ProCol® Vascular Bioprosthesis

Instructions for Use

Caution: *Federal Law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).*

1. DEVICE DESCRIPTION

The ProCol® Vascular Bioprosthesis is derived from bovine mesenteric vein processed with glutaraldehyde. Collateral branches are ligated with surgical suture and each device is inspected under pulsatile flow conditions at simulated physiological internal graft pressure. The ProCol® Vascular Bioprosthesis is a natural vein with competent valves. A beveled end identifies the inflow end of the device and a suture loop is attached to the outflow end of the device. Finished bioprostheses are immersed in buffered physiological saline and sterilized by exposure to gamma radiation.

Bioprostheses are available in the following models:

Model #	Internal Diameter (Nominal)	Minimum Length
HJL016-10-N	6 mm	10 cm
HJL016-25-N	6 mm	25 cm
HJL016-30-N	6 mm	30 cm
HJL016-40-N	6 mm	40 cm

2. INDICATIONS FOR USE

The ProCol® Vascular Bioprosthesis is intended for the creation of a bridge graft for vascular access subsequent to at least one previously failed prosthetic access graft.

3. CONTRAINDICATIONS

There are no contraindications related to the use of the ProCol® Vascular Bioprosthesis.

4. WARNINGS

- The device should not be used when host vessels are of insufficient quality to avoid anastomotic aneurysms.
- Do not flush or implant the bioprosthesis opposite the direction of flow as competent valves may cause excessive pressure and damage the integrity of the vessel.

- Storage at a constant temperature of between 5° C and 25° C is recommended. Store away from heat sources.
- Avoid freezing. Any bioprosthesis which has been frozen or is suspected of having been frozen should not be used for implantation.
- Do not use bioprostheses from containers found to be damaged, leaking, without adequate storage solution or with broken or missing seals.
- A bioprosthesis should not be opened unless it will be implanted shortly thereafter. No attempt should be made to resterilize or repackage the bioprosthesis once the package has been opened. Any remnants of the bioprosthesis should be discarded and under no circumstances should they be reused. Due to the biologic nature of the prosthesis, it cannot be returned for credit or resterilization once the sterile container has been opened.
- Do not place the container in the sterile field. The ProCol® Vascular Bioprosthesis and storage solution are sterile; **the outside of the container is not sterile.** Furthermore, the bioprosthesis and container should never be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, irradiation or alcohol.
- No other solution, drug, chemical, antibiotic, etc., should ever be added to the storage solution as irreparable damage to the tissue, which may not be apparent under visual inspection, may result.
- Use before expiration date.

5. PRECAUTIONS

- Read instructions carefully before use.
- Avoid excessive handling including pulling, stretching, twisting, squeezing or pinching. Do not allow the graft to become dry.
- Large size mismatches can result in occlusion at the anastomosis.
- The device should not be used unless there is adequate runoff. Preoperative vein mapping is highly recommended.
- The safety and effectiveness of the ProCol® Vascular Bioprosthesis in de novo patients have not been established.
- See also, Surgical Guidelines and Postoperative Care.

6. POTENTIAL ADVERSE EVENTS

The following adverse events may be associated with the use of a vascular access graft:

- needle stick damage resulting in bleeding and/or pseudoaneurysms
- hemorrhage

- anastomotic aneurysms
- steal
- patient sensitivity to device materials
- graft dilatation
- thrombosis/occlusion of graft
- infection
- pain
- swelling of affected limb
- embolic events
- stenosis
- slow wound healing
- failure to achieve access
- events associated with an invasive surgical procedure
- death

7. CLINICAL STUDIES

STUDY OBJECTIVE

A clinical study compared primary and secondary patency rates at one year and the overall incidence of postoperative complications for patients receiving the ProCol® Vascular Bioprosthesis as a vascular access graft to patients receiving standard synthetic vascular access grafts. All patients had at least one prior failed synthetic vascular access graft.

