the anastomosis if an outflow problem is suspected [5]. It is controversial, whether long-segment stenoses should be treated radiologically or surgically. While some authors recommend surgical intervention [6], either by graft interposition [7] or vein transposition, others recommend radiological intervention [8]. Studies proving the superiority of one of the two treatment options for the treatment of long-segment obstruction are not available. However, PTA of short-segment stenoses (<2 cm) has a better outcome compared with long-segment stenoses (>2 cm) [9].

Persistent stenosis

Some stenoses cannot be dilated by conventional balloon angioplasty. These 'hard' stenoses can be treated with cutting balloons or ultrahigh pressure balloons (up to 32 atm) [10,11].

Recurring stenosis

Recurring stenosis can be treated radiologically, with or without stent placement, or surgically [5]. The strategy for treatment should be made considering the individual condition of the patient in relation to the invasiveness of the surgical treatment. In spite of complete opening of the PTA balloon of sufficient diameter, the dilated vessel wall may collapse immediately after removal of the balloon. This elastic recoil can be prevented by stent implantation, especially in central veins [12]. Stent placement in the needling areas of forearm fistulae should be avoided except for PTA-induced ruptures not controllable by protracted balloon inflation.

Management of autogenous AV fistula thrombosis

Fistula thrombosis should be treated as soon as possible or within 48 h. The duration and site of AV fistula thrombosis as well as the type of access are important determinants of treatment outcome. Timely declotting allows immediate use without the need for a central venous catheter. Thrombi become progressively fixed to the vein wall, which makes surgical removal more difficult. Thrombosis may affect the

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post-anastomotic vein segment as result of anastomotic stenosis or may begin at the needle site. When the clot is localized at the anastomosis in radial-cephalic and brachial-cephalic fistulae, the outflow vein may remain patent due to the natural side branches that continue to carry venous blood flow. In these accesses it is possible to create a new proximal anastomosis [7,13]. Thrombosis in transposed basilic vein fistulae usually leads to clot propagation of the entire vein. Although comparative studies are missing, the available literature [4,5,14–22] suggests that thrombosed autogenous AV fistulae should, preferably, be treated by interventional radiology. The single exception may be forearm AV fistulae, thrombosed due to anastomotic stenosis. It is likely that in such cases, proximal re-anastomosis will provide good results.

Interventional thrombolysis

Thrombolysis can be performed mechanically or pharmacomechanically [23–25]. While the immediate success rate is higher in grafts than in autogenous AV fistulae (99 *vs* 93% in forearm fistulae), the primary patency rate of the forearm AV fistula at 1 year is much higher (49 *vs* 14%). One year secondary patency rates are 80% in forearm and 50% in upper arm AV fistulae, respectively [14]. In AV fistulae, the combination of a thrombolytic agent (urokinase or tissue plasminogen activator = tPA) with balloon angioplasty resulted in an immediate success rate of 94%. Liang *et al.* [21] reported a success rate of 93% and a primary patency rate at one year of 70%. Haage *et al.* [4] performed 81 percutaneous treatments of thrombosed AV fistulae. Flow restoration was achieved in 88.9% of the AV fistulae. The primary 1-year patency rate was 26% and the secondary 1-year patency rate 51%.

Surgical thrombectomy

Surgical thrombectomy is performed with a thrombectomy catheter (Fogarthy). Manual retrograde thrombus expression can be helpful. On-table venous outflow angiography of the recanalized vein as well as the central veins should be performed whenever possible to find/exclude additional stenoses or residual thrombus. Identification and concurrent correction of the underlying cause(s) of thrombosis are essential parts of any surgical or interventional declotting. The best results of surgery probably will be encountered after proximal re-anastomosis for anastomotic stenosis of forearm AV fistulae, which is the most frequent location of stenosis in this type of access. Primary patency of the new proximal anastomosis has been reported to be as high as 80% at 1 year and 67% at 2 years [13]. If access failure recurs frequently in a short time period, a new fistula may need to be created.

Management of AV graft stenosis

A diameter reduction of >50% of the lumen together with a significant flow decline is considered as an indication for treatment [26].

Stenosis at the arterial anastomosis

As in autogenous fistulae, most arterial inflow stenoses in grafts can successfully be treated by PTA [27]. Stenosis of the arterial anastomosis itself can be dilated, if only the afferent artery and the graft at the anastomosis are affected and there is no stenosis in the efferent artery. If there is an additional stenosis of the efferent artery, angioplasty of the anastomosis alone will enhance graft flow with the risk of peripheral ischaemia due to reduced peripheral arterial perfusion. In these patients, either dilatation of the efferent artery by interventional radiology or through surgical revision of the anastomosis may resolve the dilemma.

Intra-graft stenosis

Intra-graft (or mid-graft) stenoses are found in the cannulation segment of grafts. They result from excessive ingrowth of fibrous tissue through puncture holes. These stenoses can be treated by PTA [28], graft curettage [29], or segmental graft replacement. When only a part of the cannulation segment is replaced, the access can be used for haemodialysis without the need of a central venous catheter. When re-stenosis occurs in a non-exchanged part of the graft, this can be replaced after healing of the new segment.

Stenosis at the venous anastomosis

The most common cause for graft dysfunction and thrombosis is venous anastomotic stenosis [28,30,31]. Since grafts should be implanted only in patients with exhausted peripheral veins, vein-saving procedures like PTA or patch angioplasty should be favoured to graft extensions to more central venous segments, even though the latter may have superior patency rates. When PTA repeatedly fails, additional stent implantation should be considered [2,32,33].

When a stent or a patch fail, graft extension is still possible. This staged therapy improves cumulative graft function. In 20–30% of the grafts, PTA does not increase blood flow to >600 ml/min, indicating insufficient dilatation with an undersized balloon, immediate recurrence of stenosis, or the existence of an unidentified and not corrected stenosis either more centrally or at the arterial inflow.

Management of AV graft thrombosis

Graft thrombosis should be treated without unnecessary delay and within 48 h, at least before the next

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dialysis session. Early declotting allows for immediate use of the access without the need for a central venous catheter [34–53]. There is always a compact "arterial plug" present. Old thrombi (> 5 days) are often fixed to the vessel wall beyond the venous anastomosis, making surgical extraction more difficult. This is less of a problem for the interventional radiological treatment.

Surgical thrombectomy

Surgical thrombectomy is performed with a thrombectomy catheter. On-table angiography should be performed after completion of the arterial and venous limbs of the graft. This should visualize the central venous outflow as well as the graft. It is required to exclude residual thrombi and define the cause of thrombosis. Identification and simultaneous correction of the underlying stenosis are integral parts of any surgical or interventional declotting procedure [30,31].

Interventional thrombolysis

Prosthetic graft thrombosis can be treated with various percutaneous techniques and tools, including combinations of thromboaspiration, use of thrombolytic agents such as tissue plasminogen activator (tPA), mechanical thrombectomy and mechanical thrombectomy devices. An initial success rate of 73%, with primary patency rates of only 32 and 26% at 1 and 3 months, respectively, are reported [36–54]. Smits *et al.* [55] have compared different mechanical devices for percutaneous thrombolysis and concluded, that the treatment of the underlying stenoses was the only predictive value for graft patency. Each centre should, therefore, choose the technique according to their expertise. Independent of the applied technique it is important to perform thrombolysis as soon as possible to avoid the need for a central venous catheter and as an outpatient procedure to decrease costs, whenever possible. Post-procedural angiography to detect and correct inflow, intra-access or venous outflow stenosis is mandatory.

Recommendations for further research

Development of better catheter and balloon designs and (drug-eluting) stents may improve the outcome of interventional access treatment.

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8. Diagnosis and treatment of central venous obstruction

Guideline 8.1. If symptomatic central venous obstruction is suspected, angiography of the access and complete venous outflow tract should be performed (Evidence level III).

Guideline 8.2. Treatment should be performed by percutaneous intervention (Evidence level III).

