Formula™ 414 Renal Stent System

Instructions for Use

~~I-FORX-0909-329-04~~ New Art code used as labeling identifier, with bar code, to be established

FORMULA™ 414 RENAL STENT SYSTEM

CAUTION: U.S. federal law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

DEVICE DESCRIPTION

The Formula™ 414 Renal Stent is a balloon-expandable stent made of 316L stainless steel with a slotted tube configuration. It is pre-mounted on a balloon catheter, which serves as the delivery system. The stent is positioned between two radiopaque marker bands, which are located inside the balloon at the proximal and distal tapers of the balloon. The cannula design of the Formula™ 414 Renal Stent provides a low outside diameter profile, which permits use with a 5 French sheath and 6 French guiding catheter. The balloon-expandable Formula™ 414 Renal Stent is pre-mounted on a 80 cm or 135 cm rapid exchange balloon catheter delivery system. The stent is available in 5 -7 mm nominal expanded diameters with lengths of 12 through 20 mm, as shown in **Table 1**.

Table 1: Device Specifications (diameters and lengths)

Model	Catheter Length (cm)	Stent Diameter (mm)	Stent Length (mm)	Minimum Guiding Catheter/Sheath*- Inside Diameter (inches)	Guiding Catheter/ Sheath (French Size)
FORX4-14-80-5-12	80	5	12	.068	6F/5F
FORX4-14-80-5-16	80	5	16	.068	6F/5F
FORX4-14-80-5-20	80	5	20	.068	6F/5F
FORX4-14-80-6-12	80	6	12	.068	6F/5F
FORX4-14-80-6-16	80	6	16	.068	6F/5F
FORX4-14-80-6-20	80	6	20	.068	6F/5F
FORX4-14-80-7-12	80	7	12	.068	6F/5F
FORX4-14-80-7-16	80	7	16	.068	6F/5F
FORX4-14-80-7-20	80	7	20	.068	6F/5F
FORX4-14-135-5-12	135	5	12	.068	6F/5F
FORX4-14-135-5-16	135	5	16	.068	6F/5F
FORX4-14-135-5-20	135	5	20	.068	6F/5F
FORX4-14-135-6-12	135	6	12	.068	6F/5F
FORX4-14-135-6-16	135	6	16	.068	6F/5F
FORX4-14-135-6-20	135	6	20	.068	6F/5F
FORX4-14-135-7-12	135	7	12	.068	6F/5F
FORX4-14-135-7-16	135	7	16	.068	6F/5F
FORX4-14-135-7-20	135	7	20	.068	6F/5F

*See manufacturer specifications for French (FR) equivalent

INTENDED USE

The Formula™ 414 Balloon-Expandable Renal Stent System is indicated for use in patients with atherosclerotic disease of the renal arteries following sub-optimal percutaneous transluminal renal angioplasty (PTRA) of a de novo or restenotic lesion (≤ 18 mm in length) located within 10 mm of the renal ostium and with a reference vessel diameter of 4.5 – 7.0 mm. Suboptimal PTRA is defined as ≥ 50% residual stenosis, ≥ 20 mmHg systolic or ≥ 10 mmHg mean translesional pressure gradient, or flow-limiting dissection.

The product is intended for use by physicians trained and experienced in interventional techniques. Standard techniques for placement of arterial access sheaths, guiding catheters/introducers and wire guides should be employed.

CONTRAINDICATIONS

The Formula™ 414 Balloon-Expandable Renal Stent System is contraindicated for use in:

- Patients for whom antiplatelet and/or anticoagulant therapy is contraindicated.
- Patients who have a lesion that cannot be crossed with a wire or a balloon angioplasty catheter.
- Patients who have stenoses that cannot be dilated to permit passage of the stent.
- Patients with bleeding disorders.
- Stenting of an arterial vessel where leakage from the artery could be exacerbated by placement of a stent.
- Patients with a target lesion with a large amount of adjacent acute or subacute thrombus.

WARNINGS

- The use of this device carries the associated risks of subacute thrombosis, vascular complications and/or bleeding events. Judicious selection of patients is necessary.
- Persons allergic to 316L stainless steel may suffer an allergic reaction to this implant.

PRECAUTIONS

General

• Implantation of the stent should be performed only by physicians who have received adequate training. Adequate training consists of specific training in renal stenting techniques and procedures under the supervision of an interventional physician experienced in renal stent implantation.

• Stent placement should only be performed at hospitals where emergency renal artery bypass graft surgery can be readily performed.

• Subsequent restenosis may require redilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of endothelialized Formula™ 414 Renal Stents is unknown at present.

Stent Placement

- Manipulation of the Formula 418 Stent System requires fluoroscopic control.

- The stent is preloaded on its delivery balloon and should not be removed. Do not attempt to place stent on another balloon catheter for deployment.

- Deploy the stent over a wire guide not exceeding 0.014 inch diameter.

- DO NOT wipe or clean stent or catheter with organic solvent (i.e., isopropyl alcohol).

- DO NOT expose catheter to temperatures above 130 °F (54.4 °C).

- DO NOT use power injection systems with the delivery system.

- DO NOT rotate any part of the system during deployment.

- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is particularly important during removal of the catheter from packaging, placement over the wire guide and advancement through the large-bore Tuohy-Borst "Y" adapter and guiding catheter hub.

- Do not pre-inflate balloon prior to stent deployment. (See **Preparation of Balloon Catheter** section in these Instructions for Use)

- Use only the appropriate balloon inflation media. The standard inflation medium is a 1:1 mixture of contrast medium and normal saline. Do not use air or any gaseous substance as a balloon inflation medium.

- Expansion of the stent should not be undertaken if the stent is not properly positioned in the vessel. (See **Removal of Unexpanded Stent** section in these Instructions for Use.)

- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on the product label. Use of pressures higher than specified on the product label may result in a ruptured balloon, with possible intimal damage and dissection.

- Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stent and may cause acute closure of the vessel, requiring additional intervention (further dilatation or placement of additional stents).

- Use prior to the expiration date on the package label.

- Intended for one-time use. (Do not re-sterilize.)

- The use of mechanical atherectomy devices within an implanted stent may cause damage to the stent.

- Repositioning of the device after deployment is not possible.

MAGNETIC RESONANCE IMAGING

Non-clinical testing has demonstrated that the Formula™ renal stent is **MR Conditional** according to ASTM F2503, *Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment.* A patient with this stent can be scanned safely anytime after placement under the following conditions.

- Static magnetic field of 3-Tesla or 1.5-Tesla
- Maximum spatial magnetic gradient of 720 Gauss/cm or less
- Product of the spatial gradient and the static magnetic field of 21.6 T2/m or less
- MR system reported whole body average specific absorption rate (SAR) of 3.0 W/kg or less for 15 minutes of scanning

Non-clinical evaluation was conducted in an MR system (Excite, General Electric Healthcare) with a maximum spatial magnetic gradient field of 720 Gauss/cm as measured with a gaussmeter in the position of the static magnetic field pertinent to the patient (i.e., outside of scanner covering, accessible to a patient or individual). In non-clinical testing, single and two overlapped Formula™ renal stents produced a maximum temperature rise of 2.6 °C and 3.3 °C, respectively, during 15 minutes of MRI (i.e., for one scanning sequence) performed in a 3 Tesla MR system (3 Tesla/128 MHz, Excite, Software G3.0-052B, General Electric Healthcare) at an MR system reported whole body averaged SAR of 3.0 W/kg (associated with a calorimetry measured whole body averaged value of 2.8 W/kg).

The effect of heating in the MRI environment for stents with fractured struts is unknown.

Image Artifacts

MR image quality may be compromised if the area of interest is within the lumen or within approximately 15 mm of the Formula™ renal stent. Therefore, it may be necessary to optimize MR imaging parameters for the presence of this metallic stent.