STUDY DESIGN

The multi-center, non-randomized clinical study compared the access patency of the ProCol® Vascular Bioprosthesis (n=183) to the results of a concomitant control cohort subsequent to the loss of a previously placed synthetic vascular graft. The concomitant control cohort (n=93) were those subjects in whom vascular access was established with a synthetic access graft during the same implanting period as the treatment arm, by surgeons in the same group or center but not participating in the trial. Additionally, when the implant and abandonment dates were available for the ProCol® patient's prior failed graft (n=128), the secondary patency of the prior graft (internal control cohort) was compared to the secondary patency of the ProCol® cohort.

Efficacy was determined by primary and secondary patency of the ProCol® Vascular Bioprosthesis as compared to the concomitant control cohort and the internal control cohort (for secondary patency only). Primary patency was defined as any event that caused a loss of graft patency or required an intervention to the lumen of the graft. Secondary patency was the cumulative graft survival time from graft placement until the graft was considered no

longer salvageable and deemed abandoned. Safety was measured by comparing the frequency of anticipated and unanticipated events in the ProCol® Vascular Bioprosthesis to the concomitant control cohort.

Table 1: Characteristics of the Study Population

Characteristic	ProCol®	Concomitant Control[1]	P-value[2]
Female	59.6%	59.1%	1
Hypertension	85.8%	90.2%	0.342
Diabetes	44.8%	54.3%	0.160
Hypercoagulation	20.2%	8.7%	**0.015**
African American	71.3%	75.0%	0.221
Number prior grafts	2.08 ± 1.13	1.63 ± 0.94	**<0.001**

[1] Concomitant control = commercially available synthetic graft, generally manufactured with ePTFE.

[2] Bold indicates statistical significance.

The total implant time represented in this study was 188.16 years (ProCol® bioprosthesis) and 91.68 years (concomitant control). Primary patency was defined as any event that caused a loss of graft patency or required an intervention to the lumen of the graft. The primary patency was similar between the two cohorts. The secondary patency for the ProCol® Vascular Bioprosthesis was significantly higher, per log rank, than both the concomitant control (P=.0361) and internal control cohorts (P<.0001) (Table 2). All grafts were included in the analysis.

Table 2: Kaplan-Meier Graft Survival Rates for Hemodialysis Access

Study Cohort		Total (n)	Primary Patency			Secondary Patency		
			6 mo	12 mo	24 mo	6 mo	12 mo	24 mo
Concomitant control	Synthetic redo graft	93	44%	28%	16%	70%	56%	45%
Internal control	Study patient's prior synthetic graft	128	----	---	---	48%	34%	18%
ProCol® Cohort [1]	Redo grafts	183	45%	36%	22%	75%	65%	61%
DOQI-goal[2] Both first time and redo arteriovenous access grafts		-----	----	----	----	----	**70%**	**60%**

[1]Secondary patency significant at Log-rank P<.0361 for all grafts in intention to treat analysis.

[2]DOQI-goal stated in National Kidney Foundation-Dialysis Outcomes Quality Initiative Guideline 36.

Comparison of complications demonstrated the safety of the ProCol® Vascular Bioprosthesis relative to the concomitant control (Table 3). The linearized rate of all events, including those that resolved without intervention, was lower in the ProCol® cohort with a rate of 1.2 events/graft year compared to a rate of 2.0 events/graft year in the concomitant control group. With the high-risk population some technical complications were observed that were generally unrelated to the ProCol® bioprosthesis. The rate of infection and thrombosis was significantly lower with the ProCol® Vascular Bioprosthesis than with the concomitant control.

Table 3: Complications

Complication[1]	ProCol® (n=183 grafts)			Control (n=93 grafts)			Cox[3] P-value
	# Events	# Grafts with Event	Event Rate[2] /yr	# Events	# Grafts with Event	Event Rate[2] /yr	
Bleeding	3	3	0.0159	4	2	0.0436	0.1767
Cannulation Trauma	19	18	0.1010	8	6	0.0873	0.7456
Dilatation	6	6	0.0319	0	0	0.0000	0.0515
Infection	10	8	0.0531	18	15	0.1963	**0.0006**
Invasive Surgery	4	4	0.0213	3	3	0.0327	0.5504
Kinking	3	3	0.0159	1	1	0.0109	0.7958
Pseudoaneurysm	3	3	0.0159	5	3	0.0545	0.0814
Seroma	0	0	0.0000	6	4	0.0654	**0.0004**
Steal	3	3	0.0159	2	2	0.0218	0.6963
Swelling	20	12	0.1063	9	4	0.0982	0.8609
Technical Complication[4]	10	10	0.0531	0	0	0.0000	**0.0086**
Thrombosis	133	93	0.7068	124	59	1.3525	**<0.0001**
Wound Healing	7	7	0.0372	0	0	0.0000	**0.0327**
Total Events	221	128	1.1745	180	74	1.9633	**<0.0001**