Diagnosis of central venous obstruction

Chronic swelling of the access arm is the most important clinical sign of central venous obstruction [1]. The superficial veins may become prominent (collaterals). Pain and paraesthesia may occur. Central venous lesions have to be treated when they are severe and disabling such as those resulting in arm swelling, troublesome pain or inadequate haemodialysis [2]. In obvious central venous obstruction, angiography of the access and complete venous outflow tract must be performed, since the central veins cannot be examined with ultrasonography. Thus, to completely visualize all mediastinal veins, venography using digital subtraction technique is needed [3]. This can be done preferably with direct antegrade puncture of the access [4]. In the majority of patients central vein obstruction is due to previous inserted central vein catheters. In 40% of the patients with subclavian vein catheters central venous obstruction develops, compared with 10% of patients with jugular vein catheters. In patients without a history of central venous catheterization, other causes, such as extrinsic compression of mediastinal veins (e.g. lymphoma, goitre, thoracic aortic aneurysm, mediastinal fibrosis, pacemakers), hypercoagulopathy, thoracic outlet syndrome or pacemaker wires should be considered. In these cases plain X-rays, computed tomography or MR imaging may be helpful for the differential diagnosis. If treatment of the underlying disease is not possible or fails to resolve arm swelling, PTA with stent insertion is indicated [5].

Management of central venous obstruction

Interventional treatment

In the last decade, several studies of patients treated with PTA alone have been published. Primary patency rates of $\leq$10% at 1 year and numerous restenoses were reported [6–8]. Stent implantation has clearly been shown to improve primary 1-year patency rates to 56% and more [1,4,6,9]. Regular follow-up and reinterventions are required to maintain patency and achieve long-term clinical success [10]. These figures do not differ significantly from those of surgical intervention [1,6,9]. Nevertheless, due to the invasiveness of surgery for central venous obstructions and the less invasive interventional therapy, PTA with or without stent implantation is recommended as primary option for treatment [4]. Reports show, that symptomatic central venous obstruction in dialysis patients can be treated with a high success rate through radiological intervention [11,12]. Stent placement should avoid overlapping the ostium of a patent internal jugular vein to achieve a safe and sufficient result, since this latter vein is essential for future placement of central venous catheters. Similarly, a stent placed in the innominate vein should not overlap the ostium of the contralateral vein, otherwise contralateral stenosis may occur and preclude future use of the contralateral limb for access creation [4]. Little data are available on the use of thrombolytic agents in central venous thrombosis. It is, therefore, not recommended as a primary treatment regimen.

Surgical treatment

When interventional treatment of central venous obstruction is impossible or fails, assessment of the patient is necessary to define the most effective surgical method and to guarantee long-term vascular access. Surgical evaluation focuses on the general risk (see ASA Physical Status Classification System [13]) and life expectancy as well as on the vascular pathology. If surgery is an option, all angiograms have to be re-evaluated. If an ipsilateral surgical bypass to the jugular vein is impossible due to innominate vein obstruction, additional venography of the contralateral arm should be performed to assess whether a new access can be constructed in that arm or a subclavian–subclavian or subclavian–jugular cross-over bypass should be performed [14–16]. In case of bilateral obstruction of the mediastinal veins, including the superior caval vein, ultrasonography of ilio-caval veins is indicated in the planning of arterio-venous thigh access. Alternative surgical options for upper extremity vascular accesses with compromised venous outflow, are axillo-saphenous/iliac or right atrial bypasses [17,18].

As ultimate treatment access ligation can be considered, which will relief local symptoms.

Recommendations for further research

Improvement of central venous catheter design, may probably prevent vessel wall damage and the development of central venous stenoses. Stent improvement and newer guidewires may enhance central venous obstruction intervention and outcome.

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9. Diagnosis and treatment of access-induced ischaemia

Guideline 9.1. Access-induced ischaemia should be detected by clinical investigation and the cause should be identified by both non-invasive imaging methods and angiography (Evidence level III).

Guideline 9.2. Enhancement of arterial inflow, access flow reduction and/or distal revascularization procedures are the therapeutic options. When the above methods fail, access ligation should be considered (Evidence level II).

Rationale

Access-induced upper extremity ischaemia is a serious complication that, when not treated in time may lead to major amputation [1] From published series, it can be estimated that the incidence of symptomatic ischaemia varies from 2% to 8% of the haemodialysis population [2,3]. Elderly patients, diabetics and patients with peripheral and/or coronary arterial obstructive disease are more prone for the development of access-induced ischaemia. In addition, previous ipsilateral vascular access increases the risk. Access-induced ischaemia occurs more often in proximally located fistulas [4]. These high-flow AVFs induce a steal phenomenon with lowering of distal perfusion pressures and, when collateral circulation is inadequate, symptoms may occur [5–8]. A grade 1–4 classification for access-induced ischaemia (grade 1: pale/blue and/or cold hand without pain, grade 2: pain during exercise and/or HD, grade 3: ischaemic pain at rest and grade 4: ulceration, necrosis and gangrene) can be used to outline the severity of the disease and this ranges from minor symptoms to finger necrosis. A number of these patients have increasing pain during dialysis treatment. For grade 1 and 2 ischaemia a conservative treatment is indicated, while with grade 3 and 4, interventional treatment is indicated [9].

Diagnosis of access-induced ischaemia

Physical examination, including observation and palpation of peripheral vessels, may be inadequate and misleading for the diagnosis of symptomatic ischaemia. Additional non-invasive testing with measurement of digital pressures and calculation of the digit-to-brachial index (DBI), transcutaneous oxygen determination, ultrasonography of forearm arteries and access blood flow measurement are important steps in the diagnosis and decision-making process [10,11]. Finally, angiography with visualization of the upper extremity arterial tree from the proximal subclavian artery to the distal palmar arches with and without AVF compression to enhance distal flow, is obligatory to outline the strategy for treatment and to determine whether interventional or surgical options are preferred [12].

Management of access-induced ischaemia

The options for treatment depend on the aetiology of the ischaemia: inflow arterial obstruction and/or distal arterial lesions are recanalized with small-calibre balloons and stent implantation [13–15], high-flow AVFs, as mainly observed in patients following successful renal transplantation are eligible to flow-reducing procedures like banding and distal arterial extension [16–18]. Steal in itself may be cured by ligation of the artery distal of the arteriovenous anastomosis [19]. In most patients it is necessary to add a saphenous vein graft bypass to the forearm arteries (DRIL = distal revascularization + interval ligation). The results of these procedures are usually good with relief of symptoms and preservation of the access site (Table 1) [20–27]. A simple alternative of the DRIL procedure is the PAVA (proximal arteriovenous anastomosis) technique, in which the AV anastomosis at the elbow is disconnected and moved to the axilla by means of a graft interposition [28,29]. Intra-operative digital pressure measurement or transcutaneous oxymetry ($TcPO_2$) is mandatory to guarantee an adequate surgical intervention with acceptable outcome. A digital-brachial pressure index >0.60 or $TcPO_2$ of >40 mm Hg is indicative of a sufficient distal hand perfusion [30–32]. The same DBI threshold may be also predictive for the development of ischaemia in predialysis patients receiving new vascular access [33–35]. In some patients, AVF ligation and change in renal replacement modality (to continuous ambulatory peritoneal dialysis = CAPD) or transition to central venous catheter access, may be the only solution.

Prevention of access-induced ischaemia

An adequate preoperative evaluation and surgical technique are the keystones to avoid ischaemia. Physical examination of peripheral pulses, bruits, and measurement of bilateral arm blood pressures are essential for the work-up before AVF creation. Duplex ultrasonography is very useful in the assessment of not only superficial veins but also arteries. Preoperative measurement of digital pressures may be helpful to indicate patients at risk for ischemia. Patients with preoperative digit-to-brachial indices (DBI) <1.0 are more likely to develop steal, but there is no DBI threshold below which steal is inevitable. If there is any doubt concerning the status of the peripheral circulation, angiography or MRA is advised. Steal is more likely in patients undergoing brachial-based arteriovenous fistulae than in those receiving prosthetic grafts.

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Table 1. Results of distal revascularization and interval ligation (DRIL) procedure for the treatment of access-induced ischemia

Author	No. of patients	Success in %	AVF patency (%)
Schanzer *et al.* [20]	14	93	82
Haimov *et al.* [21]	23	96	73
Katz *et al.* [22]	6	83	100
Berman *et al.* [23]	21	100	94
Lazarides *et al.* [3]	7	94	–
Stierli *et al.* [24]	6	100	100
Knox *et al.* [25]	52	90	83
Diehl *et al.* [26]	12	100	100
Sessa *et al.* [27]	18	73	94

Therefore, a limited length of the arteriovenous anastomosis of 10 mm in radial-cephalic and 5–7 mm in graft and/or brachial-cephalic/basilic AVFs, may contribute to the prevention of large volumes of blood shunting through the AVF. Either a "non-smooth" anastomosis (90° or 180° angle) adds to a greater anastomotic resistance and thus limitation of flow.