MedicAlert Foundation

Cook recommends that the patient register the MR conditions disclosed in this IFU with the MedicAlert Foundation. The MedicAlert Foundation can be contacted at:

Mail: MedicAlert Foundation International
2323 Colorado Avenue
Turlock, CA 95382

Phone: 888-633-4298 (toll free)
209-668-3333 (from outside the US)

Fax: 209-669-2450

Web: www.medicalert.org

POTENTIAL ADVERSE EVENTS

Adverse events that may be associated with the use of a renal stent are presented in the following alphabetical list and include, but are not limited to:

- Abscess
- Allergic reaction to stainless steel or contrast agents
- Arrhythmias (ventricular fibrillation, ventricular tachycardia, other)
- Arteriovenous fistula
- Bowel infarct
- Death
- Dialysis
- Dissection
- Drug reaction to antiplatelet agents
- Drug reaction, allergic reaction to contrast media
- Emboli (air, tissue, or thrombotic emboli) resulting in tissue ischemia/infarction
- Emergency surgery to correct vascular complications
- Emergent renal artery bypass surgery
- Extremity ischemia/amputation
- Fever
- Gastrointestinal symptoms from anticoagulation/antiplatelet medication
- Hematoma at vascular access site
- Hemorrhage requiring transfusion
- Hypersensitivity reactions
- Hypotension/hypertension
- Infection and pain at vascular access site
- Intimal tear
- Kidney infarct
- Myocardial infarction
- Myocardial ischemia
- Nephrectomy
- Peripheral neuropathy
- Pseudoaneurysm at vascular access site
- Pseudoaneurysm formation
- Renal artery thrombosis, aneurysm, rupture, perforation, occlusion, spasm, or restenosis
- Renal insufficiency or failure
- Stent migration or embolization
- Stent misplacement
- Stroke/cerebral vascular accident
- Tissue necrosis or ulceration

CLINICAL STUDY

Results from a multi-center clinical study (IDE G070014, also known as the REFORM ("REnal FORMula Stent") study) demonstrate the safety and effectiveness of the Formula™ stent. Specifically, the 9-month primary patency rate was 91.7%, meeting the performance goal of 60%. In addition, use of the Formula™ stent was associated with a low rate of major adverse events (MAEs), high technical and procedural success rates, improvement in hypertension, and maintenance of renal function.

An overview of the REFORM study is presented in Table 2.

Table 2: Overview of the REFORM study

Device	Formula™ Balloon-Expandable Renal Stent System
Study Design	Non-randomized, prospective, single-arm, multi-center clinical study

Table 2: Overview of the REFORM study

Patients Enrolled	100 (44 male and 56 female)
Number of Sites	7 investigational sites
Primary Endpoint	Primary patency at 9 months, defined as the ≤60% diameter stenosis and intervention-free since the initial procedure. Analysis done on a per-lesion basis. Patency was assessed by ultrasound analysis (or quantitative angiography, if necessary) by an independent core laboratory.
Secondary Endpoints	• MAEs: Incidence of major adverse events, defined as procedure- or device-related events of death, Q-Wave MI, clinically driven target lesion revascularization (TLR), and significant embolic events (defined as unanticipated kidney/bowel infarct, lower extremity ulceration or gangrene, or kidney failure). MAEs were reported as percentage of patients with MAEs, after 30 days, 9 months, 24 months, and 36 months (from the previous period and cumulative), using all enrolled patients. In addition to MAE rate, the rates of individual events (death, Q-Wave MI, clinically driven target lesion revascularization (TLR), unanticipated kidney/bowel infarct, lower extremity ulceration or gangrene, and kidney failure) will also be reported (from the previous period and cumulative), using all enrolled patients. • Change in blood pressure: Systolic and diastolic blood pressures were measured at baseline and 1, 9, 24, and 36 months and the group average at each time point reported. The change at 9 months from baseline, for systolic and diastolic pressure, was calculated for each enrolled patient. Confidence intervals (95%) for the average changes were reported. • Change in Antihypertensive Medications: Number and dosage of antihypertensive medications at baseline and at 1, 6, 9, 12, 18, 24, and 36 months was collected. The group average number of antihypertensive medications at each time point was reported. In addition, data was reported as a percentage of patients at 9 months with a decrease in medication (in dose or amount), no change in medication, or increase in medication compared to baseline. • Change in Renal Function: Improvement and/or stabilization of renal function (as measured by estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation) were measured at baseline and at 1, 9, 24, and 36 months, with the group average reported at each time point. The change at 9 months from baseline was calculated for each enrolled patient. • Technical Success: Technical success is defined as successful delivery and deployment of a Formula™ Balloon-Expandable Stent. It was reported as a percentage of enrolled patients. • 30-day Clinical Success: 30-day clinical success is defined as a vessel with <30% residual stenosis immediately after stent placement and no major adverse events within 30 days of implant. Results are expressed as a percentage of stented arteries and a percentage of enrolled patients. • Target Lesion Revascularization: TLR is defined as any angioplasty or bypass surgery performed for thrombosis or >60% diameter restenosis of the originally treated site following the initial procedure. It was evaluated at 9 months and reported as a percentage of stented arteries and a percentage of enrolled patients. • Acute Procedural Success: Acute procedural success is defined as a

Table 2: Overview of the REFORM study

	vessel with <30% residual stenosis determined angiographically immediately after stent placement and no major adverse events before discharge. It was reported as a percentage of stented arteries and a percentage of enrolled patients.
Study Hypothesis	Renal arteries treated with the Formula™ Balloon-Expandable Stent will have a primary patency rate at 9 months on a per-stented artery basis that meets a performance goal of 60%.
Patient Follow-up	1-month clinic visit: Assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events. 6-month telephone contact: Patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient. 9-month clinic visit with ultrasound: Assessments of blood chemistry, blood pressure, antihypertensive medications, adverse events, ultrasound for evidence of stenosis. Patients with non-interpretable ultrasounds were required to have an angiogram. 12-month telephone contact: Patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient. 18-month telephone contact: Patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient. 24-month clinic visit: A 2-year office visit includes assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events. 36-month clinic visit: A 3-year office visit includes assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events.

Study Population Demographics and Baseline Parameters

Patient demographics (Table 3) and medical history (Table 4) were consistent with patient populations described in published literature of renal stent intervention. The most prevalent co-morbidities were hypertension (97%), hypercholesterolemia (83%), past or current smoker (75%), and peripheral vascular disease (57%) (Table 4). As assessed by the imaging core lab, the mean lesion length was 7.7 mm, the mean pre-procedure percent diameter stenosis was 57.4%, and the mean post-PTRA percent diameter stenosis was 46.9%.

Table 3: Patient Demographics

Demographic	Value (N = 100 patients)
Sex	
Male	44.0% (44/100)
Female	56.0% (56/100)
Age (years, mean ± SD (range))	72 ± 10 (42 - 92)
Height (inches, mean ± SD (range))	65.2 ± 4.1 (50 - 74)
Weight (lbs, mean ± SD (range))	177.4 ± 33.7 (102 - 290)
Ethnicity	
Caucasian or White	82.0% (82/100)
Black or African American	12.0% (12/100)
Hispanic or Latino	4.0% (4/100)
American Indian or Alaska Native	1.0% (1/100)
Other	1.0% (1/100)
Native Hawaiian or other Pacific Islander	0.0% (0/100)
Asian	0.0% (0/100)

Table 4: Medical History

Past or Current Medical Condition	Percent Patients (number/total number)
Diabetes	
Total	43.0% (43/100)
Type I	2.0% (2/100)
Type II	41.0% (41/100)
Hypercholesterolemia	83.0% (83/100)

Table 4: Medical History

Past or Current Medical Condition	Percent Patients (number/total number)
Hypertension[1]	
Total	97.0% (97/100)
Pre-hypertension	14.0% (14/100)
Stage 1	31.0% (31/100)
Stage 2	52.0% (52/100)
Stroke/CVA	17.0% (17/100)
Transient Ischemic Attack (TIA)	11.0% (11/100)
Asthma	9.0% (9/100)
Chronic Obstructive Pulmonary Disease (COPD)	19.0% (19/100)
Peripheral Vascular Disease	57.0% (57/100)
Left Ventricular Hypertrophy (LVH)[2]	27.8% (27/97)
Rutherford Classification (TASC 2000)[2]	
0: Asymptomatic	67.7% (63/93)
1: Mild Claudication	11.8% (11/93)
2: Moderate Claudication	7.5% (7/93)
3: Severe Claudication	10.8% (10/93)
4: Ischemic Rest Pain	2.2% (2/93)
5: Minor Tissue Loss, Ulceration	0% (0/93)
6: Major Tissue Loss, Gangrene	0% (0/93)
Microalbuminurea	
Yes	8.0% (8/100)
No	52.0% (52/100)
Unknown	40.0% (40/100)
Renal Insufficiency	46.0% (46/100)
Previous Renal Bypass	0% (0/100)
Congestive Heart Failure (CHF)	
Total	26.0% (26/100)
NYHA Class I	6.0% (6/100)
NYHA Class II	6.0% (6/100)
NYHA Class III	3.0% (3/100)
NYHA Class IV	0% (0/100)
Unknown	11.0% (11/100)
Previous Myocardial Infarction (MI)	30.0% (30/100)
Current or Past Smoker	75.0% (75/100)
Current Smoker	14.0% (14/100)

[1] Definitions for hypertension categories:
Pre-hypertension = systolic 120 - 139 mmHg, diastolic 80 - 89 mmHg.
Stage 1 = systolic 140 - 159 mmHg, diastolic 90 - 99 mmHg.
Stage 2 = systolic > 160 mmHg; diastolic > 100 mmHg.
If systolic and diastolic pressures were different categories, the higher category was chosen.
[2] "Unknown" was not an available answer for the LVH and Rutherford Classification questions; patients without available data were removed from the denominator.

