IFU0093-0

Zilver® PTX® Drug-Eluting Peripheral Stent

ZILVER® PTX® DRUG-ELUTING PERIPHERAL STENT

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 Zilver PTX Drug-Eluting Peripheral Stent is a self-expanding stent made of nitinol and coated with the drug paclitaxel. It is a flexible, slotted tube that is designed to provide support while maintaining flexibility in the vessel upon deployment. Post-deployment, the stent is designed to impart an outward radial force upon the inner lumen of the vessel, establishing patency in the stented region.
The stent is preloaded in a 6.0 French delivery catheter. Hand-loading of the stent is not possible. Stent deployment is controlled by retraction of the handle while holding the metal cannula stationary.

Table 1. Zilver PTX Drug-Eluting Peripheral Stent and delivery system product description

Zilver PTX Drug-Eluting Peripheral Stent	
Available stent lengths	20, 30, 40, 60, 80 mm
Available stent diameters	6, 7, 8 mm
Stent material	Nitinol
Drug Coating	Paclitaxel
Delivery System	
Available delivery system lengths	80, 125 cm
Wire guide compatibility	0.035 in
Catheter shaft outer diameter	6.0 Fr (2.0 mm)
Introducer sheath (minimum)	6 Fr
Guide catheter (minimum)	8 Fr

Drug Component Description
Paclitaxel is extracted from the bark, branches, or needles of the yew tree, then purified and concentrated by column chromatography, crystallization, and recrystallization. Zilver PTX Drug-Eluting Peripheral Stents are coated with paclitaxel API (active pharmaceutical ingredient) using a proprietary process. No excipients, polymers, carriers, binding agents, other materials,

or other device modifications are involved. The chemical description of paclitaxel is provided in Figure 1.

Paclitaxel

- Synonyms: Taxol, Taxol A, Hunxol I, Paclitaxelum
- IUPAC systematic name: *β-(benzoylamino)-α-hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy) 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9-yl ester,(2aR-(2a-α,4-β,4a-β,6-β,9-α(α-R*,β-S*),11-α,12-α,12a-α,2b-α))-benzenepropanoic acid*
- CAS registry number: 33069-62-4
- Chemical formula: C47H51NO14
- Structure of paclitaxel:

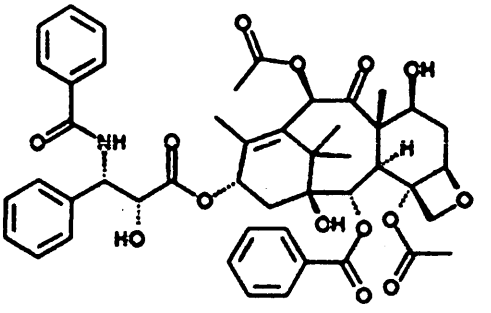


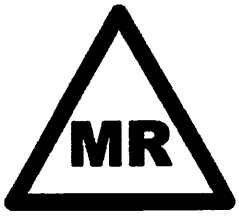
Figure 1. Chemical description of paclitaxel

Table 2 presents the stent sizes and the nominal total quantity of paclitaxel on each stent based on the established dose density of 3 μg/mm^2.

Table 2. Stent sizes and paclitaxel total quantity

Model Number		Nominal Stent Size		Nominal Total Paclitaxel (μg/stent)
80 cm delivery system	125 cm delivery system	Diameter (mm)	Length (mm)	
ZIV6-35-80-6-20-PTX	ZIV6-35-125-6-20-PTX	6	20	171
ZIV6-35-80-7-20-PTX	ZIV6-35-125-7-20-PTX	7	20	171
ZIV6-35-80-8-20-PTX	ZIV6-35-125-8-20-PTX	8	20	178
ZIV6-35-80-6-30-PTX	ZIV6-35-125-6-30-PTX	6	30	298
ZIV6-35-80-7-30-PTX	ZIV6-35-125-7-30-PTX	7	30	298
ZIV6-35-80-8-30-PTX	ZIV6-35-125-8-30-PTX	8	30	267
ZIV6-35-80-6-40-PTX	ZIV6-35-125-6-40-PTX	6	40	383
ZIV6-35-80-7-40-PTX	ZIV6-35-125-7-40-PTX	7	40	383
ZIV6-35-80-8-40-PTX	ZIV6-35-125-8-40-PTX	8	40	356
ZIV6-35-80-6-60-PTX	ZIV6-35-125-6-60-PTX	6	60	552
ZIV6-35-80-7-60-PTX	ZIV6-35-125-7-60-PTX	7	60	552
ZIV6-35-80-8-60-PTX	ZIV6-35-125-8-60-PTX	8	60	579
ZIV6-35-80-6-80-PTX	ZIV6-35-125-6-80-PTX	6	80	722
ZIV6-35-80-7-80-PTX	ZIV6-35-125-7-80-PTX	7	80	722
ZIV6-35-80-8-80-PTX	ZIV6-35-125-8-80-PTX	8	80	757

MRI Information



Non-clinical testing has demonstrated that the Zilver PTX Drug-Eluting Peripheral Stent is MR Conditional according to ASTM F2503. A patient with this stent can be scanned safely after placement under the following conditions.

- Static magnetic field of 1.5 Tesla or 3 Tesla
- Spatial magnetic gradient of 1600 Gauss/cm or less
- Normal operating mode: Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of scanning or less.

Static Magnetic Field
The static magnetic field for comparison to the above limits is the static magnetic field that is pertinent to the patient (i.e., outside of scanner covering, accessible to a patient or individual).

MR-Related Heating
- 1.5 and 3.0 Tesla Systems: Maximum MR system reported, whole-body-averaged specific absorption rate (SAR) of 2.9 W/kg for 15 minutes of scanning (i.e., per pulse sequence)

1.5 Tesla Temperature Rise
In non-clinical testing, single and overlapped Zilver stents of lengths to treat lesions up to 140 mm produced a maximum temperature rise of 3.8°C during 15 minutes of MR imaging (i.e., for one scanning sequence) performed in a MR 1.5 Tesla System (Siemens Magnetom Software Numaris/4) at an MR system reported whole-body-averaged SAR of 2.9 W/kg (associated with a calorimetry measured whole body averaged value of 2.1 W/kg).

3.0 Tesla Temperature Rise
In non-clinical testing, single and overlapped Zilver stents of lengths to treat lesions up to 140 mm produced a maximum temperature rise of 4.1°C

during 15 minutes of MR imaging (i.e., for one scanning sequence) performed in a MR 3 Tesla System (General Electric Excite, Software 14X.M5) at an MR system reported whole-body-averaged SAR of 2.9 W/kg (associated with a calorimetry measured whole body averaged value of 2.7 W/kg).

Image Artifacts
MR image quality may be compromised if the area of interest is within the lumen or within approximately 5 mm of the position of the Zilver PTX Drug-Eluting Peripheral Stent as found during non-clinical testing using T1-weighted spin echo and gradient echo pulse sequences in a 3.0 Tesla MR system (Excite, General Electric Healthcare, Milwaukee, WI). Therefore, it may be necessary to optimize MR imaging parameters for the presence of this metallic stent.

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

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

INDICATIONS FOR USE

The Zilver® PTX® Drug-Eluting Peripheral Stent is indicated for improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 7 mm and total lesion lengths up to 140 mm per limb and 280 mm per patient.

CONTRAINDICATIONS

- Women who are pregnant, breastfeeding, or plan to become pregnant in the next 5 years should not receive a Zilver PTX Drug-Eluting Peripheral Stent. It is unknown whether paclitaxel will be excreted in human milk, and

there is a potential for adverse reaction in nursing infants from paclitaxel exposure.

- Patients who cannot receive recommended anti-platelet and/or anti-coagulant therapy.
- Patients judged to have a lesion that prevents proper placement of the stent or stent delivery system.

WARNINGS

- Persons with allergic reactions to nitinol, or its components, nickel and titanium, may suffer an allergic reaction to this implant.
- Persons allergic to paclitaxel or structurally-related compounds may suffer an allergic reaction to this implant.
- The inner package should not be opened or damaged prior to use to maintain sterility; do not use if inner package is opened or damaged.
- The use of this drug-eluting stent carries the risks associated with peripheral artery stenting, including vascular complications, and/or bleeding events.
- The safety and effectiveness of implanting more than four Zilver PTX Drug-Eluting Peripheral Stents (i.e., a maximum drug coating quantity of approximately 3 mg paclitaxel) in a patient has not been clinically evaluated

PRECAUTIONS

- To avoid involvement of the common femoral artery, the most proximal stent end should be placed at least 1 cm below the origin of the superficial femoral artery. To avoid involvement of the below-the-knee popliteal artery, the most distal stent end should be placed above the plane of the femoral epicondyles.
- This product is intended for use by physicians trained and experienced in diagnostic and interventional vascular techniques. Standard techniques for interventional vascular procedures should be employed.
- Manipulation of the Zilver PTX Drug-Eluting Peripheral Stent requires fluoroscopic control.