Recommendations for further research

Further search for pre-operative indicators that outline the risk on post-operative ischaemia may help to take adequate measures for prevention.

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10. Central venous access

Guideline 10.1. Central venous catheters should be inserted as a last resort in patients without a permanent access and the need for acute haemodialysis (Evidence level III).

Guideline 10.2. The percutaneous route should be used for both acute and chronic catheter insertion. Insertion should be guided by ultrasound. A plain X-Ray (chest or abdomen) should be performed before use to locate catheter and detect any complication (Evidence level II).

Guideline 10.3. The right internal jugular vein is the preferred location for insertion (Evidence level II).

Guideline 10.4. Non-tunnelled catheters should only be used in emergency situations and should be exchanged as soon as possible for tunnelled catheters (Evidence level III).

Indications for catheter insertion

Central venous catheter insertion is required in incident CKD-stage 5 patients who need to start dialysis in an acute or emergency situation, and are not equipped with a permanent vascular access [1,2]. Catheter insertion is also indicated in prevalent CKD-stage 5 patients on renal replacement therapy presenting with vascular access failure [3], and waiting for interventional or surgical access salvage or the creation of a new access. In some patients, all surgically created arteriovenous vascular access options may have been exhausted. A central venous catheter may then represent the only access option. Some patients have a contraindication for the creation of an arteriovenous fistula (severe cardiac failure, chronic respiratory insufficiency) [4], because of the risk of heart failure.

Patients with severe pain in the hand due steal syndrome, causing peripheral ischaemia, or with major difficulties in needling [5], may also benefit from a permanent central venous catheter. Catheters offer immediate vascular access for haemodialysis and may be used over several months or years. Long-term catheters also have positive properties: they are easy to use and do not need maturation.

Technique of catheter insertion

Catheter insertion is considered a high-risk intervention which deserves careful attention, must be performed under strict aseptic conditions and should ideally be performed by trained and senior physicians. Percutaneous catheter insertion is the preferred method for catheter insertion. The right internal jugular vein is the first option for insertion, followed by the left internal jugular vein. The femoral route is preferred for short-term catheters (<1 week) since there is no risk for central vein stenosis. Ultrasound-guided insertion technique is mandatory to prevent accidental carotid artery puncture and to ensure successful cannulation [6,7]. In addition, fluoroscopy to follow and locate the position of the guide wire is advisable. In a recent study 60 patients were randomized for ultrasound guided *vs* 'blind' catheter insertion. First attempt venous cannulation success rate was 56.7% compared with 86.7% in non-guided *vs* guided insertion technique. The risk of adverse outcome was significantly greater in the blind procedure ($P = 0.020$). The ultrasound-guided procedure for internal jugular vein catheter insertion using an ordinary ultrasound machine was significantly safer and more successful as compared with the blind technique [8]. For patients presenting with acute and/or life-threatening conditions requiring immediate dialysis (pulmonary oedema, hyperkalaemia, respiratory distress) the femoral vein is the most favourable insertion site. Because of the high risk on central venous stenosis (see Guideline 8), the subclavian vein route has been abandoned [9].

Catheter performance and care

Catheter performance (maximum flow rate, blood resistance and recirculation) should comply with delivery of adequate dialysis dose without altering treatment schedule (frequency, dialysis duration) [10,11]. Tunnelled catheter morbidity (dysfunction, thrombosis, infection) is significantly reduced compared with non-tunnelled catheters and tunnelled catheters should be preferred in all patients [12]. Port-catheter devices (Dialock, LifeSite) offer comparable flow performances to long-term catheters while improving patients' aesthetic satisfaction and improving patients comfort [13,14]. Unfortunately, the risk on infection is high with these devices. Catheter care and handling conditions under aseptic manipulation are essential to prevent infection in catheter and venous port devices.

Recommendations for further research

Improvement of catheter design and locking solutions are major subjects for further research.

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11. Management of central venous access complications

Guideline 11.1. Catheter dysfunction should be corrected by local fibrinolysis designed to restore flow patency. Repetitive catheter dysfunction requires local fibrinolysis with additional catheter imaging, microbiological assessment and systemic coagulation evaluation (Evidence level III).

Rationale

Catheter dysfunction is a relatively common event for haemodialysis patients. It reduces the effective blood flow rate and reduces dialysis dose. Catheter dysfunction may be minimized by using the appropriate material, a perfect insertion technique [1] and strict protocols for catheter care [2]. Catheter design and material are essential for achieving high blood flow and adequate performance [3,4]. Tunnelled catheters provide usually higher flows (up to 400 ml/min) at low resistance and reduced recirculation compared with non-tunnelled catheters. Dual catheters with independent lines and side holes at the tip provide higher flows than dual-lumen catheters [5,6]. Catheters inserted in the right internal jugular vein offer the best flow compared with other central venous sites [7]. Catheter dysfunction must be detected and corrected early in order to restore blood flow and dialysis dose. Catheter dysfunction may occur in different ways:

(i) Complete obstruction, making dialysis impossible.
(ii) Incomplete obstruction (endoluminal fibrin deposits restricting catheter lumen or obstructing catheter side holes at the tip, external fibrin sleeves surrounding catheters) resulting in inadequate flow and/or excessive extracorporeal blood pressure alarms during the dialysis session. Depending on the location of the fibrin clot (arterial and/or venous line), there may be high negative arterial pressure (obstruction at the arterial catheter line) or high positive venous pressure (obstruction at the venous catheter line).

Catheter care and handling are very important to prevent catheter dysfunction. Prevention of catheter clot formation in the catheter tip during the interdialytic period is crucial. This may be achieved by installing an antithrombotic lock solution (standard heparin, low molecular weight heparin, sodium citrate) [8,9]. A certain amount of the antithrombotic lock solution may leak into the circulation via side- and central catheter holes. Loss of antithrombotic locking solution facilitates catheter clot formation while it increases the haemorrhagic risk. Regular use of low dose of antithrombotic drugs such as coumarin derivatives or antiplatelet agents in dialysis patients have failed to improve catheter outcomes [10–12].

Catheter performance monitoring is required to detect catheter dysfunction. Such monitoring is an integral part of the quality assurance process to ensure dialysis efficacy and to reduce catheter-related morbidity [13]. It relies on markers evaluating catheter flow performances such as estimations of effective blood flow rate, venous and arterial pressure values at constant flow, recirculation and dialysis dose delivery as measured by Kt/V [14].

Catheter maintenance is important to achieve the prescribed blood flow during dialysis sessions. To prevent and/or to correct catheter dysfunction it is recommended to clean the catheter lumen periodically by applying fibrinolytic agents (urokinase, tPA) either as lock solution or continuous infusion on both arterial and venous lines [15]. Occluded catheters are reopened either by means of a mechanical method (brush) or pharmacological method (urokinase, tPA) [16–18]. Removal of the fibrin sleeve may be achieved either by lasso wire stripping or by infusing a fibrinolytic solution (urokinase, tPA), during 3–6 h [19]. Alternatively, the catheter may be exchanged over a guidewire [20].

Recommendations for further research

Investigation into better thrombolytic agents and mechanical tools to declot thrombosed catheters are of importance.

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12. Management of the infected vascular access

Guideline 12.1. Infection of autogenous AV fistulae without fever or bacteraemia should be treated by appropriate antibiotics for at least 2 weeks (Evidence level III).

Guideline 12.2. Infection of autogenous AV fistulae with fever and/or bacteraemia should be treated by appropriate antibiotics given intravenously for 2 weeks. Excision of the fistula is required in case of infected thrombi and/or septic emboli (Evidence level IV).

Guideline 12.3. Infected graft AVFs should be treated by appropriate antibiotics given intravenously for 2 weeks and continued orally for 4 weeks. Depending on the presence of bacteraemia and/or infected thrombi segmental explantation of the graft with bypass needs to be considered (Evidence level III).

Guideline 12.4. Anastomotic infection is an indication for total graft explantation (Evidence level II).

Guideline 12.5. Catheter removal must be considered when catheter infection is suspected. Immediate removal should be performed in non-tunnelled catheters when infection is diagnosed (Evidence level III).

Guideline 12.6. In tunnelled catheters with a short febrile and/or bacteraemic reaction, a delayed removal may be considered (Evidence level III). In septicaemia, immediate removal should be performed in tunnelled catheters as well.