Safety and Effectiveness Results

Safety Results

Major adverse events included procedure- or device-related events of death, Q-wave myocardial infarction (MI), clinically-driven target lesion revascularization (clinically-driven TLR, defined as any angioplasty or bypass surgery performed for thrombosis or >60% diameter stenosis of the originally treated site following the initial procedure in the presence of clinical symptoms or laboratory evidence indicative of the need for revascularization), and significant embolic events (defined as unanticipated kidney or bowel infarct, lower extremity ulceration or gangrene, or kidney failure). All MAEs, except clinically-driven TLRs, were adjudicated by the CEC. The 9-month MAE rate was 2.2% (two clinically-driven TLRs), demonstrating the safety of the Formula™ stent (Table 5 and Table 6, respectively).

Adverse effects that occurred in the PMA clinical study

Table 5: Protocol Defined Major Adverse Events through 9 Months

Major Adverse Event	Number of Events	Percent Patients (number/total number)[1]
30-day Events		
CEC Adjudicated Death	0	0.0% (0/98)
CEC Adjudicated Q-wave Myocardial Infarction (MI)	0	0.0% (0/98)
Clinically-driven Target Lesion Revascularization (TLR)	0	0.0% (0/98)
CEC Adjudicated Significant Embolic Events	0	0.0% (0/98)
Total	0	0.0% (0/98)
9-month Events		
CEC Adjudicated Death	0	0.0% (0/92)
CEC Adjudicated Q-wave Myocardial Infarction (MI)	0	0.0% (0/92)
Clinically-driven Target Lesion Revascularization (TLR)	2	2.2% (2/92)

CEC Adjudicated Significant Embolic Events	0	0.0% (0/92)
Total	2	2.2% (2/92)

[1] Total number = patients participating in study at end of the time period (i.e., 30 days or 300 days post-procedure) plus discontinued patients who experienced a MAE during the specified time period.

Table 6: Protocol Defined Major Adverse Events, Stent Thrombosis, and Hemorrhagic Complications

Event	Number of Events	Percent Patients (number/total number)[1]	95% Confidence Interval
Major Adverse Events			
To 30-days	0	0.0% (0/98)	[0.0%, 3.7%]
Device-related Death[2]	0	0.0% (0/98)	[0.0%, 3.7%]
Index-procedure-related Death	0	0.0% (0/98)	[0.0%, 3.7%]
Q-wave Myocardial Infarction[2]	0	0.0% (0/98)	[0.0%, 3.7%]
Clinically-driven TLR[3]	0	0.0% (0/98)	[0.0%, 3.7%]
Significant Embolic Events[2]	0	0.0% (0/98)	[0.0%, 3.7%]
From 31 days to 9-months	2	2.2% (2/92)	[0.3%, 7.6%]
Device-related Death[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Q-wave Myocardial Infarction[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Clinically-driven TLR[3]	2	2.2% (2/92)	[0.3%, 7.6%]
Significant Embolic Events[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Total	0	2.2% (0/92)	[0.3%, 7.6%]

Table 6: Protocol Defined Major Adverse Events, Stent Thrombosis, and Hemorrhagic Complications

Event	Number of Events	Percent Patients (number/total number)[1]	95% Confidence Interval
Device-related Death[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Index-procedure-related Death	0	0.0% (0/92)	[0.0%, 3.9%]
Q-wave Myocardial Infarction[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Clinically-driven TLR[3]	2	2.2% (2/92)	[0.3%, 7.6%]
Significant Embolic Events[2]	0	0.0% (0/92)	[0.0%, 3.9%]
9-Month TLR[3], per lesion	2	2.0% (2/102)	[0.2%, 6.9%]
Stent Thrombosis	0	0.0% (0/97)	[0.0%, 3.7%]
Acute (≤24 hours)	0	0.0% (0/100)	[0.0%, 3.6%]
Sub-acute (>24 hours to ≤30 days)	0	0.0% (0/99)	[0.0%, 3.7%]
Late (>30 days to ≤90 days)	0	0.0% (0/97)	[0.0%, 3.7%]
Hemorrhagic Complication through 30 Days			
Major	2	2.0% (2/99)	[0.2%, 7.1%]
Intracranial hemorrhage	0	0.0% (0/99)	[0.0%, 3.7%]
GI Bleeding	1	1.0% (1/99)	[0.0%, 5.5%]
Bleeding at the access site	1	1.0% (1/99)	[0.0%, 5.5%]
Other Bleeding	0	0.0% (0/99)	[0.0%, 3.7%]
Minor[4]	1	1.0% (1/99)	[0.0%, 5.5%]

[1] Unless otherwise indicated, "Total number" = patients participating in study at end of the time period (i.e., 30 days or 300 days post-procedure) plus discontinued patients who experienced a MAE during

the specified time period.
[2] CEC Adjudicated
[3] Target Lesion Revascularization
[4] Any bleeding which does not require >1 unit packed red blood cells

Effectiveness Results

One hundred twenty-two (122) Formula™ stents were placed to treat 115 renal artery lesions. Most lesions (93.0%) were treated with single stents. Residual diameter stenosis of < 30% was seen in 95.6% (109/114) of lesions. Therefore, the Formula™ stent was effective in establishing patency at the conclusion of the procedure.

Primary Endpoint

The 9-month primary patency rate met the performance goal. The 9-month primary patency rate was 91.7% and the lower limit of the 95% two-sided confidence interval is 84.2%; the latter is greater than the performance goal of 60% ($p < 0.0001$). These results demonstrate the effectiveness of the Formula™ stent in treating atherosclerotic lesions of the renal arteries following suboptimal angioplasty.

Secondary Endpoints

Secondary endpoint analyses included major adverse events (MAEs), device-related success measures (i.e., technical success, acute procedural success, and 30-day clinical success), blood pressure-related outcomes (i.e., systolic and diastolic blood pressure, use of anti-hypertensive medications, and improved or cured hypertension), and renal function (as measured by eGFR).

Device-related success measures ranged from 94.8% to 97.4%. Technical success (successful delivery and deployment of a Formula™ stent), acute procedural success (< 30% residual stenosis post-procedure by core lab analysis and no MAEs before discharge), and 30-day clinical success (< 30% residual stenosis post-procedure by core lab analysis and no MAEs within 30 days) outcomes are summarized in Table 7. These results support the safety and effectiveness of the Formula™ stent in establishing renal artery patency.

Table 7: Device-related Success Measures

Measure	Analysis Percentage (number/total number)	
	Per Patient	**Per Lesion**
Technical Success	97.0% (97/100)	97.4% (112/115)
Acute Procedural Success	94.9% (94/99)	95.6% (109/114)
30-day Clinical Success	94.8% (92/97)	95.5% (106/111)

Blood pressure-related outcomes demonstrated significantly decreased systolic blood pressure from pre-procedure to 9-month follow-up (p = 0.003) and that most patients (85%) were taking the same number or fewer anti-hypertensive medications at 9 months (Table 8 and Table 9, respectively). These data demonstrate the clinical utility of the Formula™ stent and suggest that revascularization with the Formula™ stent does not adversely affect blood pressure outcomes.

Table 8: Blood Pressure Results

Blood Pressure	Mean ± SD (range, total patients)	
	Systolic (mmHg)	Diastolic (mmHg)
Pre-procedure	150.3 ± 20.6 (102 - 202, n = 100)	73.9 ± 12.9 (43 - 112, n = 100)
1 Month	137.9 ± 18.7 (96 - 195, n = 98)	72.9 ± 12.2 (46 - 115, n = 98)
9 Months	140.5 ± 21.0* (97 - 203, n = 87)	77.5 ± 12.9 (51 - 122, n = 87)
Change at 9 Months from Pre-procedure (Bonferroni adjusted 95% two-sided confidence interval)	[-16.5, -2.7], n = 87	[-0.3, 7.4], n = 87

*p = 0.003 compared to pre-procedure systolic blood pressure (Bonferroni adjusted p-value).

Table 9: Anti-hypertensive Medication Results

Anti-hypertensive Medications	Mean ± SD (range, total patients)
Number Per Patient	
Pre-procedure	2.7 ± 1.2 (0 - 6, n = 100)
1 Month	2.6 ± 1.2 (0 - 5, n = 98)
9 Months	2.5 ± 1.1 (0 - 5, n = 87)

Anti-hypertensive Medications	Mean ± SD (range, total patients)
Number of Medications at 9 Months *(change from pre-procedure)*	
Decrease	23.0% (20/87)
No Change	62.1% (54/87)
Increase	14.9% (13/87)
Dose of Medications at 9 Months *(change from pre-procedure)*	
Decrease	29.9% (26/87)
No Change	42.5% (37/87)
Increase	27.6% (24/87)

In addition, renal function was maintained (i.e., did not worsen) from pre-procedure to 9-month follow-up based on serum creatinine levels and eGFR), further demonstrating the clinical utility of the Formula™ stent and suggesting that revascularization with the Formula™ stent does not adversely affect renal function.

PRODUCT RECOMMENDATIONS

Wire Guide Use and Selection

The Formula™ 414 Renal Stent System is compatible with 0.014 inch wire guides.