1 Includes all reported events including those that resolved without intervention.

2 Event Rate = Events / Graft Year. Total time: ProCol® = 188.16 years; Control = 91.68 years.

3 Cox F-Test: compares total number of events. Bold indicates statistical significance.

4 Technical events: Anastomosed to known diseased vessel (3); graft physically compressed (4); sizing (1); implant technique (1); radiology infiltrated graft (1); and bleeding from native vessel (1).

The number of interventions per graft year of implant time to maintain the secondary patency was also lower with the ProCol® Vascular Bioprosthesis. Interventions to restore or maintain patency were performed at a rate of only 0.9726 / graft year for the ProCol® cohort compared to 1.3743 /graft year for the concomitant control cohort (P = .0031).

The relative risk of an event occurring in the concomitant control cohort was compared to the ProCol® Vascular Bioprosthesis. The relative risk was calculated as the linearized event rate of the control/ linearized event rate of the ProCol® cohort (Table 4).

Table 4: Relative Risk of Events Involving an Intervention or Loss of Patency in a High-risk Population

Event	ProCol® Event Rate #/graft year (Confidence interval[2])	Control Event Rate #/graft year (Confidence interval[2])	Relative Risk[1] (ProCol® = 1)
Infection	0.053 (0.087)	0.196 (0.285)	3.70
Thrombosis	0.707 0.813)	1.353 (1.564)	1.91
Total Complications	1.175 (1.310)	1.963 (2.216)	1.67
Total Interventions	0.973 (1.097)	1.374 (1.588)	1.41
Abandonment: Infection	0.027 (0.052)	0.120 (0.192)	4.51
Abandonment: Thrombosis	0.128 (0.176)	0.295 (0.400)	2.31
Graft Abandonment (all)	0.324 (0.398)	0.502 (0.365)	1.55

[1] Relative risk: is the occurrence of events observed in the concomitant control divided by the rate observed in the ProCol® cohort and suggests the higher frequency the event will occur.

[2] 95% upper confidence limit for linearized rate.

The ProCol® Vascular Bioprosthesis was successfully used for vascular access in a high-risk population. Secondary patency results achieved with the ProCol® Vascular Bioprosthesis approached the National Kidney Foundation-Dialysis Outcomes Quality Initiative goal of 70% at 12 months with lower complication and intervention rates than a concurrent concomitant control cohort implanted with synthetic grafts.

8. PATIENT COUNSELING INFORMATION

The decision to use a ProCol® Vascular Bioprosthesis must ultimately be made by the physician on an individual patient basis. The decision should be based upon a careful evaluation of the long and short term risks to the patient and after consideration of the available alternate methods of treatment.

A full explanation of the possible benefits and risks should be given to each prospective patient prior to surgery.

9. HOW SUPPLIED

Bioprostheses are individually packaged on glass mandrils, immersed in buffered physiological saline. The bioprosthesis is supplied sterile, individually packaged in a glass container with a screw-cap closure and seal. Each unit is identified by a unique serial number.

The shelf life is 54 months, devices should not be used after the expiration date.

Bioprostheses are intended for single use only.

10. INSTRUCTIONS FOR USE

PREPARATION OF BIOPROSTHESIS

Examine the packaged device prior to opening. Examine the container carefully for evidence of damage, leakage, and broken or missing seals.

Warning: Do not use bioprostheses from containers found to be damaged, leaking, without adequate storage solution, or with broken or missing seals.

Rinse the graft per the following procedure before use: Do not allow any portion of the bioprosthesis to become dry.

1) Prepare a rinse basin containing 500 ml sterile saline with 20,000 units heparin.