AVF and prosthetic graft infection

Infection of autogenous AVF usually responds well to appropriate antibiotics given either orally or intravenously according to the presence of fever and/or bacteraemia. Surgical revision or excision of the fistula is required when infected thrombi, aneurysms and/or septic emboli are detected. Infection of graft AVFs is two to three times more frequent than autogenous AVFs [1]. Infection of the graft bears a worse prognosis and requires usually a surgical revision and/or explantation in addition to the antibiotic therapy. Salvaging prosthetic grafts may be attempted in certain circumstances. Several surgical techniques have been described in combination with antibiotic therapy. For localized abscesses, incision and drainage with graft preservation is needed. For more severe infection, such as infected thrombi, false aneurysms, cellulitis, explantation of the infected graft segment and segmental bypass with a new graft is indicated. However, these salvaging techniques may be complicated because of local or generalized infection and sepsis. Therefore, in severe cases a complete explantation of all graft material with drainage is usually necessary.

Central venous catheter infection

Catheter-related infection is the major cause of morbidity in HD patients with central venous catheters [2–4]. Catheter infection is a potentially severe event that requires early diagnosis and appropriate management to prevent further complication. Diagnosis of catheter infection is relatively easy in symptomatic patients presenting with fever, pain, skin exit and/or track infection and bacteraemic episodes. It is much more difficult in silent catheter endoluminal contamination or low grade infection. In these cases, only specific blood and catheter clot culture will help to make the diagnosis [5]. Recently, it was shown that catheter clot culture after endoluminal brushing was more sensitive than blood culture to identify asymptomatic catheter infection (catheter contamination) [6,7]. Symptoms of infection includes chronic fever, bacteraemic episodes, catheter pain, inflammation of the exit site or tunnel. Infection of the catheter exit site or tunnel tract is usually observed by the dialysis nurse while clinical examination is performed at the time of dialysis connection. Silent contamination is suspected when recurrent febrile reactions during haemodialysis occur and bacterial pathogens (*Staphylococcus aureus, S. epidermidis* or other bacteria such as Gram-negatives) are identified in blood cultures. Catheter-related septicaemia is usually associated with symptoms of endocarditis, arthritis, spondylarthritis or osteomyelitis.

Specific blood markers (leucocyte count and differentiation), C-reactive protein (CRP) and procalcitonin (PCT), help to diagnose early bacterial catheter infection. Catheter-related infection should be considered as a severe and potentially lethal complication. Prevention of infection should be a permanent preoccupation for care providers, that relies on hygienic measures [8] and strict protocols for handling catheters based on aseptic manipulation [9] and using specific dressings [10]. The regular and pre-emptive use of locking solutions (Citrate) with both antithrombotic and/or antiseptic properties has been confirmed to be effective in preventing catheter infection [11–14]. The topical application of antibiotic ointment on the skin exit site has proved to be efficient in reducing the incidence of bacteraemia at the expense of selecting antibiotic-resistant strains of bacteria [15–17]. The use of antibiotic-coated catheters or silver-treated catheters has been proposed to reduce the risk of infection, but conflicting results has been reported [18–20]. Identification of patients at risk of infection is particularly important in diabetic patients and nasal

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carriers of methicillin-resistant *S. aureus* (MRSA). In the latter patients, eradication of bacteria by means of topical antibiotic ointment has been associated with a significant reduction of bacteriaemias [21,22].

Catheter removal should be considered as the first line of treatment. Catheter withdrawal must be immediate when infection occurs in non-tunnelled catheters. Removal may be postponed for several days in tunnelled catheters. When this last option is applied the risk of septic complications of delayed catheter removal should be balanced with the benefits of keeping it *in situ*. This conservative option implies that the patient is regularly and carefully observed. In addition, the catheters should be disinfected by means of antimicrobial lock solutions and dissemination of the infection must be prevented by adequate systemic antibiotic therapy. When the catheter is left in place and in the absence of precise microbial information, antimicrobial therapy should include systemic antibiotic therapy effective against Staphylococcus species plus an adjunctive antimicrobial catheter lock. Antibiotic therapy is given for 2 weeks in order to sterilize all potential bacterial foci. Topical antibiotic therapy (catheter exit site) is initiated when there is associated local infection. Imaging techniques may help to diagnose catheter-related infection. Ultrasound doppler methods can detect tunnel infection and/or subcutaneous abscesses along the catheter track. Phlebography and catheterography are indicated to diagnose infected thrombi located in the vein or fibrin sleeves surrounding the catheter tip. Isotopic imaging techniques using positron emission tomography (PET) may help to identify infected venous catheters and port devices [23].

Recommendations for further research

Improvement of needle design and education on strict aseptic cannulation techniques may possibly lower the incidence of infection in fistulae and grafts. Antibiotic-bonded grafts may possibly lower the incidence of graft infection. Newer catheter designs and locking solutions are important issues for further investigation of the prevention of central venous catheter-related infections.

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Relationship between Blood Flow in Central Venous Catheters and Hemodialysis Adequacy

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Central venous catheter dysfunction is a frequent problem and often is defined as a blood flow <300 ml/min. This prospective, cross-sectional study included 259 patients and examined the relationship between catheter blood flow and dialysis adequacy as measured by urea reduction ratio (URR), single pool urea kinetics, and online effective ionic dialysance clearance. Dialysis adequacy at blood flow rates of <300, <275, and <250 ml/min; sensitivity; specificity; and positive and negative predictive values were calculated. Mean blood flow was 352 ml/min (SD ± 48.8). Mean blood flow <300 ml/min occurred in 10.5% of the patients, and only 26% had a URR of <65%. Maximum blood flows <300 ml/min occurred in 6.9% of patients, and only 22.2% had URR <65%. The positive predictive value of mean blood flow of <300 and <275 ml/min to predict a URR <65% was 22 and 40%, respectively. Using receiver operator characteristic curves, the area under the curve was not significantly different for blood flows of 300, 275, or 250 ml/min. This study indicates that mean blood flows <300 ml/min are not commonly associated with dialysis inadequacy. Setting a single blood flow cut point of <300 ml/min to define the need for intervention will result in a significant number of unnecessary interventions. There is a need to reexamine the definition of catheter dysfunction and expand the definition beyond blood flow rates.

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Cuffed, tunneled, dual-lumen central venous catheters (CVC) have become an acceptable form of hemodialysis (HD) vascular access when other permanent vascular accesses are unavailable, despite the associated high complication rates and mortality risk (1–4). In Canada, up to 70% of patients initiate HD with a CVC, and 33% continue to use catheters 90 days after dialysis initiation (5). This is far in excess of the National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-DOQI) recommendation that CVC be used in <10% of prevalent HD patients (6).

A common complication of the CVC is its inability to deliver adequate dialysis as a result of dysfunction. The definition of CVC dysfunction varies across the literature and includes variable rates of blood flow ranging from <100 to 350 ml/min (7–16). The NKF-DOQI vascular access guideline defines CVC dysfunction as failure to attain and maintain extracorporeal blood flow that is sufficient to perform HD without significantly lengthening the HD treatment and considered insufficient extracorporeal blood flow to be <300 ml/min (6). This recommendation was opinion based and has been interpreted as the need to maintain blood flows >300 ml/min to ensure adequate dialysis. As a result of these guidelines, CVC often are run in the reverse configuration, thrombolytic agents such as thromboplastin inhibitor (t-PA) are used, or catheters are rewired when blood flow is reduced to <300 ml/min. With the increase in CVC prevalence and the corresponding increase in thrombolytic use and subsequent cost consequences, there is a clear need to clarify the relationship between CVC blood flow and dialysis adequacy. The primary objective of this study was to determine the relationship between mean blood flow in CVC and HD adequacy as measured by three parameters: urea reduction ratio (URR), single pool urea kinetics (spKt/V), and online effective ionic dialysance (EID) as measured by Diascan (Hospal Gambro, St. Leonard, Canada).

Materials and Methods

Study Population

We undertook a prospective, cross-sectional study with participants who were recruited from two regional, university-based tertiary HD care programs at London Health Sciences Centre and the University Health Network–Toronto General Hospital. Research ethics board approval and individual patient consent were not required because this was undertaken as a quality improvement study and did not require additional investigations or alteration in delivery of care. Approval for access to patients was sought from the medical directors of each dialysis unit to collect the data as part of a cost management and quality assurance program, and the confidentiality of patients was maintained throughout the study.