- Do not try to push the delivery system through stenoses that cannot be dilated to permit passage of the introducer catheter.
- Do not try to remove the stent from the introducer system before use.
- Ensure that the red safety lock is not inadvertently removed until final stent release.
- Deploy the stent over an extra stiff or ultra stiff wire guide to ensure adequate support of the system.
- Do not push the hub toward the handle during deployment..
- Do not expose the delivery system to organic solvents (e.g., alcohol).
- Do not use power injection systems with the delivery system.
- Do not rotate any part of the system during deployment.
- The device is intended for single use only. Do not resterilize and/or reuse this device.
- Repositioning of the device after deployment is not possible since the introducer catheter cannot be re-advanced over the stent once deployment begins.
- Appropriate antiplatelet/anticoagulant therapy should be administered pre- and post-procedure (see section entitled PRE- and POST-PROCEDURE ANTIPLATELET REGIMEN in these Instructions for Use). Use in patients who are unable to tolerate the appropriate antiplatelet therapy is not recommended.
- Safety and effectiveness of the Zilver PTX Drug-Eluting Peripheral Stent has not been demonstrated in patients with a history of bleeding disorders.
- Use of the Zilver PTX Drug-Eluting Peripheral Stent in an arterial vessel where leakage from the artery could be exacerbated by placement of the stent is not recommended.
- A low incidence of stent fracture has been reported (0.9% at 12 months in the randomized pivotal study). Although no clinical sequelae were associated with stent fracture in the randomized study through 12 months, the long-term clinical consequence of stent fracture is not yet established. The majority of stent fractures were associated with stent elongation $\geq$ 10% at deployment. Therefore, care should be taken when deploying the stent to minimize the risk of stent fracture due to elongation at implant.

- The stent is not designed for repositioning or recapturing.
- If multiple stents are placed in an overlapping fashion, they should be of similar composition (i.e., nitinol).
- Do not use the stent after the end of the month indicated by the "Use By" date specified on the package.
- Flow restrictions remaining after stent deployment (e.g., residual proximal or distal stenosis or dissection, or poor distal outflow) may increase the risk of stent thrombosis. Inflow and outflow should be assessed at procedure completion and additional measures considered (e.g., additional PTA, adjunctive stenting, or distal bypass) if necessary to maintain good inflow and outflow.

POTENTIAL ADVERSE EVENTS

Potential adverse events that may occur include, but are not limited to, the following:

- Allergic reaction to anticoagulant and/or antithrombotic therapy or contrast medium
- Allergic reaction to nitinol
- Atheroembolization (Blue Toe Syndrome)
- Arterial aneurysm
- Arterial rupture
- Arterial thrombosis
- Arteriovenous fistula
- Death
- Embolism
- Hematoma/hemorrhage
- Hypersensitivity reactions
- Infection
- Infection/abscess formation at access site
- Ischemia requiring intervention (bypass or amputation of toe, foot, or leg)
- Pseudoaneurysm formation

- Renal failure
- Restenosis of the stented artery
- Stent embolization
- Stent malapposition
- Stent migration
- Stent strut fracture
- Vessel perforation or rupture
- Worsened claudication/rest pain

Although systemic effects are not anticipated, refer to the Physicians' Desk Reference for more information on the potential adverse events observed with paclitaxel.

Potential adverse events, not described in the above source, may be unique to the paclitaxel drug coating:

- Allergic/immunologic reaction to the drug coating
- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage, or necrosis
- Myalgia/Arthralgia
- Myelosuppression
- Peripheral neuropathy

PRE- and POST-PROCEDURE ANTIPLATELET REGIMEN

In the clinical trial, the recommended antiplatelet therapy was clopidogrel or ticlopidine starting at least 24 hours prior to the procedure, or a loading dose during the procedure. The most common loading dose was 300 mg clopidogrel or 200 mg ticlopidine. It was recommended that the patient remain on clopidogrel or ticlopidine for 60 days post-procedure along with aspirin indefinitely. Nearly all patients were discharged taking aspirin (dose ranged from 81 to 325 mg) and clopidogrel (most common dose was 75 mg) or ticlopidine (most common dose was 200 mg twice daily) and approximately 90% of patients continued to take aspirin from 1 month through 2 years. Usage of clopidogrel or ticlopidine was lower, with approximately 90% of patients remaining on this medication at 1 month, 70% at 3 months, and 60% through 2 years.

It is recommended that patients receive aspirin as well as clopidogrel or ticlopidine daily. Aspirin should be administered indefinitely; the optimal duration of antiplatelet therapy, specifically clopidogrel or ticlopidine, is not known and the regimens recommended and used in the clinical study are described in the previous paragraph. Stent thrombosis may still occur despite continued therapy.

Prior to peripheral intervention, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the treating physician and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate treatment option. Following peripheral intervention, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy.

DRUG INFORMATION

Mechanism of Action

The mechanism by which a Zilver PTX Drug-Eluting Peripheral Stent affects neointimal production has not been fully established. Paclitaxel is known to bind to microtubules and inhibit their molecular disassembly into tubulin, thus arresting mitosis. This action can prevent the smooth muscle

cell proliferation and migration known to occur during the restenotic process in arteries. Several studies in animal models have shown that paclitaxel applied locally reduces restenosis by inhibiting smooth muscle cell proliferation and neointimal hyperplasia.

Pharmacokinetics

The pharmacokinetics are described in the section entitled SUMMARY OF CLINICAL INVESTIGATIONS in these Instructions for Use.

Drug Interactions

Because systemic levels of paclitaxel post-stent placement in clinical trials were extremely low and rapidly cleared (C_{max} <10 ng/mL; < 1 ng/mL after 8 hours), possible interactions of paclitaxel with concomitantly administered medications are unlikely to be detectable. The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4 which are cytochrome P450 isoenzymes. Formal drug interaction studies have not been conducted with the Zilver PTX Drug-Eluting Peripheral Stent. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

Carcinogenicity, Genotoxicity, and Reproductive Toxicology

Formal long-term carcinogenicity testing of paclitaxel in animals has not been performed. The mechanism of action of the paclitaxel drug is microtubule stabilization and subsequent cell growth inhibition. One consequence is the potential loss of whole chromosomes via interactions with spindle microtubules during cell division. Due to this, paclitaxel carries a risk of chromosomal disruption and therefore is classified as an aneugen. It is not known whether paclitaxel has a separate direct action on DNA in the generation of DNA strand breaks or fragments. *In vivo* and *in vitro* micronucleus genotoxicity studies which are capable of detecting DNA fragments have demonstrated a dose-dependent genotoxic potential of paclitaxel, whereas *in vitro* assays for gene mutation (bacterial reverse mutation and chromosomal aberration test) showed no evidence of genotoxicity. *In vivo*, no genotoxic effects were observed at a dose of 1

mg/kg; however, effects were noted at 50 mg/kg[1]. A dose of 50 mg/kg is approximately 1000 times greater than the total 3 mg paclitaxel amount (adjusted for a 70 kg adult) available from the maximum recommended number of Zilver PTX Drug-Eluting Peripheral Stents for a patient. In addition, the total quantity of paclitaxel with the maximum recommended number of Zilver PTX Drug-Eluting Peripheral Stents provides a total delivered quantity that is 20 times lower than a dose reported to have no observed genotoxic effect in animals (1 mg/kg). *In vivo* reproductive toxicity of paclitaxel has previously been evaluated in rabbits and rats. Although no teratogenic effects were observed in rabbits, impairment of fertility was noted at 1 mg/kg of paclitaxel in rats[2]. This daily dose is approximately 90 times greater than the total 757 µg paclitaxel quantity from the single largest Zilver PTX Drug-Eluting Peripheral Stent (adjusted for a 70 kg adult).

USE IN SPECIAL POPULATIONS

Pregnancy and Lactation

Pregnancy Category C: There are no adequate and well controlled studies in pregnant women of paclitaxel or Zilver PTX Drug-Eluting Peripheral Stents. The Zilver PTX Drug-Eluting Peripheral Stent is contraindicated in women who are pregnant, breastfeeding, or plan to become pregnant in the next 5 years. It is unknown whether paclitaxel will be excreted in human milk, and there is a potential for adverse reaction in nursing infants from paclitaxel exposure.

Gender

Clinical studies of the Zilver PTX Drug-Eluting Peripheral Stent did not include formal analysis of differences in safety and effectiveness between male and female patients.

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[1] Tinwell H and Ashby J. Genetic toxicity and potential carcinogenicity of taxol. *Carcinogenesis* 1994;15(8):1499-1501.

[2] Physician's Desk Reference, 52nd edition, *Medical Economics Company Inc.*, 1998, pp 762-766.