2) Use forceps to grasp the plastic serial number tag and lift the bioprosthesis from the container **leaving the glass mandril in the packaging container**. Forceps should not be allowed to grip the bioprosthesis. Do not pour the contents from the container.

3) Transfer the bioprosthesis into the rinse basin.

4) Use a syringe with an intubation needle to irrigate the lumen of the bioprosthesis with at least 100 ml of the rinse solution. Hold the inflow (beveled) end of the vessel and insert the intubation needle into the lumen. Use light pressure to irrigate the device. Do not flush in the opposite direction. There should be no backpressure observed during irrigation. Backpressure indicates that the irrigation device has punctured the wall or is improperly positioned. If backpressure is noted, withdraw and reposition before continuing.

   Warning: Flush only from the beveled end to maintain direction of flow since there may be competent valves inside the device.

5) After filling the lumen, return the graft to the heparin-saline basin and cover with a sterile drape to maintain the graft in a submerged and wet condition. Allow the graft to remain submerged in the heparin-saline solution for a minimum of 5 minutes before implantation. The graft must be maintained wet, immersed in sterile saline/heparin until the time of implantation. Prior to implantation, allow the heparin-saline solution to drain from the distal end of the graft.

6) Cut the green suture loop and remove the product identification tag leaving the suture attached to the outflow end of the bioprosthesis. Flow direction is indicated by a beveled inflow end and a green suture tag at the outflow end of the bioprosthesis. The green suture loop at the outflow end of the bioprosthesis should remain attached until after orientation has been established and at least one anastomosis has been accomplished.

Warning: Do not flush or implant the bioprosthesis in the opposite direction of flow as competent valves may cause excessive pressure and damage the integrity of the vessel.

SURGICAL GUIDELINES

The bioprosthesis may be placed in a straight or loop configuration. The actual choice of surgical technique, modified in accordance with the instructions described herein, is left to the discretion of the individual surgeon. However, certain guidelines for the use of the bioprosthesis must be observed.

1) Preoperative vein mapping is highly recommended.

2) A 10mm diameter tunneler should be prepared for the implant procedure. A sheath type tunneler is highly recommended.

3) The use of atraumatic clamps with inserts is advised.

4) Aseptic technique must be observed during implantation and postoperatively.

5) The physician should consider the need for intraoperative and postoperative patient anticoagulation therapy.

6) The ProCol® Vascular Bioprosthesis is a natural vein with competent valves. It is essential to follow standard techniques for use of a vein with competent valves. **Do not reverse the graft direction.** The beveled cut at the inflow is intended to assist in preimplantation irrigation and should be trimmed to accommodate the anastomosis site.

7) Self lubricating synthetic sutures on a vascular needle are advised. Everting stitches which result in intima to intima contact and incorporate all layers of both vessels are essential - *an intimal flap will compromise patency.* In addition, the use of special atraumatic vascular instruments is strongly advised.

8) The anastomoses must be precise with meticulous attention to detail (e.g., no flaps, evenly spaced everting sutures, excellent hemostasis, etc.). End to side anastomoses can accommodate minor size discrepancies between the bioprosthesis and the host vessel thereby preventing narrowing at the anastomosis site. Large size discrepancies can result in occlusion of the anastomosis .

9) Whenever possible, the arterial anastomosis should be accomplished first and the bioprosthesis allowed to fill and elongate for approximately 5-10 minutes. Irrigate the graft frequently to prevent drying.

10) After at least one anastomosis has been established, trim the outflow end of the vessel to remove the green suture loop.

11) Create a tunnel approximately 1cm in diameter. It is recommended that configurations that may compress or kink the bioprosthesis such as loops with a very small radius or passage across the flexor side of a joint should be avoided. **To avoid impingement of the graft and to maximize compliance it is critical to prepare a properly sized tunnel using a tunneler with a 10mm diameter. A sheath type tunneler is recommended.**

12) Pass the graft through the tunnel. The graft should be pressurized when passing through the tunnel, to reduce the potential for kinking or twisting.

13) For loop configurations, the loop should be generous to avoid kinking. The bioprosthesis should not cross a joint.