Patients were included when they were on maintenance HD and using a cuffed-tunneled permanent CVC, located in the internal jugular vein, and were hemodynamically stable (de-

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fined as stable BP on dialysis without the need for saline bolus for the previous 2 wk). Patients received thrice-weekly, in-center dialysis using a single-use, high-flux polysulfone dialyzer. Patients at both centers underwent dialysis using the Integra (Gambro) dialysis machine. Patients at London Health Sciences Centre underwent dialysis using Permcath (Quinton Instrument Co., Seattle, WA) 12f caliber and 36 to 45 cm length, with a 2.5-cm separation between the arterial (proximal) lumen and venous (distal) tip. University Health Network patients used Uldall-Cook Catheter (Cook Canada Inc., Stouville, Canada), HIGHFLOW Dialysis Catheter (CardioMed Supplies Inc., Gormley, ON, Canada), Opti-flow/HemoGlide dual-lumen permanent dialysis catheter (Bard Access Systems, Mississauga, Canada), and Vaxcel Plus Chronic Dialysis Catheter (Boston Scientific, Boston, MA).

Assessment of Dialysis Adequacy

The Kt/V is a method of assessing the amount of dialysis that is delivered in terms of urea removal. This parameter was calculated using the Daugirdas formula $Kt/V = -\ln(R - 0.03) + [(4 - 3.5R) \times (UF/W)]$, where UF is the ultrafiltration volume in liters, W is the postdialysis weight in kg, and R is the ratio of the postdialysis-to-predialysis urea (17). Patients with residual renal function were included in this study, but the renal clearance was not included in the Kt/V. The URR is a second method to estimate dialysis adequacy and was calculated by the equation (pre-urea − post-urea)/pre-urea. Blood samples for the determination of plasma urea concentrations were drawn at the start and the end of the same dialysis as per the recommended guidelines using the slow flow method (18). Blood urea samples were analyzed using an enzymatic conductivity rate method (Synchron LX System; Beckman Instruments, Inc., Mississauga, Canada). The third measure of dialysis adequacy used the Diascan to measure the EID. EID uses conductivity measurements of both blood and dialysate to determine the clearance of sodium ions across the dialysis membrane. Several researchers have shown a relationship between EID and urea clearance and that it is possible to use ionic dialysance as an indicator of treatment efficacy (19–23). The principle previously has been described extensively (24). The EID expresses clearance (K) as ml/min. K was used in the Diascan Kt/V calculation, where V was calculated as 60% of target body weight (kg) for men and 55% of target weight for women, and t was time on dialysis (in minutes). Dialysis treatment time varied according to the patient prescription. Dialysate flow rates were held constant at 500 ml/min during each treatment. Ultrafiltration rates depended on each patient's requirements but were kept constant during sampling periods.

All blood measurements and Transonic monitoring was done during the midweek dialysis session concurrent with monthly blood work. Access recirculation was measured using the Transonic HDO1 monitor (Transonic Systems Inc., Ithaca, NY) (25). Three research nurses, trained in HD and in the use of the Transonic equipment, undertook data collection and Transonic measurements. The mean blood flow for that session (ml/min) was calculated by dividing the total liters processed by the number of minutes on dialysis. Demographics, cause of ESRD, comorbid conditions, and location of dialysis were collected at baseline. Adequate clearance was defined as a single pool (sp) Kt/V ≥1.2, URR ≥65%, and Diascan Kt/V ≥1.0.

Statistical Analyses

Mean and SD were calculated for continuous variables. Sensitivities, specificities, positive predictive values (PPV), and negative predictive values (NPV) of mean blood flow categories (<250, <275, and <300 ml/min) as an indicator of URR >65% were calculated. Receiver operator characteristic (ROC) curves were used to determine the relationship between blood flow rates and URR ≥65%.

Bivariate analyses were performed to evaluate the relationship between URR ≥65% and the following variables: Mean blood flow, catheter locking solution, percentage of recirculation, and line configuration. The bivariate analyses used a succession of independent sample *t* test for equality of means and repeated measures ANOVA (with categorical determinants), and correlation analyses (with continuous determinants). Variables whose coefficients were significant at $P < 0.05$ were included in a multivariate analysis to determine the relationship to URR. All statistical analyses were conducted using SPSS for Windows, Release 10.1.0, Standard Version (SPSS Inc., Chicago, IL).

Results

A total of 259 patients completed the study. A subgroup of 89 patients had all three measures of dialysis adequacy (%URR, Kt/V, and Diascan Kt/V), whereas the remainder had measures of URR only. The baseline demographics and clinical characteristics of the 259 patients as well as the subgroup of 89 patients are presented in Table 1. The mean patient age was 66.0 ± 15.2 yr, and 51.0% were female. The percentage with hypertension, diabetes, and coronary artery disease were 79.5, 46.4, and 42.3%, respectively. The catheter and dialysis characteristics are described in Table 2 for both the total and the subgroup. The mean catheter age was 57.4 ± 61.6 wk with a range from 2 to 379 wk. The average duration of dialysis was 216.8 min, and the mean blood volume processed was 76.14 L. The calculated mean blood flow was 352.1 ± 48.8 ml/min. Recirculation was present in 108 (41.7%) of CVC; 28.7% occurred with CVC in the straight configuration, and 71.3% occurred in the reversed configuration. Recirculation of >10 and >20% occurred in 27.3 and 7.6% of the CVC, respectively. The catheter locking solution was heparin 1:500, heparin 1; 10,00, and 4% citrate in 32.3, 51.0, and 14.4% of lines, respectively. The remainders were locked with t-PA or were participants in the Pre-CLOT study (26).

The mean %URR for the total group was 73.8% (range 44 to 97%). The mean URR as well as the proportion of patients with a %URR <65 for each category of blood flow rate is described in Table 3. The mean URR for each blood flow category was not different ($P = 0.07$). Ten percent of patients had a URR <65%. Mean blood flow of <300 ml/min occurred in 27 (10.5%) patients, and 26% of these had URR <65%. Mean blood flow of >400 ml/min occurred in 11.3% of patients, and 13.8% of those had a mean URR <65%.

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Table 1. Baseline demographic and clinical characteristics[a]

	Total (n = 259)	Subgroup (n = 89)
Demographic characteristics		
age (yr)	66.2 (15.2)	68.6 (14.3)
gender (% female)	51.0	43.8
Cause of ESRD (%)		
diabetes	35.4	40.4
hypertension	19.3	15.7
glomerulonephritis	13.9	7.9
polycystic kidney disease	3.2	3.4
other	26.2	31.5
unknown	2.0	1.1
Comorbid conditions (% yes)		
hypertension	79.5	80.7
diabetes	46.4	55.1
coronary artery disease[b]	42.3	42.7
congestive heart failure	16.7	22.1
peripheral vascular disease[c]	15.9	22.4

[a]Data are mean (SD) or %.
[b]Includes coronary artery bypass surgery, angina, and myocardial infarction.
[c]Includes history of peripheral vascular disease, limb amputation, absent foot pulses, and symptoms of claudication.

In the subgroup of 89 patients, the mean %URR was 74.6% (± 6.1), spKt/V was 1.65 (± 0.3), and Diascan Kt/V was 1.16 (± 0.23). The %URR, spKt/V, and Diascan Kt/V, categorized by blood flow rate, are presented in Table 4. The percentage of patients with URR <65%, spKt/V <1.2, Diascan Kt/V <1.0, and Diascan Kt/V <1.2 was 6.7, 5.9, 20, and 54.1%, respectively. Mean blood flow of <300 ml/min occurred in four patients, and only one patient had inadequate dialysis as measured by a URR <65%, spKt/V <1.2, and Diascan Kt/V <1.0.

Intervention to improve blood flow usually is based on a trend in blood flow or a single blood flow measurement *versus* a mean blood flow for the entire session. To explore this, we examined the maximal blood flow achieved during each dialysis session. The mean %URR and the proportion of patients with URR <65% for each category of maximal blood flow are listed in Table 5. The difference in mean %URR by maximum blood flow classification approached statistical significance (P = 0.055). Maximal blood flows <300 ml/min occurred in 6.9% of patients, and 18% had URR <65%.

We explored the diagnostic accuracy of mean blood flow to determine an adequate clearance as defined by URR ≥65%. We examined mean blood flow rates of <250, < 275, and <300 ml/min. The sensitivity, specificity, PPV, and area under the curve (AUC) in a ROC curve for mean blood flow rate are reported in Table 6. The PPV value, that is the proportion of patients who had a blood flow rate less than targeted when the URR indicated inadequate dialysis (URR <65%), increased from 22 to 40% when the target blood flow decreased from 300 to 250 ml/min. Lowering the target blood flow from 300 to 250 ml/min resulted in a small, NS decrease in NPV from 91.5 to 90%.