Ethnicity

Clinical studies of the Zilver PTX Drug-Eluting Peripheral Stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity, either by individual category or when grouped by Caucasian and non-Caucasian.

Pediatric Use

The safety and effectiveness of the Zilver PTX Drug-Eluting Peripheral Stent in pediatric patients have not been established.

Geriatric Use

Clinical studies of the Zilver PTX Drug-Eluting Peripheral Stent did not have an upper age limit. In the pivotal study, there were 148 patients in the primary Zilver PTX treatment group who were age 65 or older, and 511 in the single arm study. There were 25 primary Zilver PTX Drug-Eluting Peripheral Stent patients in the pivotal study who were age 80 or older, and 71 in the single arm study. Clinical studies of the Zilver PTX Drug-Eluting Peripheral Stent did not include formal analysis of differences in safety and effectiveness between patients under 65 and over 65 years of age.

SUMMARY OF CLINICAL INVESTIGATIONS

The Zilver PTX Drug-Eluting Peripheral Stent has been the subject of a multicenter randomized clinical study (IDE #G030251) and a multicenter single arm clinical study. As detailed below, results from the randomized IDE study support the safety and effectiveness of the Zilver PTX Drug-Eluting Peripheral Stent. Specifically, the event-free survival rate for the Zilver PTX treatment group was non-inferior (i.e., equivalent or superior) to the PTA control group. Moreover, the rate of event-free survival in the Zilver PTX group was significantly higher than in the PTA group, suggesting that primary stenting with the Zilver PTX Drug-Eluting Peripheral Stent is associated with a lower MAE rate than the current standard care of PTA with provisional stenting. The primary patency rate (patency defined as duplex ultrasound measured peak systolic velocity ratio < 2.0 indicating less than 50% diameter stenosis) for the Zilver PTX Drug-Eluting Peripheral Stent was significantly higher than the primary patency rate for PTA, demonstrating that primary stenting with the Zilver

PTX Drug-Eluting Peripheral Stent is significantly more effective than PTA. Additionally, the Zilver PTX Drug-Eluting Peripheral Stent demonstrated superior effectiveness to the bare Zilver stent in a randomized comparison in lesions with acute PTA failure. Results from the single arm clinical study provide additional evidence supporting the safety of the Zilver PTX Drug-Eluting Peripheral Stent in a broader patient population including more complex lesions.

RANDOMIZED CLINICAL STUDY

Primary Objective

The primary objective of the Zilver PTX randomized study was to demonstrate the safety and effectiveness of the Zilver PTX Drug-Eluting Peripheral Stent compared to percutaneous balloon angioplasty (PTA) for the treatment of *de novo* or restenotic lesions of the above-the-knee femoropopliteal artery. The patients in the PTA control group included those with optimal PTA and suboptimal (failed) PTA that underwent a secondary randomization to stenting with either Zilver PTX or bare Zilver stents.

Study Overview

The Zilver PTX randomized study is a prospective, controlled, multi-center, multinational study enrolling patients in the United States, Japan, and Germany with *de novo* or restenotic native lesions of the above-the-knee femoropopliteal artery. Patients were randomized 1:1 to treatment with the Zilver PTX Drug-Eluting Peripheral Stent (treatment group) or with PTA (control group). Recognizing that balloon angioplasty may not be successful acutely, the trial design mandated provisional stent placement immediately after failure of balloon angioplasty in instances of acute PTA failure. Therefore, patients with suboptimal (failed) PTA underwent a secondary randomization (1:1) to stenting with either Zilver PTX or bare Zilver stents (Figure 2). This secondary randomization allows evaluation of the Zilver PTX Drug-Eluting Peripheral Stent compared to a bare metal stent.

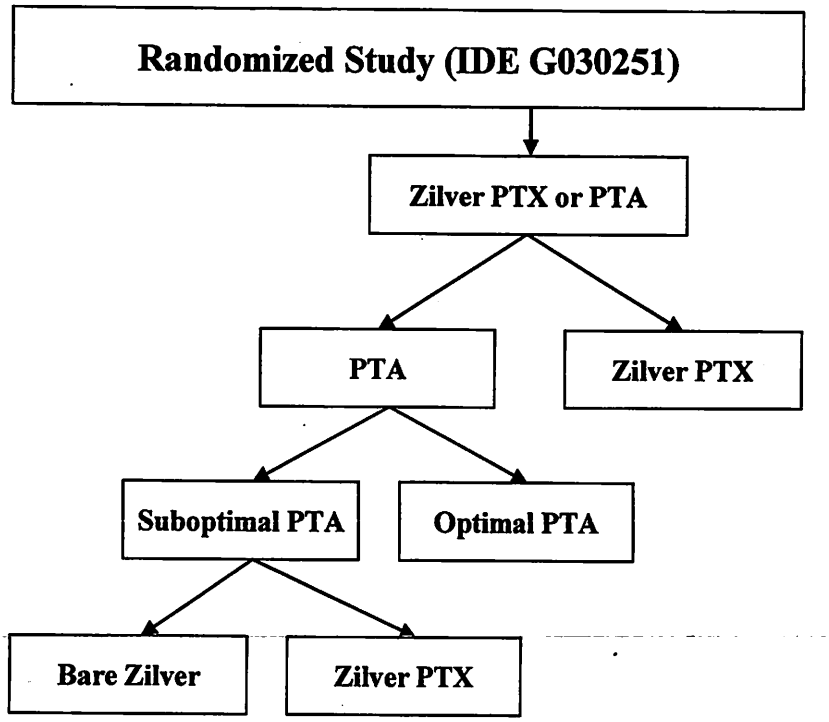


Figure 2. Patient enrollment

The study was designed to assess primary safety and effectiveness hypotheses regarding the Zilver PTX treatment group compared to the PTA control group. Specifically, the primary safety hypothesis was non-inferior (i.e., equivalent or superior) event-free survival (defined as freedom from the clinical events committee (CEC) adjudicated major adverse events of death, target lesion revascularization, target limb ischemia requiring surgical intervention or surgical repair of the target vessel, and freedom from worsening of the Rutherford classification by 2 classes or to class 5 or 6) at 12 months. The primary effectiveness hypothesis was superior primary patency at 12 months for the Zilver PTX treatment group compared to the PTA control group. Secondary analyses included evaluation of the effectiveness of the Zilver PTX Drug-Eluting Peripheral Stent compared to a bare metal stent.

Subjects eligible to be enrolled in the study had single or bilateral stenotic or occluded atherosclerotic lesions (≤ 14 cm long) of the above-the-knee femoropopliteal artery with a reference vessel diameter of 4 mm to 9 mm and Rutherford classification 2 to 6. Fifty-five (55) institutions enrolled 479 patients, including 238 in the PTA control group and 241 in the Zilver PTX treatment group. Five patients in the Zilver PTX group were enrolled as live cases (i.e., with no randomization) and are included in analyses of the

as-treated population but not the intent-to-treat or per-protocol populations. Acute PTA failure was common, occurring in 120 patients in the control group, and these patients underwent a second randomization to provisional stenting with either Zilver PTX Drug-Eluting Peripheral Stents or bare Zilver stents.

Follow-up included clinical assessment and ultrasound imaging prior to discharge, at 6 and 12 months, and annually thereafter. Additionally, x-rays were required prior to discharge and at 1, 3, and 5 years to assess stent integrity. Telephone contact was scheduled for 1, 3, 9, and 18 months. Patient subsets were assigned to a pharmacokinetic substudy and to an IVUS/angiography substudy.

The study was overseen by an independent data safety monitoring board (DSMB) comprised of physicians and a biostatistician. An independent CEC adjudicated major adverse events, including all patient deaths, and independent core laboratories provided uniformly defined imaging analysis.

Demographics

Baseline patient characteristics, angiographic data, lesion location, and lesion characteristics were generally similar between the PTA control group and Zilver PTX treatment group with a more frequent history of hypertension and more severe calcification and inflow tract stenosis in the Zilver PTX Drug-Eluting Peripheral Stent treatment group (Tables 3 – 7).

Table 3. Demographics

Demographic	Control Group	Treatment Group[3]	Diff. (95% CI)[1]	*P*-value[2]
Age (years)	67.7 ± 10.6 (238) (28 – ≥90)	67.9 ± 9.6 (236) (39 – 87)	-0.1 (-2.0, 1.7)	0.88
Gender				
Male	63.9% (152/238)	65.7% (155/236)	-1.8 (-10.4, 6.8)	0.70
Female	36.1% (86/238)	34.3% (81/236)	1.8 (-6.8, 10.4)	
Ethnicity				
Asian	14.1% (29/206)	11.9% (25/210)	2.2 (-4.3, 8.6)	
Black/African American	11.2% (23/206)	11.9% (25/210)	-0.7 (-6.9, 5.4)	0.81
Hispanic/Latino	5.3% (11/206)	7.1% (15/210)	-1.8 (-6.5, 2.8)	
White/Caucasian	69.4% (143/206)	69.0% (145/210)	0.4 (-8.5, 9.2)	
Height (in)	66.4 ± 4.4 (238)	66.7 ± 3.6 (236)	-0.2 (-1.0, 0.5)	0.55
Weight (lbs)	178.5 ± 44.3 (238)	180.4 ± 40.0 (236)	-1.9 (-9.5, 5.8)	0.62
Body mass index	28.2 ± 5.6 (238)	28.4 ± 5.3 (236)	-0.2 (-1.2, 0.8)	0.71

[1] Confidence interval is the difference in means for continuous variables and difference in percentages for categorical variables.
[2] *P* values are based on *t*-test for continuous variables and Fisher's exact test for categorical variables.
[3] Five patients treated as live cases not included.