Guiding Catheter/Introducer Selection

Correct guiding catheter/introducer selection and technique are necessary for use of the stent. Ensure that the inside lumen of the guiding catheter/introducer is of sufficient size to allow unobstructed passage of the Formula 414 Renal Stent System. **NOTE:** Minimum inside diameter requirements for the guiding catheter/introducer are shown in Table 1.

Standard renal catheter curves must be selected to provide adequate guiding catheter/introducer "back-up support" to achieve successful stent placement.

Stent Size Selection

The stent selected should have an expanded diameter approximately equal to, or slightly larger than, the estimated reference diameter of the artery to be stented. The length of the stent should be chosen to adequately cover the length of the lesion. A compliance card is provided with the product to facilitate selection of an appropriate size of stent.

INSTRUCTIONS FOR USE

The Formula 414 Renal Stent System is used in conjunction with equipment required for a conventional PTA procedure including, but not limited to, a vascular access set, arterial sheath, guiding catheter, wire guide and inflation device.

Lesion/Vessel Preparation

Stent placement must take into account proximal atherosclerotic plaque, which may inhibit advancement of the stent, as well as atherosclerotic plaque beyond the lesion which may prevent advancement of the device across the primary lesion. In preparing the vessel, optimal renal vasodilation, anticoagulant and antiplatelet therapy are essential. This device is intended for treatment following suboptimal angioplasty.

Preparation of Balloon Catheter

1. Remove the Formula 414 Renal Stent System from the package, remove protective sleeve from distal tip of catheter and inspect the stent to ensure it has not been damaged.

2. Prepare balloon lumen with a standard 1:1 contrast-saline mixture as follows:

WARNING: Do not attempt pre-inflation technique to purge balloon lumen. Do not use air or any gaseous medium to inflate the balloon.

a. Using a 20 cc syringe containing 5 cc of contrast-saline mixture, apply negative pressure for 20-30 seconds.

b. Release pressure, allowing negative pressure to draw mixture into balloon lumen.

c. Detach syringe, leaving a meniscus of mixture on the hub of the balloon lumen.

d. Prepare inflation device in standard manner and purge to remove all air from syringe and tubing.

e. Attach inflation device to balloon lumen directly, ensuring no air bubbles remain at connection.

f. Pull negative pressure on inflation device.

CAUTION: Significant amounts of air in the balloon may cause uneven expansion of the stent and difficulty in deployment of the stent.

3. Moisten the stent with heparinized saline.

CAUTION: Do not use gauze sponges, as fibers may disrupt stent.

4. Flush the wire guide lumen of the balloon catheter as follows:

a. Remove the protective tube from the flushing sheath.

b. Attach a syringe filled with heparinized normal saline to a flushing hub, which is provided with a protective sheath, and inject this saline into the lumen, or c. Attach a syringe filled with heparinized normal saline to the flushing tool, insert the flushing tool into the distal end of the catheter and inject this saline into the lumen.

d. Flush solution should be seen coming out of the wire guide port proximal to the balloon.

Follow this procedure for any additional flushing.

5. Before inserting the Formula 418 Renal Stent System into the guiding catheter or introducer, be sure that a largebore Tuohy-Borst "Y" adapter or introducer valve is on the guiding catheter/introducer.

6. Advance a 0.014 wire guide of appropriate length across the lesion.

7. Insert the appropriate guiding catheter/introducer (see **Table 1**).

8. Advance the premounted stent/balloon catheter over the wire into either the introducer valve or Tuohy-Borst "Y" adapter, making sure that the wire guide exits the wire guide port proximal to the balloon.

a. If using an introducer with a valve, make sure the flared end of the insertion tool (provided in the package) is loaded over the premounted stent on the balloon catheter. Pass the insertion tool loaded with the premounted stent through the introducer valve. Push the stent/balloon catheter into the body of the introducer. Slide the insertion tool proximally up the catheter shaft away from the guiding catheter/introducer. A slight contact of the stent with the introducer may be felt, but there must be no resistance.

b. If using a Tuohy-Borst "Y" adapter, advance the premounted stent/balloon catheter over the wire and into the fully opened large-bore Tuohy-Borst "Y" adapter. Gently advance the stent/balloon catheter completely through the Tuohy-Borst "Y" adapter, taking care to maintain wire guide position. Then advance the stent/balloon catheter into the guiding catheter/introducer. A slight contact of the stent with the guiding catheter/introducer may be felt, but there must be no resistance.

WARNING: If resistance is encountered, do not force passage. Resistance may indicate damage to stent.

Positioning the Stent

1. Ensure guiding catheter/introducer stability before advancing the stent delivery balloon into the renal artery.

WARNING: If initial guiding catheter/introducer position is lost, avoid pulling or pushing the guiding catheter/introducer over the stent. If this is done, the distal end of the guiding catheter/ introducer may damage the stent.

2. Position the stent across the lesion, using both the distal and proximal balloon markers as reference points. Optimal placement requires the ends of the stent to extend beyond the margin of the lesion to be stented.

WARNING: If the Formula 414 Renal Stent System does not readily advance through the vessel, do not force. If the stent will not advance in spite of good guiding catheter/introducer support, consider dilating proximal obstructing plaque, or changing the wire guide or the guiding catheter/introducer. (Refer to instructions for Removal of Unexpanded Stent.)

NOTE: When stenting long dissections, be sure to cover the distal portion of the dissection first. It is very important not to leave distal dissections uncovered. Frequent injections of contrast around the uninflated stent/balloon will allow visualization of the extent of dissection and facilitate accurate placement of the stent.

Balloon Expansion/Stent Deployment

1. Prior to stent expansion, utilize high-resolution fluoroscopy to verify that the stent has not been dislodged during positioning.

2. Complete expansion and apposition of the stent against the vessel wall is necessary for clinical success. Do not exceed rated burst pressure of the balloon as indicated on the product label.

3. Once the stent has been deployed, post-deployment inflation is at the discretion of the operator to achieve optimum angiographic appearance. The stent may be post-dilated up to 1 mm beyond nominal labeled stent diameter.

Balloon Deflation and Removal

1. Completely deflate the balloon, by pulling a negative pressure on the inflation device or a 20 cc syringe.

WARNING: Allow enough time for the balloon to fully deflate prior to removal.

2. Slowly withdraw the balloon catheter from the stent while maintaining negative pressure on the balloon. Maintain position of the guiding catheter/introducer to prevent it from being drawn into the renal vessel. Observe under fluoroscopy to ensure that the balloon disengages from the stent.

Removal of Unexpanded Stent

Do not attempt to pull an unexpanded stent back into the guiding catheter/introducer. The stent/ balloon catheter (stent delivery system) should be withdrawn until the proximal end of the stent is aligned with the distal tip of the guiding catheter/sheath introducer. Withdraw the guiding catheter/sheath and stent delivery system as a single unit, leaving the wire guide in place.

WARNING: If stent is removed, do not attempt to reuse the device. Damage to the stent may occur upon removal.

Stent-Assisted, High-Pressure Balloon Dilatation

A deployed Formula Renal Stent may be further expanded using a low-profile, high-pressure balloon catheter. The stent should have been well embedded into the vessel wall by the deployment balloon before the lesion is recrossed. If recrossing is necessary, the position of the stent should be monitored and care should be taken to avoid displacing the stent with subsequent manipulation of wire guides and balloons. An appropriate balloon catheter should be used with a very flexible wire guide. If a Formula Renal Stent is dilated with a high-pressure balloon, the balloon should be appropriately sized for the vessel diameter. The stent may be post-dilated up to 1mm beyond nominal labeled stent diameter. Use of a new balloon for post-deployment dilatation is suggested. Avoid balloon catheters with stiff tips that might displace the stent during advancement. Avoid balloons that "wing out" and/or re-wrap inconsistently, which might displace the stent during withdrawal of the balloon from the stent.

HOW SUPPLIED

Supplied sterilized by ethylene oxide gas in peel-open packages. Intended for one-time use. Sterile if package is unopened or undamaged. Do not use the product if there is doubt as to whether the product is sterile. Store in a dark, dry, cool place. Avoid extended exposure to light. Upon removal from package, inspect the product to ensure no damage has occurred.

REFERENCES

These instructions for use are based on experience from physicians and (or) their published literature. Refer to your local Cook sales representative for information on available literature.