The AUC indicates the overall predictive accuracy of a test. A test with perfect predictive accuracy has a combined AUC of 1.0, whereas a test with no predictive accuracy has an AUC of 0.5. The AUC for blood flows of 250, 275, and 300 ml/min were 0.53, 0.55, and 0.57 (P = 0.89).

Patient age, gender, mean blood flow, percentage of recirculation, catheter age, catheter locking solution, and predialysis weight were examined in a bivariate analysis to examine the association with %URR. Line configuration and maximal blood flows were not included because of the close correlation with percentage of recirculation and mean blood flows, respectively. The following variables were significantly associated with increased %URR: Lower predialysis weight (kg; P = 0.001), higher mean blood flow (ml/min; P = 0.012), lower percentage of recirculation (P = 0.001), female gender (P = 0.04), and increased patient age (P = 0.04). Catheter capping solution was not associated with dialysis adequacy. Using variables that were significant at $P < 0.05$ in the bivariate analysis and including dialysis time, several variables continued to be associated with increased URR, including higher mean blood flow (P = 0.001), female gender (P = 0.001), longer dialysis time (P = 0.001), and increased age (P = 0.004). As expected, a higher dialysis weight (P = 0.001) and increased recirculation were associated with lower %URR. Altogether, these six independent variables explained a significant variation in %URR using the following regression equation with inclusion of standardized β coefficients in order of decreasing influence on %URR: URR = 50.3 − 0.476 (predialysis weight) + 0.288 (mean blood flow) + 0.223 (if female) + 0.222 (time) − 0.202 (recirculation) + 0.147 (age).

The clinical interpretation of this is as follows: Each increase of 1 kg in predialysis weight results in a decrease of 0.476% in URR. Each increase of 1 ml/min in mean blood flow results in an increase of 0.288% in URR. Female patients' URR averages 0.223% higher than male patients' URR. Each increase of 1 min in session length results in an increase of 0.222% in URR. Each increase of 1 yr in patient age results in an increase of 0.147% in URR.

Discussion

Current vascular access guidelines recommend an intervention in a CVC when one fails to attain and maintain extracorporeal blood flow that is sufficient to perform HD without significantly lengthening the HD treatment. The guidelines then state a blood flow of <300 ml/min could be considered insufficient (6). The results of this study would challenge the validity of this recommendation. In this study, we found that 10.5% of dialysis sessions had a mean blood flow of <300 ml/min, and 75% of these achieved adequate dialysis as defined by a URR ≥65%. When we examined other measures of dialysis adequacy, only one of four patients had inadequate dialysis with mean blood flows <300 ml/min. Even when we looked at the proportion of patients with a maximal blood flow of <300 ml/min throughout the dialysis session, only 22% of

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Table 2. Catheter and dialysis session variables[a]

	Total (n = 259)	Subgroup (n = 89)
Catheter age (wk)	57.4 (61.6)	56.2 (56.4)
Locking solution (%)		
heparin 1:10,000	51.0	
heparin 1:5000	32.3	93.3
4% citrate	14.4	2.2
t-PA	1.2	1.1
Pre-CLOT study protocol	1.2	3.4
Dialysis machine (%)		
Integra	97.5	95.5
Cobe	0.8	—
Fresenius	1.7	4.5
Dialysis shift (%)		
morning	39.0	41.6
afternoon	42.9	42.7
evening	18.1	15.7
Dialysis		
predialysis weight (kg)	71.7 (22.2)	76.9 (24.6)
weight loss during dialysis (kg)	1.92 (1.12)	2.08 (1.19)
blood volume processed (L)	76.14 (13.82)	75.45 (14.45)
time on dialysis (min)	216.8 (30.4)	206.2 (29.2)
mean blood flow (ml/min)	352.1 (48.8)	366.5 (40.1)
URR (%)	73.8 (7.4)	74.6 (6.1)
% with lines reversed	34.0	27.0
% with recirculation	41.7	37.2
spKt/V	—	1.65 (0.30)
Diascan Kt/V	—	1.16 (0.23)

[a]Data are mean (SD) or %. spKt/V, single pool Kt/V; t-PA, thromboplastin inhibitor; URR, urea reduction ratio.

Table 3. URR by mean blood flow (n = 259)

Blood Flow (ml/min)	% of Patients	URR (% ± SD)	% with URR <65%[a]
<250	1.9	71.8 ± 11.4	40.0
250 to 300	8.6	70.5 ± 10.7	22.7
301 to 350	39.7	73.5 ± 7.3	7.8
351 to 400	38.5	75.2 ± 6.1	6.1
>400	11.3	73.1 ± 7.7	13.8
Total	100.0	73.8 ± 7.5	10.0

[a]Percentage within blood flow grouping.

patients had inadequate dialysis. A mean blood flow cut point between 250 and 300 ml/min had low predictive accuracy in determining a dialysis session with a URR <65%. Last, we have shown that several variables play a role in determining dialysis adequacy. Interventions to maintain adequacy, based on blood flow alone, will result in an inappropriate increase in intervention and cost.

CVC are used in an increasing proportion of patients who are on HD (2,5). The reported incidence of catheter dysfunction ranges from 5 to 80%, depending on the definition, population, and catheter characteristics (7–16). The interpretation of studies that use blood flow as a measure of catheter dysfunction are challenging without knowledge of blood pump setting, use of average *versus* episodic measures of blood flow, percentage of recirculation, and other dialysis variables. There is an increasing use of long daily, nocturnal dialysis and slow low-efficiency dialysis, all of which use lower blood flows (27,28). Defining dysfunctional catheters by blood flows of <300 ml/min in this population would lead to unnecessary intervention in the majority of patients.

Few, if any, studies have defined catheter dysfunction as the inability to deliver an adequate dialysis prescription, which is the overall goal of dialysis. The availability, acceptance, and further validation of online measurements of EID may aid in describing the dialysis dose at each session and allow for identification of inadequate dialysis in a more timely and precise manner. In this study, we empirically used a Diascan Kt/V >1.0 as the measure of adequate dialysis after we identified that >50% of the patients had a Diascan Kt/V <1.2. This Diascan Kt/V target has not been validated with clinical outcomes. We chose a lower Diascan Kt/V target because EID has been shown consistently to underestimate delivered dialysis dose, even after correcting for recirculation and urea distribu-

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Table 4. URR, spKt/V, and Diascan Kt/V by mean blood flow (n = 89)

Blood Flow (ml/min)	% of Patients	URR (% ± SD)	% with URR <65%[a]	spKt/V (±SD)	% with spKt/V <1.2	Diascan Kt/V (±SD)	% with Diascan Kt/V <1.0[a]
<250	1.1	65.7	0	1.28	0	0.57 ± —	100.0
250 to 300	3.4	69.5 ± 10.8	33.3	1.37 ± 0.49	33.3	1.09 ± 0.27	33.3
301 to 350	26.4	74.7 ± 4.1	0	1.64 ± 0.23	0	1.18 ± 0.20	19.0
351 to 400	52.9	75.0 ± 6.3	6.5	1.67 ± 0.030	4.8	1.16 ± 0.24	23.9
>400	16.1	76.0 ± 6.4	7.1	1.71 ± 0.33	7.1	1.23 ± 0.19	0.0
Total	100.0	74.8 ± 6.0	6.7	1.66 ± 0.30	5.9	1.17 ± 0.23	20.0

[a]Percentage within blood flow grouping.

Table 5. URR by maximum blood flow (n = 259)

Blood Flow (ml/min)	% of Patients	URR (% ± SD)	% with URR <65%
<250	0	—	—
250 to 300	6.9	69.9 ± 9.9	22.2
301 to 350	34.4	73.2 ± 8.1	13.5
351 to 400	46.3	74.7 ± 6.6	6.7
>400	12.4	74.5 ± 6.5	6.3
Total	100.0	73.8 ± 7.5	10.0

Table 6. Sensitivity and specificity of mean blood flow as an indicator of URR ≥65%[a]

Mean Blood Flow (ml/min) Cut Point	Sensitivity	Specificity	Area under the ROC Curve
250	0.080	0.987	0.534
275	0.160	0.961	0.561
300	0.240	0.914	0.577

[a]ROC, receiver operator characteristic.

tion volume (19–29). Further studies using EID clearance and its relationship to blood flow and adequacy using a CVC need to be performed.