Table 4. Medical history

Condition	Control Group	Treatment Group[4]	Diff. (95% CI)[1]	*P*-value[2]
Diabetes	42.0% (100/238)	49.6% (117/236)	-7.6 (-16.5, 1.4)	0.11
Diabetes type				
Type I	13.0% (13/100)	16.2% (19/117)	-3.2 (-12.6, 6.2)	0.56
Type II	87.0% (87/100)	83.8% (98/117)	3.2 (-6.2, 12.6)	
Hypercholesterolemia	69.7% (166/238)	76.3% (180/236)	-6.5 (-14.5, 1.5)	0.12
Hypertension	81.5% (194/238)	89.0% (210/236)	-7.5 (-13.8, -1.1)	0.02*
Carotid disease	20.2% (48/238)	18.2% (43/236)	2.0 (-5.1, 9.0)	0.64
Renal disease	10.5% (25/238)	10.2% (24/236)	0.3 (-5.2, 5.8)	> 0.99
Pulmonary disease	16.0% (38/238)	19.1% (45/236)	-3.1 (-9.9, 3.7)	0.39
Congestive heart failure	10.5% (25/238)	11.9% (28/236)	-1.4 (-7.0, 4.3)	0.66
Previous cardiac arrhythmia	13.0% (31/238)	10.6% (25/236)	2.4 (-3.4, 8.2)	0.47
Previous MI	17.2% (41/238)	21.2% (50/236)	-4.0 (-11.0, 3.1)	0.29
Smoking status				
Never smoked	15.5% (37/238)	13.6% (32/236)	2.0 (-4.4, 8.3)	
Quit	51.7% (123/238)	55.5% (131/236)	-3.8 (-12.8, 5.1)	0.70
Still smokes	32.4% (77/238)	30.9% (73/236)	1.4 (-7.0, 9.8)	
Unknown	0.4% (1/238)	0.0% (0/236)	0.4 (N/A)	
Existing tissue loss[3]	8.4% (20/238)	9.4% (22/235)	-1.0 (-6.1, 4.2)	0.74

Condition	Control Group	Treatment Group[4]	Diff. (95% CI)[1]	*P*-value[2]
Rutherford Classification				
Class 1	0.8% (2/236)	0.8% (2/236)		
Class 2	46.2% (109/236)	52.5% (124/236)		
Class 3	44.5% (105/236)	37.7% (89/236)	N/A	0.59
Class 4	4.7% (11/236)	5.9% (14/236)		
Class 5	3.4% (8/236)	3.0% (7/236)		
Class 6	0.4% (1/236)	0.0% (0/236)		
Currently taking medications	99.2% (236/238)	99.6% (235/236)	-0.4 (-1.8, 1.0)	> 0.99

[1] Confidence interval is the difference in means for continuous variables and difference in percentages for categorical variables.
[2] *P* values are based on *t*-test for continuous variables and Fisher's exact test for categorical variables.
[3] Tissue loss includes amputations, gangrene, and ischemic ulcers.
[4] Five patients treated as live cases not included.
* Statistically significant.

Table 5. Baseline angiographic data (core lab reported)

Baseline Angiographic Data	Control Group	Treatment Group	Diff. (95% CI)[1]	*P*-value[2]
Stenosed lesion length (mm)[3]	53.2 ± 40.3 (248) (5.8 – 220.3)	54.6 ± 40.7 (242) (5.9 – 262.3)	-1.3 (-8.5, 5.9)	0.71
Normal-to-normal Lesion length (mm)[4]	63.2 ± 40.5 (251) (2.0 – 140.0)	66.4 ± 38.9 (246) (5.5 – 140.0)	-3.2 (-10.2, 3.8)	0.36
Proximal RVD (mm)	5.0 ± 1.0 (249) (2.7 – 8.1)	5.1 ± 0.9 (242) (2.5 – 7.9)	-0.05 (-0.2, 0.1)	0.58
Distal RVD (mm)	5.0 ± 1.0 (249) (2.9 – 10.4)	5.0 ± 1.0 (242) (2.9 – 8.0)	-0.01 (-0.2, 0.2)	0.95
MLD in lesion (mm)	1.1 ± 0.9 (249) (0.0 – 4.1)	1.0 ± 0.9 (242) (0.0 – 3.1)	0.1 (-0.1, 0.2)	0.38
Percent diameter stenosis (%)	78.4 ± 17.1 (249) (31.5 – 100.0)	79.8 ± 17.0 (242) (47.1 – 100.0)	-1.3 (-4.4, 1.7)	0.38

[1] Confidence interval is the difference in means for continuous variables and difference in percentages for categorical variables.
[2] *P* values are based on *t*-test for continuous variables and Fisher's exact test for categorical variables.
[3] Region with > 20% diameter stenosis
[4] Site reported diseased lesion length

Table 6. Lesion location

Vessel[1]	Control Group	Treatment Group	Diff. (95% CI)[2]	*P*-value[3]
Left proximal SFA	10.8% (27/251)	8.9% (22/247)	2.9 (-4.3, 10.1)	0.63
Right proximal SFA	12.0% (30/251)	10.9% (27/247)		
Left proximal SFA/distal SFA	3.6% (9/251)	5.7% (14/247)	-2.1 (-6.7, 2.5)	
Right proximal SFA/distal SFA	2.8% (7/251)	2.8% (7/247)		
Left distal SFA	34.7% (87/251)	30.4% (75/247)	-1.0 (-9.5, 7.4)	
Right distal SFA	28.7% (72/251)	34.0% (84/247)		
Left distal SFA/popliteal artery	0.4% (1/251)	0.8% (2/247)	-1.3 (-4.3, 1.8)	
Right distal SFA/popliteal artery	2.0% (5/251)	2.8% (7/247)		
Left popliteal artery	2.0% (5/251)	0.8% (2/247)	1.5 (-2.1, 5.1)	
Right popliteal artery	3.2% (8/251)	2.8% (7/247)		

[1] Bilateral lesions were treated in 13 patients in the control group and 11 patients in the treatment group.
[2] Confidence interval is the difference in means for continuous variables and difference in percentages for categorical variables.
[3] *P* values are based on *t*-test for continuous variables and Fisher's exact test for categorical variables.

Table 7. Lesion characteristics

Characteristics		Control Group	Treatment Group	Diff. (95% CI)[2]	*P*-value[3]
Lesion class (TASC)[1]	A	36.0% (86/239)	29.4% (69/235)	6.6 (-1.8, 15.04)	0.07
	B	25.9% (62/239)	22.6% (53/235)	3.4 (-4.3, 11.1)	
	C	31.0% (74/239)	42.6% (100/235)	-11.6 (-20.2, -3.0)	
	D	7.1% (17/239)	5.5% (13/235)	1.6 (-2.8, 6.0)	
Accessibility	Readily accessible	100% (215/215)	100% (215/215)	0 (0, 0)	N/A
	Moderate tortuosity	0.0% (0/215)	0.0% (0/215)	N/A	
	Excessive tortuosity	0.0% (0/215)	0.0% (0/215)	N/A	
Lesion angulation	Non-angulated	95.2% (237/249)	95.4% (228/241)	-0.3 (-4.0, 3.5)	> 0.99
	Moderate	4.8% (12/249)	4.6% (11/241)	0.3 (-3.5, 4.0)	
Calcification	None	4.8% (12/249)	1.7% (4/241)	3.2 (0.05, 6.3)	< 0.01*
	Little	38.2% (95/249)	25.7% (62/241)	12.4 (4.3, 20.6)	
	Moderate	22.1% (55/249)	35.3% (85/241)	-13.2 (-21.1, -5.3)	
	Severe	34.9% (87/249)	37.3% (90/241)	-2.4 (-10.9, 6.1)	