Manufacturer

COOK INCORPORATED

750 Daniels Way

Bloomington, IN 47404 U.S.A.

www.cookmedical.com

EC Representative

WILLIAM COOK EUROPE ApS

Sandet 6, DK-4632

Bjaeverskov, DENMARK

PRINTING DATE

Formula 418® Renal Stent System

Instructions for Use

~~T_FORMR_REV0~~ New Art code used as labeling identifier, with bar code, to be established

FORMULA 418® RENAL STENT SYSTEM

CAUTION: U.S. federal law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

DEVICE DESCRIPTION

The Formula™ Renal Stent is a balloon-expandable stent made of 316L stainless steel with a slotted tube configuration. It is pre-mounted on an over-the-wire balloon catheter, which serves as the delivery system. The stent is positioned between two radiopaque marker bands, which are located inside the balloon at the proximal and distal tapers of the balloon. The cannula design of the stent provides a low outside diameter profile, which permits use with a 5.0 French sheath and 6.0 French guiding catheter for 4-6 mm diameter sizes; and a 6.0 French sheath and 7.0 French guiding catheter for the 7.0 mm diameter size. The Formula Renal Stent is pre-mounted on 80 and 135 cm balloon catheter delivery systems. The stent is available in nominal expanded diameters of 4, 5, 6 and 7 mm with lengths of 12, 16, and 20 mm each. **(Table 1)**

Table 1: Device Specifications (diameters and lengths)

Model	Catheter Length (cm)	Stent Diameter (mm)	Stent Length (mm)	Minimum Guiding Catheter/Sheath*- Inside Diameter (inches)	Guiding Catheter/ Sheath (French Size)
FOR4-18-80-4-12	80	4	12	.068	6F/5F
FOR4-18-80-4-16	80	4	16	.068	6F/5F
FOR4-18-80-4-20	80	4	20	.068	6F/5F
FOR4-18-80-5-12	80	5	12	.068	6F/5F
FOR4-18-80-5-16	80	5	16	.068	6F/5F
FOR4-18-80-5-20	80	5	20	.068	6F/5F
FOR4-18-80-6-12	80	6	12	.068	6F/5F
FOR4-18-80-6-16	80	6	16	.068	6F/5F
FOR4-18-80-6-20	80	6	20	.068	6F/5F
FOR4-18-80-7-12	80	7	12	.078	7F/6F
FOR4-18-80-7-16	80	7	16	.078	7F/6F
FOR4-18-80-7-20	80	7	20	.078	7F/6F
FOR4-18-135-4-12	135	4	12	.068	6F/5F
FOR4-18-135-4-16	135	4	16	.068	6F/5F
FOR4-18-135-4-20	135	4	20	.068	6F/5F
FOR4-18-135-5-12	135	5	12	.068	6F/5F
FOR4-18-135-5-16	135	5	16	.068	6F/5F
FOR4-18-135-5-20	135	5	20	.068	6F/5F
FOR4-18-135-6-12	135	6	12	.068	6F/5F
FOR4-18-135-6-16	135	6	16	.068	6F/5F
FOR4-18-135-6-20	135	6	20	.068	6F/5F
FOR4-18-135-7-12	135	7	12	.078	7F/6F
FOR4-18-135-7-16	135	7	16	.078	7F/6F
FOR4-18-135-7-20	135	7	20	.078	7F/6F

*See manufacturer specifications for French (FR) equivalent

INTENDED USE

The Formula™ 418 Balloon-Expandable Renal Stent System is indicated for use in patients with atherosclerotic disease of the renal arteries following sub-optimal percutaneous transluminal renal angioplasty (PTRA) of a de novo or restenotic lesion (≤ 18 mm in length) located within 10 mm of the renal ostium and with a reference vessel diameter of 4.0 – 7.0 mm. Suboptimal PTRA is defined as ≥ 50% residual stenosis, ≥ 20 mmHg systolic or ≥ 10 mmHg mean translesional pressure gradient, or flow-limiting dissection.

The product is intended for use by physicians trained and experienced in diagnostic and interventional techniques. Standard techniques for placement of vascular access sheaths, angiographic catheters and wire guides should be employed.

CONTRAINDICATIONS

The Formula™ 418 Balloon-Expandable Renal Stent System is contraindicated for use in:

- Patients for whom antiplatelet and/or anticoagulant therapy is contraindicated.
- Patients who have a lesion that cannot be crossed with a wire or a balloon angioplasty catheter.
- Patients who have stenoses that cannot be dilated to permit passage of the stent.
- Patients with bleeding disorders.
- Stenting of an arterial vessel where leakage from the artery could be exacerbated by placement of a stent.
- Patients with a target lesion with a large amount of adjacent acute or subacute thrombus.

WARNINGS

• The use of this device carries the associated risks of subacute thrombosis, vascular complications and/or bleeding events. Judicious selection of patients is necessary.

• Persons allergic to 316L stainless steel may suffer an allergic reaction to this implant.

PRECAUTIONS

General

• Implantation of the stent should be performed only by physicians who have received adequate training. Adequate training consists of specific training in renal stenting techniques and procedures under the supervision of an interventional physician experienced in renal stent implantation.

• Stent placement should only be performed at hospitals where emergency renal artery bypass graft surgery can be readily performed.

• Subsequent restenosis may require redilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of an endothelialized Formula 418 Renal Stent is unknown at present.

Stent Placement

• Manipulation of the Formula 418 Stent System requires fluoroscopic control.

• The stent is preloaded on its delivery balloon and should not be removed. Do not attempt to place stent on another balloon catheter for deployment.

• Deploy the stent over a wire guide not exceeding 0.018 inch diameter.

• DO NOT wipe or clean stent or catheter with organic solvent (i.e., isopropyl alcohol).

• DO NOT expose catheter to temperatures above 130 °F (54.4 °C).

• DO NOT use power injection systems with the delivery system.

• DO NOT rotate any part of the system during deployment.

• Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is particularly important during removal of the catheter from packaging, placement over the wire guide and advancement through the large-bore Tuohy-Borst "Y" adapter and guiding catheter hub.

• Do not pre-inflate balloon prior to stent deployment. (See **Preparation of Balloon Catheter** section in these Instructions for Use)

• Use only the appropriate balloon inflation medium. The standard inflation medium is a 1:1 mixture of contrast medium and normal saline. Do not use air or any gaseous substance as a balloon inflation medium.

• Expansion of the stent should not be undertaken if the stent is not properly positioned in the vessel. (See **Removal of Unexpanded Stent** section in these Instructions for Use.)

• Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on the product label. Use of pressures higher than specified on the product label may result in a ruptured balloon, with possible intimal damage and dissection.

• Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stent and may cause acute closure of the vessel, requiring additional intervention (further dilatation or placement of additional stents).

• Use prior to the expiration date on the package label.

• Intended for one-time use. (Do not re-sterilize.)

• The use of mechanical atherectomy devices within an implanted stent may cause damage to the stent.

• Repositioning of the device after deployment is not possible.

MAGNETIC RESONANCE IMAGING

Non-clinical testing has demonstrated that the Formula™ renal stent is **MR Conditional** according to ASTM F2503, *Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment*. A patient with this stent can be scanned safely anytime after placement under the following conditions.

- Static magnetic field of 3-Tesla or 1.5-Tesla
- Maximum spatial magnetic gradient of 720 Gauss/cm or less
- Product of the spatial gradient and the static magnetic field of 21.6 T2/m or less
- MR system reported whole body average specific absorption rate (SAR) of 3.0 W/kg or less for 15 minutes of scanning

Non-clinical evaluation was conducted in an MR system (Excite, General Electric Healthcare) with a maximum spatial magnetic gradient field of 720 Gauss/cm as measured with a gaussmeter in the position of the static magnetic field pertinent to the patient (i.e., outside of scanner covering, accessible to a patient or individual). In non-clinical testing, single and two overlapped Formula™ renal stents produced a maximum temperature rise of 2.6 °C and 3.3 °C, respectively, during 15 minutes of MRI (i.e., for one scanning sequence) performed in a 3 Tesla MR system (3 Tesla/128 MHz, Excite, Software G3.0-052B, General Electric Healthcare) at an MR system reported whole body averaged SAR of 3.0 W/kg (associated with a calorimetry measured whole body averaged value of 2.8 W/kg).

The effect of heating in the MRI environment for stents with fractured struts is unknown.

Image Artifacts

MR image quality may be compromised if the area of interest is within the lumen or within approximately 15 mm of the Formula™ renal stent. Therefore, it may be necessary to optimize MR imaging parameters for the presence of this metallic stent.