We calculated the sensitivity, specificity, PPV, and NPV of mean blood flow as a diagnostic tool to predict dialysis adequacy in CVC. A mean blood flow of <300 ml/min had a PPV of 22%, whereas a mean blood flow <250 ml/min had a PPV of 40%. This indicates that at a mean blood flow of <300 ml/min, only 22% of patients had a URR <65%, whereas 40% had a URR <65% at a blood flow of <250 ml/min. The tradeoff between sensitivity and specificity was examined using the ROC curves. The AUC was not significantly different for the blood flow cut points of 250, 275, and 300 ml/min.

There are significant clinical and cost implications of defining catheter malfunction on the basis of blood flow alone. The misconception that blood flows <300 ml/min lead to inadequate dialysis often results in nursing personnel's reversing the line to maintain flows >300 ml/min. Carson *et al.* (30) recently described the relationship among blood flow, line configuration, percentage of recirculation, and clearance. Despite documented recirculation, it is possible to achieve acceptable clearance if the blood flow is sufficiently high; however, there are tradeoffs, and some patients will have unacceptable clearances in the reversed configuration (30). Patients may be subjected to unnecessary line changes and increased intervention with t-PA. The costs that are attributed to the use of t-PA and line exchange are not known. A recent cost analysis of vascular access calculated CVC at $9180 Can (median $3812; interquartile range $2250 to $7762) per patient-year (16). In this study, catheter dysfunction was defined as blood flow of <200 ml/min, and the cost of t-PA was $199 per patient-year at risk. Increasing the intervention target to a blood flow of 300 ml/min would significantly increase costs. In our institutions, the cost of 2 mg of t-PA to each port is approximately $120.00 Can. If all patients in this study who had a blood flow <250 ml/min were treated (n = 5), then the cost of t-PA for that session would have been $325.00 Can. If we intervened in all lines with a mean blood flow <300 ml/min, as per K/DOQI recommendations, then we would have treated 28 lines at a cost of $1820.00 Can. The cost of t-PA would have increased five to six times from changing the target blood flow for intervention from 250 to 300 ml/min. Importantly, this use would be justified if mean blood flow <300 ml/min correlated with an important clinical consequence, such as inadequate dialysis; however, our data suggest that 22 (80%) of 27 lines would have been treated unnecessarily at an excess cost of $1365.00 for a single dialysis session.

Dialysis adequacy was associated with patient variables age, predialysis weight, and female gender, as well as dialysis variables time, mean blood flow, and percentage of recirculation. Although this is well-established knowledge in nephrology (31,32), it serves as a reminder that multiple variables influence the delivery of adequate dialysis dose, in addition to blood flow.

The question, then, is which blood flow rate should be used to assist in determining the need for intervention to maintain adequacy? Clearly this cannot be established for a general HD population. For a 40-yr-old, 100-kg man, a mean blood flow of 300 ml/min or more may be needed to maintain adequacy, whereas an 80-yr-old, 55-kg woman may have adequate clearance with a mean blood flow of 275 ml/min. The recent Canadian Hemodialysis Clinical Practice Guidelines on vascular access have defined CVC dysfunction as the inability to main-

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tain pump speed >200 ml/min for one run or difficulty aspirating from either lumen of the catheter (33). This may be a more conservative estimate of the blood flow cut point. None of the patients in our study had blood flows <200 ml/min, so we were not able to examine the relationship between dialysis adequacy and this blood flow cut point. On the basis of the trend of our data, blood flows <200 ml/min would result in inadequate dialysis in the majority of patients.

Our study has a number of limitations. We used a calculated mean blood flow that was based on the liters processed and time on dialysis, which some consider inferior to recorded average blood flow from the blood pump or the gold standard of blood flow as measured using ultrasound dilution techniques (34–36). Interventions in CVC usually are based on an intermittently low blood flow or inability to withdraw blood at the initiation of dialysis *versus* mean blood flow as used in this study. To address this, we examined dialysis sessions with maximum blood flows <300 ml/min and found that 82% of these sessions provided adequate clearance, thus confirming our original results. Given the cross-sectional nature of our study, we were unable to examine trends in blood flows and dialysis adequacy.

The strengths of our study include the use of a large number of dialysis patients from two separate sites, which increases the generalizability of the results. We were able to correlate various levels of blood flow with three separate and complementary measures of dialysis adequacy.

Conclusion

In this study, mean blood flow rates <300 ml/min were not commonly associated with dialysis inadequacy. Setting a single blood flow cut point of <300 ml/min to define the need for intervention will result in a significant number of unnecessary interventions and associated increased costs. There is a need to reexamine the definition of catheter dysfunction and expand the definition beyond blood flow rates.

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Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

AAMI / ANSI / ISO 11135-1:2007, Sterilization of health care products - Ethylene oxide - Part 1: Requirements for the developme

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3] # 14-228		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☑	☐
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☑	☐
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☑	☐
If yes, was the guidance document followed in preparation of this 510k?	☑	☐

Title of guidance: 510(k) SUBMISSION FOR SHORT-TERM AND LONG-TERM INTRAVASCULAR CATHETERS

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
AAMI / ANSI / ISO 11135-1:2007, Sterilization of health care products - Ethylene oxide - Part 1: Requirements for the developme

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *
(b)(4)

DESCRIPTION
(b)(4)

JUSTIFICATION
(b)(4)

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *
(b)(4)

DESCRIPTION
(b)(4)

JUSTIFICATION
(b)(4)

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *
N/A

DESCRIPTION
(b)(6) 2010-05-12

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

* Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

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Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to:

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Department of Health and Human Services
Food and Drug Administration

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

EN 556-1:2002 Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☐	☑
FDA Recognition number [3] #		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☑	☐
If yes, was the guidance document followed in preparation of this 510k?	☑	☐

Title of guidance: 510(k) SUBMISSION FOR SHORT-TERM AND LONG-TERM INTRAVASCULAR CATHETERS

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

EN 556-1:2002 Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION		
JUSTIFICATION	n/a (b)(6) 2010-05-12	

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION		
JUSTIFICATION		

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 594-1:1986 Conical fittings with a 6% (Luer) taper for syringes, needles and certain other medical equipment – Part 1: Genera

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3]	# 6-11	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☑

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

ISO 594-1:1986 Conical fittings with a 6% (Luer) taper for syringes, needles and certain other medical equipment – Part 1: Genera

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED •

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED •

DESCRIPTION

N/a

JUSTIFICATION

(b)(6) 2010-05-12

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED •

DESCRIPTION

JUSTIFICATION

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 594-2:1998 Conical fittings with a 6% (Luer) taper for syringes, needles and certain other medical equipment – Part 2

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3]	# 6-129	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☑

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

ISO 594-2:1998 Conical fittings with a 6% (Luer) taper for syringes, needles and certain other medical equipment – Part 2

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

N/a

JUSTIFICATION

(b)(6) 2010-05-12

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

Form Approved: OMB No. 0910-0120; Expiration Date: 8/31/10

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 11607-1:2006 Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3] # 14-193		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☑	☐
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☑	☐
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☑	☐
If yes, was the guidance document followed in preparation of this 510k?	☑	☐

Title of guidance: 510(k) SUBMISSION FOR SHORT-TERM AND LONG-TERM INTRAVASCULAR CATHETERS

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

ISO 11607-1:2006 Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

(b)(4)

DESCRIPTION

(b)(4)

JUSTIFICATION

(b)(4)

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

(b)(4)

DESCRIPTION

(b)(4)

JUSTIFICATION

(b)(4)

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

(b)(4)

DESCRIPTION

(b)(4)

JUSTIFICATION

(b)(4)

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

ISO 11607-1:2006 Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

(b)(4)

DESCRIPTION

(b)(4)

JUSTIFICATION

(b)(4)

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

(b)(4)

DESCRIPTION

(b)(4)

JUSTIFICATION

(b)(4)

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

n/a

DESCRIPTION

(b)(6) 2010-05-12

JUSTIFICATION

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

DIN EN 868-5:2002 Packaging for terminally sterilized medical devices - Part 5

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☐	☑
FDA Recognition number [3] # _____		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☑
Title of guidance: _____		

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
DIN EN 868-5:2002 Packaging for terminally sterilized medical devices - Part 5

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED •

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED •

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED •

DESCRIPTION

JUSTIFICATION

N/A

(b)(6) 2010-05-12

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

EN 980:2008 Graphical symbols for use in the labelling of medical devices

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3]	# 5-32	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☑

Title of guidance: _____

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
EN 980:2008 Graphical symbols for use in the labelling of medical devices