Characteristics		Control Group	Treatment Group	Diff. (95% CI)[2]	*P*-value[3]
Other stenosis in artery	None	51.4% (111/216)	51.7% (107/207)	-0.3 (-9.8, 9.2)	0.71
	≤ 50%	34.3% (74/216)	31.4% (65/207)	2.9 (-6.1, 11.8)	
	> 50%	14.4% (31/216)	16.9% (35/207)	-2.6 (-9.5, 4.4)	
Inflow tract stenosis	None	41.6% (96/231)	37.1% (76/205)	4.5 (-4.7, 13.7)	0.03*
	≤ 50%	45.5% (105/231)	40.5% (83/205)	5.0 (-4.3, 14.3)	
	> 50%	13.0% (30/231)	22.4% (46/205)	-9.5 (-16.6, -2.3)	
Patent runoff vessels	0	17.3% (26/150)	14.8% (22/149)	2.6 (-5.8, 10.9)	0.47
	1	52.7% (79/150)	47.7% (71/149)	5.0 (-6.3, 16.3)	
	2	21.3% (32/150)	22.8% (34/149)	-1.5 (-10.9, 7.9)	
	3	8.0% (12/150)	14.1% (21/149)	-6.1 (-13.2, 1.0)	
Ulceration		19.0% (47/248)	16.7% (40/240)	2.3 (-4.5, 9.1)	0.55
Total Occlusion		27.4% (68/248)	32.8% (79/241)	-5.4 (-13.5, 2.8)	0.20

[1] TASC lesion class was determined by the site and was not evaluated by the core lab.
[2] Confidence interval is the difference in means for continuous variables and difference in percentages for categorical variables.
[3] *P* values are based on *t*-test for continuous variables and Fisher's exact test for categorical variables.
* Statistically significant.

Results

Patient availability for study follow-up through 24 months is summarized in Table 8.

Table 8. Clinical and imaging follow-up data

Follow-up	Eligible for Follow-up[1]	Percent of Data Available			Events Occurring Before Next Visit			
		Clinical Follow-up[2]	Core Laboratory X-ray Follow-up	Core Laboratory Ultrasound Follow-up[3]	Death	Withdrawn	Lost to Follow-up	Other Endpoint[4]
PTA Control Group								
Procedure	238	100.0% (238/238)	97.5% (117/120)[5]	86.6% (206/238)	2	3	0	1
6-month	232	94.0% (218/232)	76.5% (13/17)[5,6]	80.6% (187/232)	2	4	2	2
12-month	222	97.3% (216/222)	76.0% (114/150)[5]	83.3% (185/222)	4	5	0	3
2-year	210	83.3% (175/210)	n/a[8]	66.7% (84/126)[10]	n/a			
Zilver PTX Treatment Group								
Procedure	236[7]	100.0% (236/236)	96.2% (227/236)	89.4% (211/236)	0	1	1	0
6-month	234	94.0% (220/234)	86.2% (25/29)[6]	80.3% (188/234)	9	4	4	0
12-month	217	97.7% (212/217)	84.3% (183/217)	87.1% (189/217)	9	4	3	3
2-year	198	83.8% (166/198)	n/a[8]	51.0% (101/198)	n/a			

[1] Eligible for follow-up = previous eligibility for follow-up – (previous death + withdrawn + LTF).

[2] Includes cases with at least one of any of the following submitted: clinical form, death form, withdrawn form, or lost to follow-up form.

[3] Includes only ultrasound studies considered diagnostic by the core lab.

[4] Patients who reached an "other endpoint" include 2 patients who received a non-study stent during reintervention and 1 patient who moved but has not formally withdrawn from the trial.

[5] Only patients implanted with stents (i.e., acute PTA failure) were required to have x-ray follow-up.

[6] Only first 60 patients enrolled were required to have 6-month x-ray follow-up.

[7] Five patients treated as live cases not included.

Safety

The primary safety endpoint of non-inferior (i.e., equivalent or superior) safety for the Zilver PTX Drug-Eluting Peripheral Stent compared to PTA (including provisional stenting (bare and PTX-coated) in the PTA group) was met with an event-free survival rate at 12 months of 90.4% for the Zilver PTX treatment group and 83.9% for the PTA control group ($p < 0.01$[3]), as illustrated in Figure 3 and Table 9. The most common major adverse event was TLR (Table 10), which occurred approximately 70% more often in the PTA group relative to the Zilver PTX group (16.3% vs. 9.6%, respectively; $p = 0.04$). No patient deaths were adjudicated by the CEC as related to the device or procedure. Non-inferiority of the Zilver PTX Drug-Eluting Peripheral Stent was maintained through 24 months.

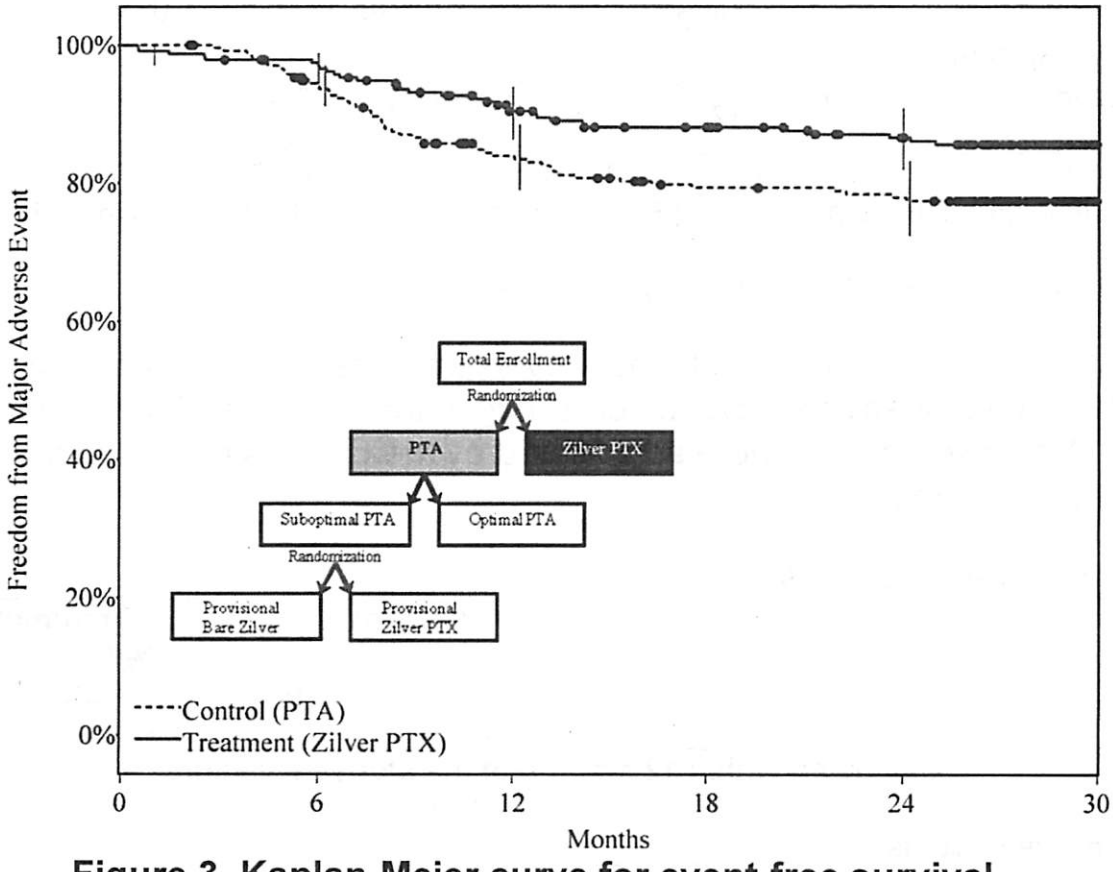


Figure 3. Kaplan-Meier curve for event-free survival

[3] Adjusted for multiplicity.

Table 9. Kaplan-Meier estimates for event-free survival at 0, 1, 6, 12, and 24 months

Months Post-procedure	Event-free Survival Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatmer (Zilver PTX)
0	100.0%	100.0%	0.0%	0.0%	0	0	0	0	236	235
1	100.0%	99.1%	0.0%	0.6%	0	2	0	0	236	233
6	94.4%	97.0%	1.5%	1.1%	13	7	6	3	217	225
12	83.9%	90.4%	2.4%	1.9%	37	22	15	16	184	197
24	77.9%	86.6%	2.8%	2.3%	50	30	22	33	164	172

Table 10. Rates of individual major adverse events at 12 months

Major Adverse Event	Control (PTA)[1]	Treatment (Zilver PTX)[1]	P-value	Diff. (95% CI)[3]
Clinically-driven TLR	16.3% (36/221)[2]	9.6% (21/219)	0.04	(0.5, 12.9)
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	0.9% (2/221)[2]	0.0% (0/219)	0.49	-
Amputation	0.0% (0/221)	0.5% (1/219)	0.49	-

[1] One patient experienced a worsening Rutherford and a TLR and is included in both categories in this table.
[2] Confidence interval is the difference in percentages.