MedicAlert Foundation

Cook recommends that the patient register the MR conditions disclosed in this IFU with the MedicAlert Foundation. The MedicAlert Foundation can be contacted at:

Mail: MedicAlert Foundation International
2323 Colorado Avenue
Turlock, CA 95382

Phone: 888-633-4298 (toll free)
209-668-3333 (from outside the US)

Fax: 209-669-2450

Web: www.medicalert.org

POTENTIAL ADVERSE EVENTS

Adverse events that may be associated with the use of a renal stent are presented in the following alphabetical list and include, but are not limited to:

- Abscess
- Allergic reaction to stainless steel or contrast agents
- Arrhythmias (ventricular fibrillation, ventricular tachycardia, other)
- Arteriovenous fistula
- Bowel infarct
- Death
- Dialysis
- Dissection
- Drug reaction to antiplatelet agents
- Drug reaction, allergic reaction to contrast media
- Emboli (air, tissue, or thrombotic emboli) resulting in tissue ischemia/infarction
- Emergency surgery to correct vascular complications
- Emergent renal artery bypass surgery
- Extremity ischemia/amputation
- Fever
- Gastrointestinal symptoms from anticoagulation/antiplatelet medication
- Hematoma at vascular access site
- Hemorrhage requiring transfusion
- Hypersensitivity reactions
- Hypotension/hypertension
- Infection and pain at vascular access site
- Intimal tear
- Kidney infarct
- Myocardial infarction
- Myocardial ischemia
- Nephrectomy
- Peripheral neuropathy
- Pseudoaneurysm at vascular access site
- Pseudoaneurysm formation
- Renal artery thrombosis, aneurysm, rupture, perforation, occlusion, spasm, or restenosis
- Renal insufficiency or failure
- Stent migration or embolization
- Stent misplacement
- Stroke/cerebral vascular accident
- Tissue necrosis or ulceration

CLINICAL STUDY

Results from a multi-center clinical study (IDE G070014, also known as the REFORM ("REnal FORMula Stent") study) demonstrate the safety and effectiveness of the Formula™ stent. Specifically, the 9-month primary patency rate was 91.7%, meeting the performance goal of 60%. In addition, use of the Formula™ stent was associated with a low rate of major adverse events (MAEs), high technical and procedural success rates, improvement in hypertension, and maintenance of renal function.

An overview of the REFORM study is presented in Table 2.

Table 2: Overview of the REFORM study

Device	Formula™ Balloon-Expandable Renal Stent System
Study Design	Non-randomized, prospective, single-arm, multi-center clinical study

Table 2: Overview of the REFORM study

Patients Enrolled	100 (44 male and 56 female)
Number of Sites	7 investigational sites
Primary Endpoint	Primary patency at 9 months, defined as the ≤60% diameter stenosis and intervention-free since the initial procedure. Analysis done on a per-lesion basis. Patency was assessed by ultrasound analysis (or quantitative angiography, if necessary) by an independent core laboratory.
Secondary Endpoints	• MAEs: Incidence of major adverse events, defined as procedure- or device-related events of death, Q-Wave MI, clinically driven target lesion revascularization (TLR), and significant embolic events (defined as unanticipated kidney/bowel infarct, lower extremity ulceration or gangrene, or kidney failure). MAEs were reported as percentage of patients with MAEs, after 30 days, 9 months, 24 months, and 36 months (from the previous period and cumulative), using all enrolled patients. In addition to MAE rate, the rates of individual events (death, Q-Wave MI, clinically driven target lesion revascularization (TLR), unanticipated kidney/bowel infarct, lower extremity ulceration or gangrene, and kidney failure) will also be reported (from the previous period and cumulative), using all enrolled patients. • Change in blood pressure: Systolic and diastolic blood pressures were measured at baseline and 1, 9, 24, and 36 months and the group average at each time point reported. The change at 9 months from baseline, for systolic and diastolic pressure, was calculated for each enrolled patient. Confidence intervals (95%) for the average changes were reported. • Change in Antihypertensive Medications: Number and dosage of antihypertensive medications at baseline and at 1, 6, 9, 12, 18, 24, and 36 months was collected. The group average number of antihypertensive medications at each time point was reported. In addition, data was reported as a percentage of patients at 9 months with a decrease in medication (in dose or amount), no change in medication, or increase in medication compared to baseline. • Change in Renal Function: Improvement and/or stabilization of renal function (as measured by estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation) were measured at baseline and at 1, 9, 24, and 36 months, with the group average reported at each time point. The change at 9 months from baseline was calculated for each enrolled patient. • Technical Success: Technical success is defined as successful delivery and deployment of a Formula™ Balloon-Expandable Stent. It was reported as a percentage of enrolled patients. • 30-day Clinical Success: 30-day clinical success is defined as a vessel with <30% residual stenosis immediately after stent placement and no major adverse events within 30 days of implant. Results are expressed as a percentage of stented arteries and a percentage of enrolled patients. • Target Lesion Revascularization: TLR is defined as any angioplasty or bypass surgery performed for thrombosis or >60% diameter restenosis of the originally treated site following the initial procedure. It was evaluated at 9 months and reported as a percentage of stented arteries and a percentage of enrolled patients. • Acute Procedural Success: Acute procedural success is defined as a vessel with <30% residual stenosis determined angiographically immediately after stent placement and no major adverse events before

Table 2: Overview of the REFORM study

	discharge. It was reported as a percentage of stented arteries and a percentage of enrolled patients.
Study Hypothesis	Renal arteries treated with the Formula™ Balloon-Expandable Stent will have a primary patency rate at 9 months on a per-stented artery basis that meets a performance goal of 60%.
Patient Follow-up	1-month clinic visit: Assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events. 6-month telephone contact: Patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient. 9-month clinic visit with ultrasound: Assessments of blood chemistry, blood pressure, antihypertensive medications, adverse events, ultrasound for evidence of stenosis. Patients with non-interpretable ultrasounds were required to have an angiogram. 12-month telephone contact: Patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient. 18-month telephone contact: Patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient. 24-month clinic visit: A 2-year office visit includes assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events. 36-month clinic visit: A 3-year office visit includes assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events.

Study Population Demographics and Baseline Parameters

Patient demographics (Table 3) and medical history (Table 4) were consistent with patient populations described in published literature of renal stent intervention. The most prevalent co-morbidities were hypertension (97%), hypercholesterolemia (83%), past or current smoker (75%), and peripheral vascular disease (57%) (Table 4). As assessed by the imaging core lab, the mean lesion length was 7.7 mm, the mean pre-procedure percent diameter stenosis was 57.4%, and the mean post-PTRA percent diameter stenosis was 46.9%.

Table 3: Patient Demographics

Demographic	Value (N = 100 patients)

Table 3: Patient Demographics

Demographic	Value (N = 100 patients)
Sex	
Male	44.0% (44/100)
Female	56.0% (56/100)
Age (years, mean ± SD (range))	72 ± 10 (42 - 92)
Height (inches, mean ± SD (range))	65.2 ± 4.1 (50 - 74)
Weight (lbs, mean ± SD (range))	177.4 ± 33.7 (102 - 290)
Ethnicity	
Caucasian or White	82.0% (82/100)
Black or African American	12.0% (12/100)
Hispanic or Latino	4.0% (4/100)
American Indian or Alaska Native	1.0% (1/100)
Other	1.0% (1/100)
Native Hawaiian or other Pacific Islander	0.0% (0/100)
Asian	0.0% (0/100)

Table 4: Medical History

Past or Current Medical Condition	Percent Patients (number/total number)
Diabetes	
Total	43.0% (43/100)
Type I	2.0% (2/100)
Type II	41.0% (41/100)
Hypercholesterolemia	83.0% (83/100)
Hypertension[1]	
Total	97.0% (97/100)
Pre-hypertension	14.0% (14/100)
Stage 1	31.0% (31/100)
Stage 2	52.0% (52/100)

Table 4: Medical History

Past or Current Medical Condition	Percent Patients (number/total number)
Stroke/CVA	17.0% (17/100)
Transient Ischemic Attack (TIA)	11.0% (11/100)
Asthma	9.0% (9/100)
Chronic Obstructive Pulmonary Disease (COPD)	19.0% (19/100)
Peripheral Vascular Disease	57.0% (57/100)
Left Ventricular Hypertrophy (LVH) [2]	27.8% (27/97)
Rutherford Classification (TASC 2000) [2]	
0: Asymptomatic	67.7% (63/93)
1: Mild Claudication	11.8% (11/93)
2: Moderate Claudication	7.5% (7/93)
3: Severe Claudication	10.8% (10/93)
4: Ischemic Rest Pain	2.2% (2/93)
5: Minor Tissue Loss, Ulceration	0% (0/93)
6: Major Tissue Loss, Gangrene	0% (0/93)
Microalbuminurea	
Yes	8.0% (8/100)
No	52.0% (52/100)
Unknown	40.0% (40/100)
Renal Insufficiency	46.0% (46/100)
Previous Renal Bypass	0% (0/100)
Congestive Heart Failure (CHF)	
Total	26.0% (26/100)
NYHA Class I	6.0% (6/100)
NYHA Class II	6.0% (6/100)
NYHA Class III	3.0% (3/100)
NYHA Class IV	0% (0/100)
Unknown	11.0% (11/100)
Previous Myocardial Infarction (MI)	30.0% (30/100)
Current or Past Smoker	75.0% (75/100)
Current Smoker	14.0% (14/100)

[1] Definitions for hypertension categories:
Pre-hypertension = systolic 120 - 139 mmHg, diastolic 80 - 89 mmHg.
Stage 1 = systolic 140 - 159 mmHg, diastolic 90 - 99 mmHg.
Stage 2 = systolic > 160 mmHg; diastolic > 100 mmHg.
If systolic and diastolic pressures were different categories, the higher category was chosen.
[2] "Unknown" was not an available answer for the LVH and Rutherford Classification questions; patients without available data were removed from the denominator.