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION	n/a	
JUSTIFICATION	(b)(6) 2010-05-12	

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION		
JUSTIFICATION		

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

EN 1041:2008 Information supplied by the manufacturer with medical devices

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☐	☑
FDA Recognition number [3] #		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☑

Title of guidance: _____

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

EN 1041:2008 Information supplied by the manufacturer with medical devices

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED •		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED •		
DESCRIPTION		
JUSTIFICATION		

n/a

(b)(6) 2010-05-12

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED •		
DESCRIPTION		
JUSTIFICATION		

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

DIN EN ISO 10555-1_2004 Sterile, single-use intravascular catheters Part 1_ General requirements

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3] # 6-161		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☑
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☑	☐
If yes, was the guidance document followed in preparation of this 510k?	☑	☐

Title of guidance: 510(K) SUBMISSION FOR SHORT-TERM AND LONG-TERM INTRAVASCULAR CATHETERS

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
DIN EN ISO 10555-1_ 2004 Sterile, single-use intravascular catheters Part 1_ General requirements

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION		
JUSTIFICATION		

N/a

(b)(6)

2010-05-12

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

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Form Approved: OMB No. 0910-0120; Expiration Date: 8/31/10

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 10555-3_ 1996 Sterile, single-use intravascular catheters Part 3_ Central venous catheters

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3] # 6-171		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☑
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☑	☐
If yes, was the guidance document followed in preparation of this 510k?	☑	☐

Title of guidance: [510(K)] SUBMISSION FOR SHORT-TERM AND LONG-TERM INTRAVASCULAR CATHETERS

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

ISO 10555-3_ 1996 Sterile, single-use intravascular catheters Part 3_ Central venous catheters

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED •		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED •		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED •		
DESCRIPTION		
JUSTIFICATION		

n/a

(b)(6) 2010-05-12

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 10993-1:2003 Biological evaluation of medical devices – Part 1: Evaluation and testing

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3]	# 2-98	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☑	☐
If yes, was the guidance document followed in preparation of this 510k?	☑	☐

Title of guidance: [510(K)] SUBMISSION FOR SHORT-TERM AND LONG-TERM INTRAVASCULAR CATHETERS

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

ISO 10993-1:2003 Biological evaluation of medical devices – Part 1: Evaluation and testing

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION n/a

JUSTIFICATION (b)(6) 2010-05-12

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

JUSTIFICATION

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 11070:1998 Sterile single-use intravascular catheter introducers ; German version EN ISO 11070:1999

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☐	☑
FDA Recognition number [3] # _____		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☑	☐
If yes, was the guidance document followed in preparation of this 510k?	☑	☐

Title of guidance: 510(k) SUBMISSION FOR SHORT-TERM AND LONG-TERM INTRAVASCULAR CATHETERS

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[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

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EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE

ISO 11070:1998 Sterile single-use intravascular catheter introducers ; German version EN ISO 11070:1999

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED •

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED • N/A

DESCRIPTION

JUSTIFICATION

(b)(6)

2010-05-12

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED •

DESCRIPTION

JUSTIFICATION

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

DIN EN ISO 13485:2007 Medical devices-Quality management systems-Requirements for regulatory purposes (ISO 13485:2003)

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☐	☑
FDA Recognition number [3] # _____		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☑

Title of guidance: _____

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

DIN EN ISO 13485:2007 Medical devices-Quality management systems-Requirements for regulatory purposes (ISO 13485:2003)

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☑ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED * n/a

DESCRIPTION

(b)(6) 2010-05-12

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

JUSTIFICATION

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TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 14971:2007 Medical devices – Application of risk management to medical devices

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3]	# 5-40	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☐	☑
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☑	☐
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☑

Title of guidance: _____

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
ISO 14971:2007 Medical devices – Application of risk management to medical devices

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ◆
(b)(4)

DESCRIPTION
(b)(4)

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ◆
(b)(4)

DESCRIPTION
(b)(4)

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ◆
(b)(4)

DESCRIPTION
(b)(4)

JUSTIFICATION

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EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE

ISO 14971:2007 Medical devices – Application of risk management to medical devices

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

(b)(4)

DESCRIPTION

(b)(4)

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

(b)(4)

DESCRIPTION

(b)(4)

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

(b)(4)

DESCRIPTION

(b)(4)

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

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Paperwork Reduction Act Statement

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Records processed under FOIA Request 2024-3852; Released by CDRH on 09-13-2024

EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
ISO 14971:2007 Medical devices – Application of risk management to medical devices

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
(b)(4)		☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ◆
(b)(4)

DESCRIPTION
(b)(4)

JUSTIFICATION

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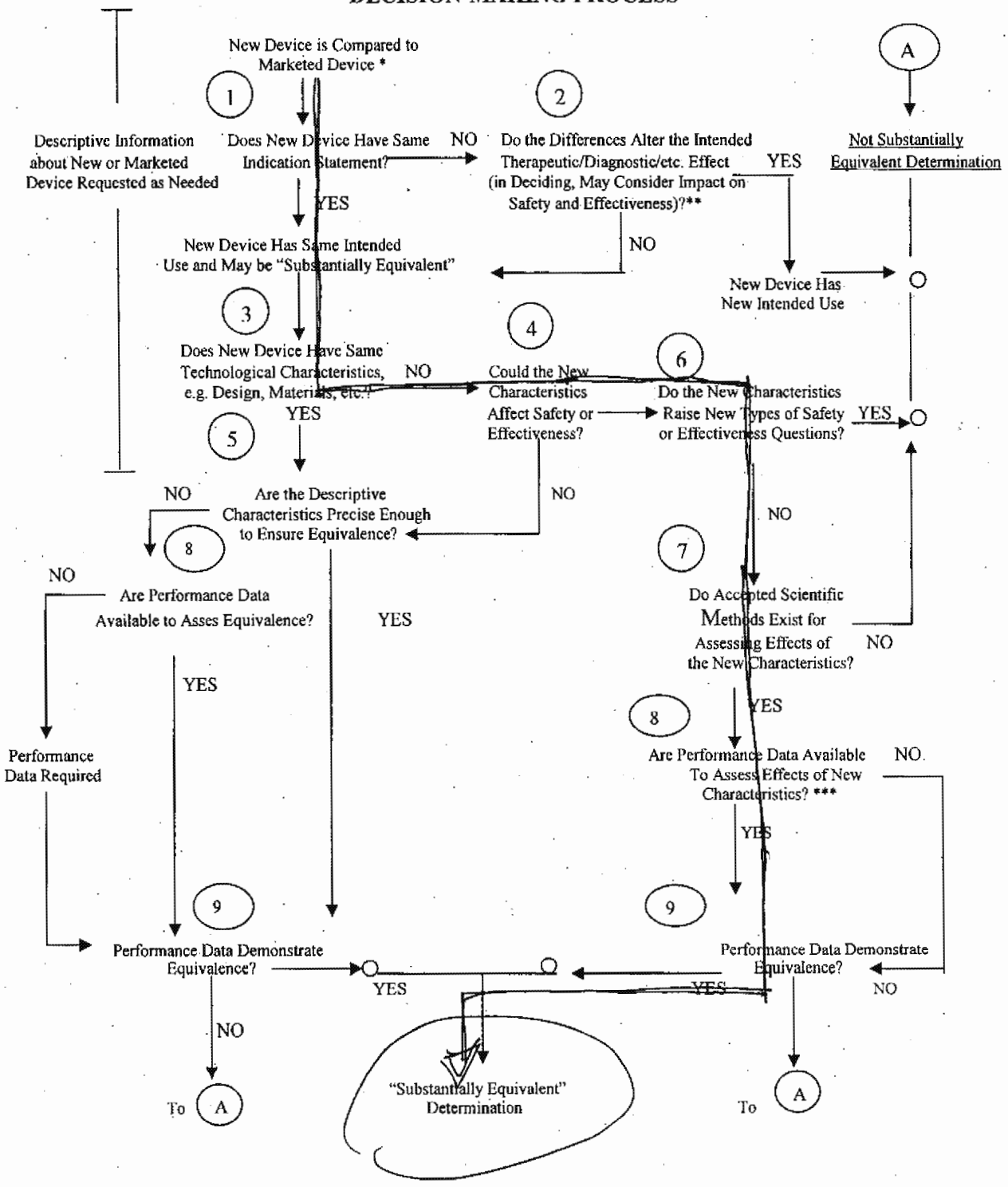
510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices: FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

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