Table 11 provides a summary of other adverse events through 24 months, not including major adverse events, occurring in the control and treatment groups. No patient deaths were adjudicated by the CEC as related to the study device or procedure.

Table 11. Adverse events

Event Type	Control		Treatment	
	% (n) N = 236 patients	Events	% (n) N = 235 patients[1]	Events
Occurring within 12 months of the study procedure				
Death	1.7% (4)	4	3.4% (8)	8
Major Adverse Events				
Clinically-driven TLR	15.3% (36)	36	8.9% (21)	21
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	0.8% (2)	2	0.0% (0)	0
Amputation	0.0% (0)	0	0.4% (1)	1
Cardiovascular Events				
Cardiac ischemia requiring intervention	3.0% (7)	7	3.8% (9)	13

Event Type	Control		Treatment	
Non-Q-Wave MI	0.4% (1)	1	0.9% (2)	2
Congestive heart failure	0.8% (2)	2	3.0% (7)	7
Refractory hypertension	0.4% (1)	1	0.0% (0)	0
Arrhythmia requiring intervention or new treatment	1.7% (4)	5	3.4% (8)	9
Other cardiovascular events	12.3% (29)	41	7.7% (18)	20
Pulmonary Events				
Pulmonary edema requiring treatment	0.0% (0)	0	0.4% (1)	1
Ventilation greater than 24 hours in duration	0.4% (1)	1	1.3% (3)	3
Pneumonia requiring antibiotics	2.1% (5)	6	5.1% (12)	14
Supplemental oxygen at time of discharge (exclude if for high altitude)	0.0% (0)	0	0.4% (1)	1
Re-intubation	0.0% (0)	0	0.4% (1)	1
COPD	1.7% (4)	5	0.9% (2)	4
Other pulmonary events	3.0% (7)	11	8.5% (20)	28
Renal Events				
UTI requiring antibiotic treatment	0.8% (2)	3	2.6% (6)	7
Serum creatinine rise greater than 30% above baseline resulting in persistent value greater than 2 mg/dl	0.8% (2)	2	0.0% (0)	0
Other renal events	2.5% (6)	8	4.3% (10)	12
Gastrointestinal Events				
Other gastrointestinal events	3.8% (9)	12	10.2% (24)	30
Wound Events				
Wound infection/abscess formation	1.3% (3)	3	1.7% (4)	5
Tissue necrosis requiring debridement	1.3% (3)	3	0.4% (1)	1
Wound complication requiring return to operating room	1.7% (4)	5	0.9% (2)	3
Other wound events	2.5% (6)	6	0.9% (2)	2
Vascular Events				
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to the study vessel	8.1% (19)	22	5.5% (13)	14
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to another vessel	16.9% (40)	52	21.3% (50)	62
Ischemia requiring surgical intervention (i.e., bypass or amputation) of another vessel	2.5% (6)	6	1.7% (4)	4
Embolism distal to treated study vessel	0.4% (1)	1	0.9% (2)	2
Embolism within another vessel	0.0% (0)	0	1.3% (3)	3
Thrombosis of the study lesion	0.8% (2)	2	2.6% (6)	6
Thrombosis other than study lesion	0.0% (0)	0	0.9% (2)	2
Blue toe syndrome	0.0% (0)	0	0.4% (1)	1
Aneurysm (other)	0.0% (0)	0	0.9% (2)	2

Event Type	Control		Treatment	
Deep vein thrombosis	0.4% (1)	1	0.9% (2)	2
Hematoma requiring intervention at access site	0.4% (1)	1	0.4% (1)	1
Pulmonary embolism	0.4% (1)	1	0.0% (0)	0
Pseudoaneurysm or AV fistula of the study vessel	0.8% (2)	2	0.4% (1)	1
Pseudoaneurysm or AV fistula of another vessel	0.4% (1)	1	0.4% (1)	2
Study vessel spasm	0.0% (0)	0	0.4% (1)	1
Worsened claudication/rest pain	6.8% (16)	21	4.3% (10)	12
Stroke	0.8% (2)	2	0.4% (1)	1
Vascular/surgical repair of injury to another vessel (other than amputation or bypass)	0.4% (1)	1	0.9% (2)	3
Post-procedure transfusion	4.2% (10)	15	5.5% (13)	13
Other vascular events	16.5% (39)	47	9.8% (23)	29
Miscellaneous Events				
Drug reaction (including contrast reaction)	2.1% (5)	5	3.8% (9)	10
Hypersensitivity/allergic reaction	2.1% (5)	5	2.1% (5)	6
Other miscellaneous events	26.7% (63)	120	28.1% (66)	115
Occurring between 12 and 24 months following the study procedure				
Death	1.7% (4)	4	4.3% (10)	10
Major Adverse Events				
Clinically-driven TLR	4.7% (11)	11	3.4% (8)	8
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	1.7% (4)	4	0.0% (0)	0
Cardiovascular Events				
Cardiac ischemia requiring intervention	3.0% (7)	7	3.4% (8)	8
Non-Q-Wave MI	0.8% (2)	2	0.4% (1)	1
Congestive heart failure	1.3% (3)	4	1.3% (3)	6
Refractory hypertension	0.4% (1)	1	0.0% (0)	0
Arrhythmia requiring intervention or new treatment	0.8% (2)	2	1.7% (4)	5
Other cardiovascular events	7.6% (18)	30	3.8% (9)	10
Pulmonary Events				
Pulmonary edema requiring treatment	0.0% (0)	0	0.4% (1)	1
Pneumonia requiring antibiotics	1.3% (3)	3	1.7% (4)	4
Supplemental oxygen at time of discharge (exclude if for high altitude)	0.0% (0)	0	0.4% (1)	1
COPD	0.8% (2)	2	0.0% (0)	0
Pleural effusion requiring treatment	0.0% (0)	0	0.4% (1)	2
Other pulmonary events	3.0% (7)	7	3.4% (8)	10
Renal Events				
UTI requiring antibiotic treatment	0.8% (2)	2	0.4% (1)	1

Event Type	Control		Treatment	
Serum creatinine rise greater than 30% above baseline resulting in persistent value greater than 2 mg/dl	0.8% (2)	2	0.0% (0)	0
Other renal events	1.7% (4)	8	2.1% (5)	5
Gastrointestinal Events				
Other gastrointestinal events	3.4% (8)	9	2.6% (6)	6
Wound Events				
Wound infection/abscess formation	0.4% (1)	2	1.3% (3)	3
Wound complication requiring return to operating room	0.4% (1)	1	0.0% (0)	0
Other wound events	0.0% (0)	0	1.3% (3)	3
Vascular Events				
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to the study vessel	5.1% (12)	14	3.8% (9)	9
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to another vessel	5.9% (14)	16	6.0% (14)	16
Ischemia requiring surgical intervention (i.e., bypass or amputation) of another vessel	0.8% (2)	2	1.7% (4)	4
Embolism distal to treated study vessel	0.0% (0)	0	0.4% (1)	1
Embolism within another vessel	0.4% (1)	1	0.0% (0)	0
Thrombosis of the study lesion	0.0% (0)	0	0.4% (1)	1
Blue toe syndrome	0.0% (0)	0	0.4% (1)	1
Deep vein thrombosis requiring surgical or lytic therapy	0.0% (0)	0	0.4% (1)	1
Worsened claudication/rest pain	2.5% (6)	6	3.4% (8)	9
Stroke	1.7% (4)	4	1.3% (3)	3
Vascular/surgical repair of injury to the study vessel (other than amputation or bypass)	0.0% (0)	0	0.4% (1)	2
Vascular/surgical repair of injury to another vessel (other than amputation or bypass)	0.4% (1)	1	0.0% (0)	0
Post-procedure transfusion	0.0% (0)	0	1.7% (4)	5
Other vascular events	4.7% (11)	12	3.4% (8)	10
Miscellaneous Events				
Hypersensitivity/allergic reaction	0.0% (0)	0	0.4% (1)	1
Other miscellaneous events	14.0% (33)	44	15.7% (37)	55

[1] One patient was not treated with a Zilver PTX stent so is not included in this analysis

Effectiveness

The primary effectiveness endpoint of superior primary patency (conservatively defined as a PSV ratio < 2.0) for the Zilver PTX Drug-Eluting Peripheral Stent compared to PTA was met ($p < 0.01$[4]) with a primary patency rate at 12 months of 82.7% for the Zilver PTX treatment group and 32.7% for the PTA control group, as illustrated in Figure 4 and Table 12. The benefit of the Zilver PTX Drug-Eluting Peripheral Stent was maintained through 24 months.