Safety and Effectiveness Results

Safety Results

Major adverse events included procedure- or device-related events of death, Q-wave myocardial infarction (MI), clinically-driven target lesion revascularization (clinically-driven TLR, defined as any angioplasty or bypass surgery performed for thrombosis or >60% diameter stenosis of the originally treated site following the initial procedure in the presence of clinical symptoms or laboratory evidence indicative of the need for revascularization), and significant embolic events (defined as unanticipated kidney or bowel infarct, lower extremity ulceration or gangrene, or kidney failure). All MAEs, except clinically-driven TLRs, were adjudicated by the CEC. The 9-month MAE rate was 2.2% (two clinically-driven TLRs), demonstrating the safety of the Formula™ stent (Table 5 and Table 6, respectively).

Adverse effects that occurred in the PMA clinical study

Table 5: Protocol Defined Major Adverse Events through 9 Months

Major Adverse Event	Number of Events	Percent Patients (number/total number)[1]
30-day Events		
CEC Adjudicated Death	0	0.0% (0/98)
CEC Adjudicated Q-wave Myocardial Infarction (MI)	0	0.0% (0/98)
Clinically-driven Target Lesion Revascularization (TLR)	0	0.0% (0/98)
CEC Adjudicated Significant Embolic Events	0	0.0% (0/98)
Total	0	0.0% (0/98)
9-month Events		
CEC Adjudicated Death	0	0.0% (0/92)
CEC Adjudicated Q-wave Myocardial Infarction (MI)	0	0.0% (0/92)
Clinically-driven Target Lesion Revascularization (TLR)	2	2.2% (2/92)
CEC Adjudicated Significant Embolic Events	0	0.0% (0/92)
Total	2	2.2% (2/92)

[1] Total number = patients participating in study at end of the time period (i.e., 30 days or 300 days post-procedure) plus discontinued patients who experienced a MAE during the specified time period.

Table 6: Protocol Defined Major Adverse Events, Stent Thrombosis, and Hemorrhagic Complications

Event	Number of Events	Percent Patients (number/total number)[1]	95% Confidence Interval
Major Adverse Events			
To 30-days	0	0.0% (0/98)	[0.0%, 3.7%]
Device-related Death[2]	0	0.0% (0/98)	[0.0%, 3.7%]
Index-procedure-related Death	0	0.0% (0/98)	[0.0%, 3.7%]
Q-wave Myocardial Infarction[2]	0	0.0% (0/98)	[0.0%, 3.7%]
Clinically-driven TLR[3]	0	0.0% (0/98)	[0.0%, 3.7%]
Significant Embolic Events[2]	0	0.0% (0/98)	[0.0%, 3.7%]
From 31 days to 9-months	2	2.2% (2/92)	[0.3%, 7.6%]
Device-related Death[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Q-wave Myocardial Infarction[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Clinically-driven TLR[3]	2	2.2% (2/92)	[0.3%, 7.6%]
Significant Embolic Events[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Total	0	2.2% (0/92)	[0.3%, 7.6%]
Device-related Death[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Index-procedure-related Death	0	0.0% (0/92)	[0.0%, 3.9%]
Q-wave Myocardial Infarction[2]	0	0.0% (0/92)	[0.0%, 3.9%]

Table 6: Protocol Defined Major Adverse Events, Stent Thrombosis, and Hemorrhagic Complications

Event	Number of Events	Percent Patients (number/total number)[1]	95% Confidence Interval
Clinically-driven TLR[3]	2	2.2% (2/92)	[0.3%, 7.6%]
Significant Embolic Events[2]	0	0.0% (0/92)	[0.0%, 3.9%]
9-Month TLR[3], per lesion	2	2.0% (2/102)	[0.2%, 6.9%]
Stent Thrombosis	0	0.0% (0/97)	[0.0%, 3.7%]
Acute (≤24 hours)	0	0.0% (0/100)	[0.0%, 3.6%]
Sub-acute (>24 hours to ≤30 days)	0	0.0% (0/99)	[0.0%, 3.7%]
Late (>30 days to ≤90 days)	0	0.0% (0/97)	[0.0%, 3.7%]
Hemorrhagic Complication through 30 Days			
Major	2	2.0% (2/99)	[0.2%, 7.1%]
Intracranial hemorrhage	0	0.0% (0/99)	[0.0%, 3.7%]
GI Bleeding	1	1.0% (1/99)	[0.0%, 5.5%]
Bleeding at the access site	1	1.0% (1/99)	[0.0%, 5.5%]
Other Bleeding	0	0.0% (0/99)	[0.0%, 3.7%]
Minor[4]	1	1.0% (1/99)	[0.0%, 5.5%]

[1] Unless otherwise indicated, "Total number" = patients participating in study at end of the time period (i.e., 30 days or 300 days post-procedure) plus discontinued patients who experienced a MAE during the specified time period.
[2] CEC Adjudicated
[3] Target Lesion Revascularization
[4] Any bleeding which does not require >1 unit packed red blood cells

Effectiveness Results

One hundred twenty-two (122) Formula™ stents were placed to treat 115 renal artery lesions. Most lesions (93.0%) were treated with single stents. Residual diameter stenosis of < 30% was seen in 95.6% (109/114) of lesions. Therefore, the Formula™ stent was effective in establishing patency at the conclusion of the procedure.

Primary Endpoint

The 9-month primary patency rate met the performance goal. The 9-month primary patency rate was 91.7% and the lower limit of the 95% two-sided confidence interval is 84.2%; the latter is greater than the performance goal of 60% ($p < 0.0001$). These results demonstrate the effectiveness of the Formula™ stent in treating atherosclerotic lesions of the renal arteries following suboptimal angioplasty.

Secondary Endpoints

Secondary endpoint analyses included major adverse events (MAEs), device-related success measures (i.e., technical success, acute procedural success, and 30-day clinical success), blood pressure-related outcomes (i.e., systolic and diastolic blood pressure, use of anti-hypertensive medications, and improved or cured hypertension), and renal function (as measured by eGFR).

Device-related success measures ranged from 94.8% to 97.4%. Technical success (successful delivery and deployment of a Formula™ stent), acute procedural success (< 30% residual stenosis post-procedure by core lab analysis and no MAEs before discharge), and 30-day clinical success (< 30% residual stenosis post-procedure by core lab analysis and no MAEs within 30 days) outcomes are summarized in Table 7. These results support the safety and effectiveness of the Formula™ stent in establishing renal artery patency.

Table 7: Device-related Success Measures

Measure	Analysis Percentage (number/total number)	
	Per Patient	**Per Lesion**
Technical Success	97.0% (97/100)	97.4% (112/115)
Acute Procedural Success	94.9% (94/99)	95.6% (109/114)
30-day Clinical Success	94.8% (92/97)	95.5% (106/111)

Blood pressure-related outcomes demonstrated significantly decreased systolic blood pressure from pre-procedure to 9-month follow-up (p = 0.003) and that most patients (85%) were taking the same number or fewer anti-hypertensive medications at 9 months (Table 8 and Table 9, respectively). These data demonstrate the clinical utility of the Formula™ stent and suggest that revascularization with the Formula™ stent does not adversely affect blood pressure outcomes.

Table 8: Blood Pressure Results

Blood Pressure	Mean ± SD (range, total patients)	
	Systolic (mmHg)	Diastolic (mmHg)
Pre-procedure	150.3 ± 20.6 (102 - 202, n = 100)	73.9 ± 12.9 (43 - 112, n = 100)
1 Month	137.9 ± 18.7 (96 - 195, n = 98)	72.9 ± 12.2 (46 - 115, n = 98)
9 Months	140.5 ± 21.0* (97 - 203, n = 87)	77.5 ± 12.9 (51 - 122, n = 87)
Change at 9 Months from Pre-procedure (Bonferroni adjusted 95% two-sided confidence interval)	[-16.5, -2.7], n = 87	[-0.3, 7.4], n = 87

*p = 0.003 compared to pre-procedure systolic blood pressure (Bonferroni adjusted p-value).

Table 9: Anti-hypertensive Medication Results

Anti-hypertensive Medications	Mean ± SD (range, total patients)
Number Per Patient	
Pre-procedure	2.7 ± 1.2 (0 - 6, n = 100)
1 Month	2.6 ± 1.2 (0 - 5, n = 98)
9 Months	2.5 ± 1.1 (0 - 5, n = 87)

Anti-hypertensive Medications	Mean ± SD (range, total patients)
Number of Medications at 9 Months *(change from pre-procedure)*	
Decrease	23.0% (20/87)
No Change	62.1% (54/87)
Increase	14.9% (13/87)
Dose of Medications at 9 Months *(change from pre-procedure)*	
Decrease	29.9% (26/87)
No Change	42.5% (37/87)
Increase	27.6% (24/87)

In addition, renal function was maintained (i.e., did not worsen) from pre-procedure to 9-month follow-up based on serum creatinine levels and eGFR), further demonstrating the clinical utility of the Formula™ stent and suggesting that revascularization with the Formula™ stent does not adversely affect renal function.