14) Determination of the final length should be made with the bioprosthesis pressurized and slight tension applied to avoid post implantation lengthening and possible kinking. The length of the bioprosthesis may be trimmed as necessary.

15) After both anastomoses are completed, observe the graft while under pressure to insure that the bioprosthesis does not kink or twist.

16) Examine the bioprosthesis for leakage. An initial small amount of oozing is acceptable. A leaking branch may be repaired with suture following standard surgical techniques.

17) It is important to determine by Doppler or direct flow measurements that blood flow is adequate and that graft integrity has not been compromised during implantation.

18) Prophylactic measures to prevent infection should be taken before, during and after surgery.

11. POSTOPERATIVE CARE

TREATMENT

1) Prophylactic measures to prevent infection should be taken.

2) The physician should consider the need for postoperative patient anticoagulation therapy.

3) Observe for indications of steal phenomenon. The bioprosthesis is amenable to banding procedures.

4) Whenever possible a thrombectomy should be attempted to salvage a nonpatent ProCol® Vascular Bioprosthesis. Techniques to avoid damaging the luminal lining should be utilized. The thrombus can usually be extracted through standard atraumatic percutaneous or surgical methods. When a cause has not been identified, vein mapping is recommended to determine the suitability of the patient's own vasculature and determine the source of the problem so preventive measures can be taken.

5) If additional graft length is required to complete a graft revision it is recommended that another ProCol® Vascular Bioprosthesis be used to provide the additional material. A 10cm length model is available for this purpose.

6) There should be adequate outflow to prevent exposing the device to elevated internal pressures for a prolonged period of time. If increased venous pressure is observed, the potential for graft dilatation should be considered and the cause of the venous outflow obstruction addressed. When necessary, revision should be performed to excise the dilated area and replace the excised section with a section of a new ProCol® bioprosthesis.

7) Improper cannulation methods can result in the formation of a pseudoaneurysm. When necessary, revision should be performed to excise the pseudoaneurysm and replace the excised section with a section of a new ProCol® bioprosthesis.

PATIENT INSTRUCTIONS

The health care provider is responsible for instructing the patient as to proper postoperative care.

1) Patients should be counseled that the graft site should be kept clean.

2) Patients should be should be cautioned not to compress the graft during normal activities and that compression can be a cause of thrombosis.

3) The patient should advise the clinic that they have a biologic access graft with characteristics similar to a native fistula.

4) Needle sites should be rotated.

5) The application of clamps, compression bandages and blood pressure cuffs should be avoided.

6) The physician should instruct the patient to monitor the graft frequently for the presence of flow to allow prompt intervention when a thrombus occurs.

INSTRUCTIONS TO THE DIALYSIS CLINIC

The health care provider is responsible for instructing the dialysis clinic in proper use of the graft.

1) The dialysis clinic should be notified that the patient has a bioprosthetic vascular access graft with characteristics similar to a native fistula.

2) At least two weeks should be allowed prior to use for vascular access. The physician will determine when the bioprosthesis may be accessed.

3) The bioprosthesis will provide minimal resistance, as would native tissue, and one should exercise caution so as not to lacerate completely through both sides of the graft. This is best accomplished by inserting the needle at a 25 degree angle.

4) When the beveled edges of the needles are rotated during use and not returned to the puncture position prior to removal, a laceration may occur to any graft.

5) Procedures applicable to accessing a native fistula should be practiced.

   Following is a recommended procedure for beginning to access the graft. Whenever the patient has an existing catheter, it is preferable to begin with single needle access. A single 17 gauge needle and a flow rate of 200-250 ml/min. should be used for initial access. After one week, switch to a 16 gauge needle. Continue to use one needle for three weeks at a 300-350 ml/min. flow rate, keeping arterial and venous pressures under 200 mmHg. After four weeks, two needle access may be initiated using 16 gauge needles at a 350 ml/min. flow rate, keeping arterial and venous pressures under 200 mmHg. After six weeks, a 15 gauge needle may be used with no restrictions.

6) Hemostasis can be achieved with light finger pressure. The application of clamps and compression bandages should be avoided.

7) Rotation of needle sites is essential.

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