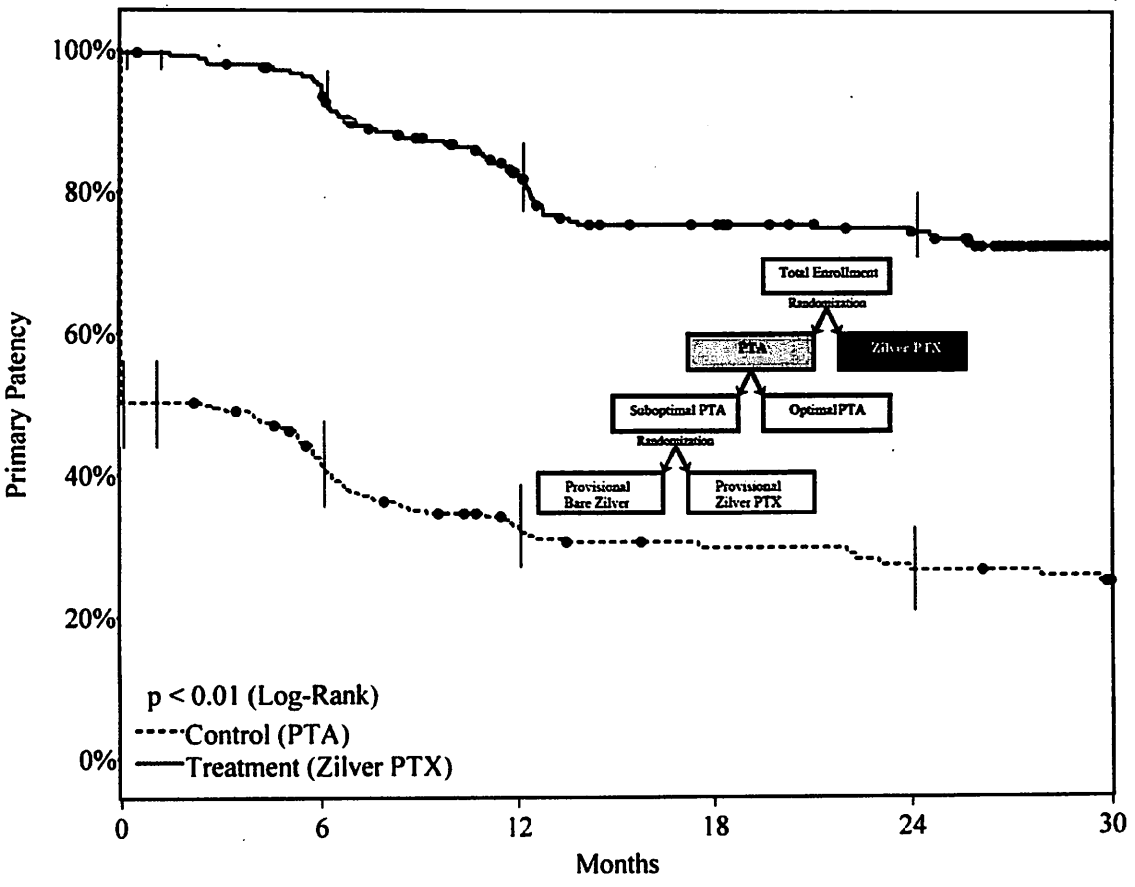


Figure 4. Kaplan-Meier curve for primary patency

[4] Adjusted for multiplicity.

Table 12. Kaplan-Meier estimates for primary patency at 0, 1, 6, 12, and 24 months

Months Post-procedure	Primary Patency Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)
0	50.2%	99.6%	3.2%	0.4%	125	1	0	0	126	245
1	50.2%	99.6%	3.2%	0.4%	125	1	0	1	126	244
6	41.6%	95.1%	3.1%	1.4%	146	12	5	4	100	230
12	32.7%	82.7%	3.0%	2.5%	167	41	11	23	73	182
24	26.5%	74.8%	3.1%	2.9%	177	58	41	39	33	149

Comparison of the results for patients treated with the Zilver PTX Drug-Eluting Peripheral Stent to those treated with the bare metal Zilver stent when used in a similar patient population (i.e., those patients who had acute failure of PTA) provides an evaluation of the paclitaxel drug effect. Both patient populations were selected in the same way (and randomized), and both stents have the identical stent platform; therefore, this comparison provides a direct measurement of the effectiveness of the Cook PTX® drug coating on the Zilver PTX Drug-Eluting Peripheral Stent. As illustrated in Figure 5 and Table 13, there was a significant difference in patency outcomes between the groups ($p < 0.01$[5]), with the Zilver PTX group exhibiting a higher primary patency rate at 12 months of 90.2% compared to 72.9% for the bare Zilver group. The benefit of the Zilver PTX Drug-Eluting Peripheral Stent was maintained through 24 months with a 24-month patency rate of 83.4% for the Zilver PTX group compared to 64.1% for the bare Zilver group.

[5] Adjusted for multiplicity.

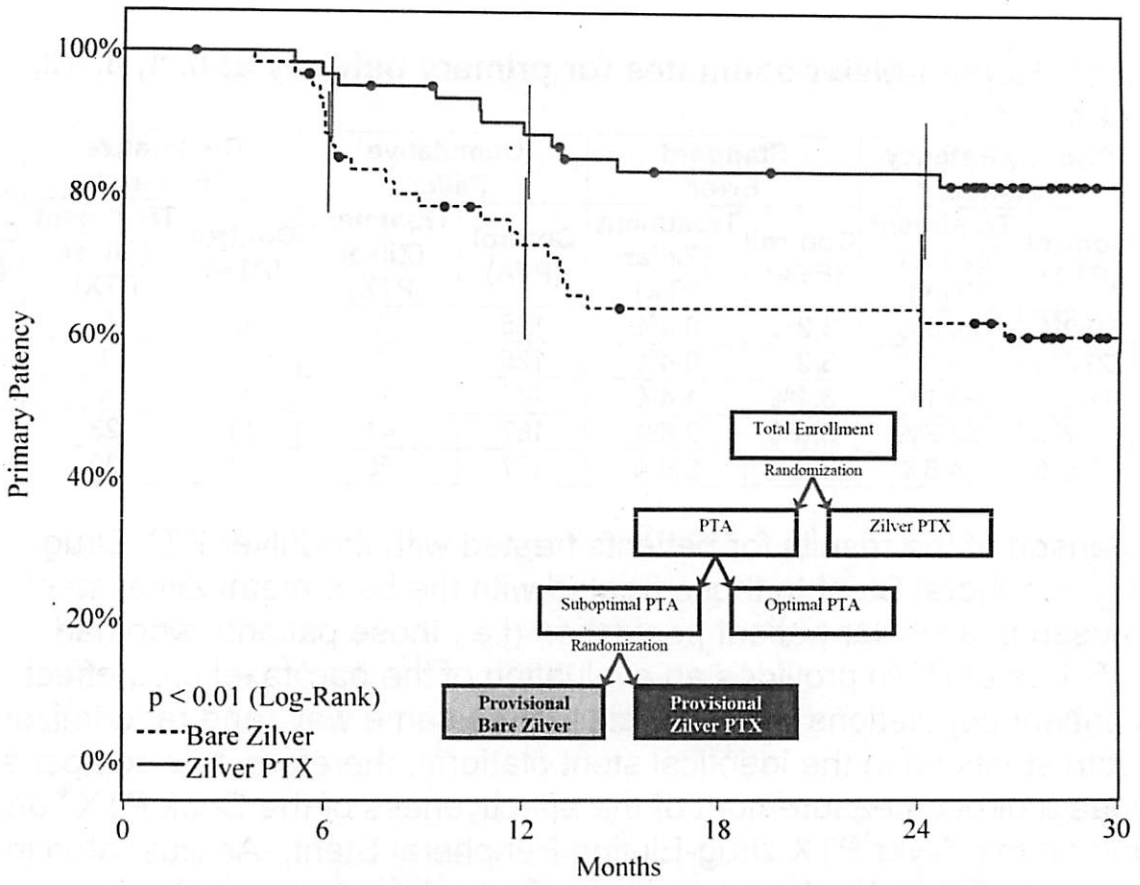


Figure 5. Kaplan-Meier estimate plot for primary patency for provisional bare Zilver vs. provisional Zilver PTX (ITT)

Table 13. Kaplan-Meier estimates for bare Zilver vs. Zilver PTX

Months Post-procedure	Primary Patency Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX
0	100.0%	100.0%	0.0%	0.0%	0	0	0	0	62	63
1	100.0%	100.0%	0.0%	0.0%	0	0	0	0	62	63
6	88.4%	96.8%	4.1%	2.2%	7	2	2	1	53	60
12	72.9%	90.2%	5.8%	3.8%	16	6	5	3	41	54
24	64.1%	83.4%	6.3%	4.8%	21	10	6	7	35	46

In summary, the primary patency rate at 12 months was 82.7% in the Zilver PTX treatment group and 32.7% in the PTA control group. The effect of covariates, including diabetes, lesion length, and occluded/stenosed lesions, was not significantly different between the Zilver PTX and PTA groups.