PRODUCT RECOMMENDATIONS

Wire Guide Use and Selection

The Formula 418 Renal Stent System is compatible with 0.018 inch wire guides.

Guiding Catheter/Introducer Selection

Correct guiding catheter/introducer selection and technique are necessary for use of the stent. Ensure that the inside lumen of the guiding catheter/introducer is of sufficient size to allow unobstructed passage of the Formula 418 Renal Stent System. **NOTE:** Minimum inside diameter requirements for the guiding catheter/introducer are shown in Table 1.

Standard renal catheter curves must be selected to provide adequate guiding catheter/introducer "back-up support" to achieve successful stent placement.

Stent Size Selection

The stent selected should have an expanded diameter approximately equal to, or slightly larger than, the estimated reference diameter of the artery to be stented. The length of the stent should be chosen to adequately cover the length of the lesion. A compliance card is provided with the product to facilitate selection of an appropriate size of stent.

INSTRUCTIONS FOR USE

The Formula 418 Renal Stent System is used in conjunction with equipment required for a conventional PTA procedure including, but not limited to, a vascular access set, arterial sheath, guiding catheter, wire guide and inflation device.

Lesion/Vessel Preparation

Stent placement must take into account proximal atherosclerotic plaque, which may inhibit advancement of the stent, as well as atherosclerotic plaque beyond the lesion which may prevent advancement of the device across the primary lesion. In preparing the vessel, optimal renal vasodilation, anticoagulant and antiplatelet therapy are essential. This device is intended for treatment following suboptimal angioplasty.

Preparation of Balloon Catheter

1. Remove the Formula 418 Renal Stent System from the package, remove protective sleeve from the distal tip of the catheter and inspect the stent to ensure it has not been damaged.

2. Prepare the balloon lumen with a standard 1:1 contrast-saline mixture as follows:

WARNING: Do not attempt pre-inflation technique to purge the balloon lumen. Do not use air or any gaseous medium to inflate the balloon.

a. Using a 20 ml syringe containing 5 ml of contrast-saline mixture, apply negative pressure for 20-30 seconds.

b. Release pressure, allowing negative pressure to draw mixture into balloon lumen.

c. Detach syringe, leaving a meniscus of mixture on the hub of the balloon lumen.

d. Prepare inflation device in standard manner and purge to remove all air from syringe and tubing.

e. Attach inflation device to balloon lumen directly, ensuring no air bubbles remain at connection.

f. Pull negative pressure on inflation device.

CAUTION: Significant amounts of air in the balloon may cause uneven expansion of the stent and difficulty in deployment of the stent.

3. Moisten the stent with heparinized saline.

CAUTION: Do not use gauze sponges, as fibers may disrupt stent.

4. Flush the wire guide lumen of the balloon catheter in standard fashion to purge air.

a. Remove the protective tube from the flushing sheath.

b. Attach a syringe filled with heparinized normal saline to a flushing hub, which is provided with a protective sheath, and inject this saline into the lumen, or c. Attach a syringe filled with

heparinized normal saline to the flushing tool, insert the flushing tool into the distal end of the catheter and inject this saline into the lumen.

d. Flush solution should be seen coming out of the wire guide port proximal to the balloon.

Follow this procedure for any additional flushing.

5. Before inserting the Formula 418 Renal Stent System into the guiding catheter or introducer, be sure that a largebore Tuohy-Borst "Y" adapter or introducer valve is on the guiding catheter/introducer.

6. Advance a 0.018 inch wire guide of appropriate length across target lesion.

7. Insert the appropriate guiding catheter/introducer (see **Table 1**).

8. Advance the premounted Formula 418 Renal Stent System over the wire into either the introducer valve or Tuohy-Borst "Y" adapter.

a. If using an introducer with a valve, make sure the flared end of the insertion tool (provided in the package) is loaded over the premounted stent on the balloon catheter. Pass the insertion tool loaded with the premounted stent through the introducer valve. Push the Formula 418 Renal Stent System into the body of the introducer. Slide the insertion tool proximally up the catheter shaft away from the guiding catheter/introducer. A slight contact of the stent with the introducer may be felt, but there must be no resistance.

b. If using a Tuohy-Borst "Y" adapter, advance the premounted Formula 418 Renal Stent System over the wire and into the fully opened large-bore Tuohy-Borst "Y" adapter. Gently advance the Formula 418 Renal Stent System completely through the Tuohy-Borst "Y" adapter and into the guiding catheter/introducer. A slight contact of the stent with the guiding catheter/introducer may be felt, but there must be no resistance.

WARNING: If resistance is encountered, do not force passage. Resistance may indicate damage to stent.

Positioning the Stent

1. Ensure guiding catheter/introducer stability before advancing the stent delivery balloon into the renal artery.

WARNING: If initial guiding catheter/introducer position is lost, avoid pulling or pushing the guiding catheter/introducer over the stent. If this is done, the distal end of the guiding catheter/introducer may damage the stent.

2. Position the Formula Renal Stent across the lesion, using both the distal and proximal balloon markers as reference points. Optimal placement requires the ends of the stent to extend beyond the margin of the lesion to be stented.

WARNING: If the Formula 418 Renal Stent System does not readily advance through the vessel, do not force. If the stent will not advance in spite of good guiding catheter/introducer support, consider dilating the lesion again, or changing the wire

guide or the guiding catheter/introducer. (Refer to Removal of Unexpanded Stent section in these Instructions for Use.)

NOTE: When stenting long lesions, be sure to cover the distal portion of the lesion first. It is very important not to leave distal lesions uncovered. Frequent injections of contrast around the uninflated Formula 418 Renal Stent System will allow visualization of the extent of the lesion and facilitate accurate placement of the stent.

Balloon Expansion/Stent Deployment

Prior to stent expansion, utilize high-resolution fluoroscopy to verify that the stent has not been dislodged during positioning.

1. To expand the stent, inflate the balloon with a 1:1 contrast-saline mixture to the recommended expansion pressure indicated on product label. Do not move stent system during deployment.

2. Complete expansion and apposition of the stent against the vessel wall is necessary for clinical success. Do not exceed rated burst pressure of the balloon as indicated on the product label.

3. Once the stent has been deployed, post-deployment inflation is at the discretion of the operator to achieve optimum angiographic appearance. The stent may be post-dilated up to 1 mm beyond nominal labeled stent diameter.

Balloon Deflation and Removal

1. Completely deflate the balloon, by pulling negative pressure with the inflation device or a 20 ml syringe. This usually requires 10 seconds or less.

WARNING: Allow enough time for the balloon to fully deflate prior to removal.

2. Slowly withdraw the balloon catheter from the stent while maintaining negative pressure on the balloon. Maintain position of the guiding catheter/introducer to prevent it from being drawn into the renal vessel. Observe under fluoroscopy to ensure that the balloon disengages from the stent.

Removal of Unexpanded Stent

Do not attempt to pull an unexpanded stent back into the guiding catheter/introducer. The Formula 418 Renal Stent System should be withdrawn until the proximal end of the stent is aligned with the distal tip of the guiding catheter/introducer. Withdraw the guiding catheter/introducer and stent delivery system as a single unit, leaving the wire guide in place.

WARNING: If stent is removed, do not attempt to reuse the device. Damage to the stent may occur upon removal.

Stent-Assisted, High-Pressure Balloon Angioplasty

A deployed Formula Renal Stent may be further expanded using a low-profile, high-pressure balloon catheter. The stent should have been well embedded into the vessel wall by the

deployment balloon before the lesion is recrossed. If recrossing is necessary, the position of the stent should be monitored and care should be taken to avoid displacing the stent with subsequent manipulation of wire guides and balloons. An appropriate balloon catheter should be used with a very flexible wire guide. If a Formula Renal Stent is dilated with a high-pressure balloon, the balloon should be appropriately sized for the vessel diameter. The stent may be post-dilated up to 1mm beyond nominal labeled stent diameter. Use of a new balloon for post-deployment dilatation is suggested. Avoid balloon catheters with stiff tips that might displace the stent during advancement. Avoid balloons that "wing out" and/or re-wrap inconsistently, which might displace the stent during withdrawal of the balloon from the stent.

HOW SUPPLIED

Supplied sterilized by ethylene oxide gas in peel-open packages. Intended for one-time use. Sterile if package is unopened or undamaged. Do not use the product if there is doubt as to whether the product is sterile. Store in a dark, dry, cool place. Avoid extended exposure to light. Upon removal from package, inspect the product to ensure no damage has occurred.

REFERENCES

These instructions for use are based on experience from physicians and (or) their published literature. Refer to your local Cook sales representative for information on available literature.

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