In conclusion, the primary effectiveness hypothesis of the study was met, indicating that treatment with the Zilver PTX Drug-Eluting Peripheral Stent is significantly more effective than treatment with PTA. Additionally, results from patient groups within the secondary randomization demonstrated that stenting with the paclitaxel-coated Zilver PTX Drug-Eluting Peripheral Stent is significantly more effective in maintaining primary patency than stenting with the same bare (uncoated) stent, indicating that the PTX® coating has a significant effect and further supporting the effectiveness of the Zilver PTX Drug-Eluting Peripheral Stent.

Secondary Endpoints

Secondary endpoint analyses include procedural success, the patient-centered measure of freedom from worsening symptoms of ischemia (i.e., sustained clinical benefit), clinical status (i.e., clinical improvement defined as improvement by 1 Rutherford class and clinical success defined as improvement by 2 Rutherford classes), and functional status (measured by ABI and Walking Impairment Questionnaire).

Procedural success (< 30% residual stenosis) was significantly higher ($p < 0.01$) in the Zilver PTX treatment group (95.0%; 229/241) compared to the PTA control group (57.7%; 143/248), demonstrating that the Zilver PTX Drug-Eluting Peripheral Stent is effective in establishing acute patency.

Sustained clinical benefit (i.e., freedom from worsening symptoms of ischemia) was evaluated in terms of freedom from the patient-centered measures of worsening claudication, worsening Rutherford class, tissue loss, and other symptoms indicating the need for reintervention (e.g., rest pain, ulcer, persistent claudication), and was considered to provide a clinically-based evaluation of patient benefit in this study, without the inclusion of surrogate endpoints. In this evaluation, patients in the Zilver PTX treatment group achieved a higher sustained clinical benefit compared to patients in the PTA control group (86.9% vs. 75.4% at 12 months). Similarly, in subgroups within the PTA control group, patients receiving provisional Zilver PTX Drug-Eluting Peripheral Stents achieved a higher sustained clinical benefit compared to patients receiving optimal PTA (87.3% vs. 69.4% at 12 months) or provisional bare Zilver stents (87.3% vs. 72.3% at 12 months).

Substudies

Pharmacokinetic Substudy

A subgroup of 60 patients from the Zilver PTX treatment group was included in the pharmacokinetic (PK) substudy to evaluate systemic paclitaxel delivery. Each patient was assigned 3 of a possible 11 time points, which included post-procedure (time 0), 20 min, 40 min, and 1, 1.5, 2, 3, 4, 6, 8, and 12 hours. Patients were divided into two groups based on the number of stents with which they were implanted. The number of patients and total quantity of paclitaxel for each group are shown in Table 14.

Table 14. Pharmacokinetic substudy groups

# of Stents	# of Patients[1]	# of Samples	Paclitaxel Dose Range (µg)
1	42	125	312 - 864 (mean ± SD = 694 ± 200)
2	16	48	1083 - 1728 (mean ± SD = 1398 ± 228)

[1] Two patients were not included in the analysis; samples from one patient were assayed beyond the known stability timeframe; one patient received three Zilver PTX Drug-Eluting Peripheral Stents.

A parametric curve was fit to the data and the maximum observed plasma paclitaxel concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration-time curve (AUC), half-life ($t_{1/2}$), and paclitaxel total clearance (CL_{plasma}) were estimated, along with 95% confidence intervals (Table 15). Additionally, a curve was fit to previously reported pharmacokinetic results obtained for animals implanted with Zilver PTX Drug-Eluting Peripheral Stents with a total of 876 µg paclitaxel coating per animal, and C_{max}, T_{max}, AUC, $t_{1/2}$, and CL_{plasma} were estimated.

Table 15. Pharmacokinetic parameters (with 95% confidence intervals)

Parameter	One Stent (n = 42)	Two Stents (n = 16)	Animal PK Study (n = 2)[1]
T_{max} (min)	20	22	20
C_{max} (ng/mL)	4.4 (4.2 - 4.6)	6.6 (6.3 - 6.9)	7.1
$AUC_{0\text{-}last}$[2] (ng·h/mL)	6.5 (4.7 - 8.5)	14.0 (10.7 - 17.2)	12.8
$AUC_{0\text{-}inf}$[3] (ng·h/mL)	6.5 (4.7 - 8.5)	14.9 (11.2 - 18.7)	12.8
$t_{1/2}$ (h)	2.4 (1.8 - 3.3)	7.0 (5.2 - 10.8)	1.6
CL_{plasma} (L/h)	107 (81.4 - 147.3)	93.3 (74.6 - 124.7)	68.5

[1] Confidence intervals were not calculated for this group because of the sample size of 2.
[2] AUC from time zero to time of last measured concentration.
[3] AUC from time zero to infinity.

Angiographic/IVUS Substudy

IVUS was intended to confirm the lack of aneurysm or stent malapposition related to the Zilver PTX Drug-Eluting Peripheral Stent, consistent with previous results from animal studies, and angiography was intended to confirm the concordance of angiography and duplex ultrasound for assessing vessel patency at follow-up. For the first 60 patients enrolled in the study, IVUS was required post-stenting and at 6 months for those patients receiving stents. An additional, eighty (80) patients, 40 each from the control and treatment groups, were assigned to an angiographic/ IVUS substudy. Patients in the substudy required angiography at the 12-month follow-up and substudy patients in the Zilver PTX treatment group also required IVUS post-stenting and at the 12-month follow-up.

The angiographic analysis includes all patients with both angiography and duplex ultrasound obtained at the 12-month follow-up and analyzed by the core laboratories. The agreement of angiography and duplex ultrasound for assessing lesion patency was evaluated. At 12-month follow-up, approximately 89% of lesions assessed by both angiography and duplex ultrasound were determined to be either patent or not patent by both measures and this excellent concordance between angiography and ultrasound confirms the validity of duplex ultrasound for assessing patency in the absence of angiography.

IVUS results demonstrate that no aneurysm or stent malapposition was detected at the 6-month or 12-month follow-ups, and the rate of aneurysm and stent malapposition was low immediately after stenting (2.4%, 2/85 aneurysm, 2/84 malapposition) and was not associated with clinical sequelae. Moreover, both events of aneurysm and stent malapposition detected immediately post-stenting were associated with a pre-existing aneurysm visible on the angiogram prior to stent implantation.

Stent Integrity

Zilver stent integrity (including both the Zilver PTX stent and the bare metal Zilver stent used in bailout stenting procedures) was evaluated prior to discharge and at 12 months by high resolution stent x-rays intended to provide visualization of the individual stent struts. As shown in Table 16, no stent fractures were detected upon procedure completion (0/528) and only four stent fractures (4/457) were detected at 12 months, for a 12-month stent fracture rate of 0.9%. Two of the four stent fractures were Type I (single strut) and two were Type III (multiple strut fractures resulting in complete transection of the stent, without displacement of the stent segments). All four of the patients with a stent fracture maintained primary patency and remained free from TLR through 12-month follow-up, indicating that the stent fractures did not adversely affect patient safety or the effectiveness of the Zilver PTX Drug-Eluting Peripheral Stent.

Table 16. Stent integrity prior to discharge and at 12 months

Time Point	Stents Visualized by X-ray	Stents with Fracture	Stent Fracture Rate
Prior to discharge	528	0	0%
12 months	457	4	0.9%

Stent Thrombosis

Through 24 months, stent thrombosis (or abrupt stent closure) was reported for 3.6% (2/56) of patients receiving bare Zilver stents (after provisional stenting in the PTA control group) and for 2.3% (7/305) of patients receiving Zilver PTX Drug-Eluting Peripheral Stents (in the Zilver PTX treatment group and after provisional stenting in the PTA control group).

Results Summary

The primary safety and effectiveness hypotheses of the study were both met and the study was successful. The results indicate that primary treatment with the Zilver PTX Drug-Eluting Peripheral Stent is as safe as or

safer than treatment with PTA with provisional stenting ($p < 0.01$) and that the Zilver PTX Drug-Eluting Peripheral Stent provides a significantly higher rate of primary patency compared to PTA ($p < 0.01$). Additionally, stenting with the paclitaxel-coated Zilver PTX Drug-Eluting Peripheral Stent is significantly more effective ($p < 0.01$) in maintaining primary patency through 12 months than stenting with the bare (uncoated) stent.

SINGLE ARM CLINICAL STUDY

The Zilver PTX single arm study was a prospective, non-randomized, open-label, multicenter study enrolling patients in Europe, Canada, and Korea with *de novo* or restenotic lesions of the above-the-knee femoropopliteal artery. All patients enrolled in the study were treated with the Zilver PTX Drug-Eluting Peripheral Stent.

Study Overview

The study was designed to quantify the safety and performance of the Zilver PTX Drug-Eluting Peripheral Stent. The primary hypothesis was that the event-free survival rate at 6 months for patients receiving the Zilver PTX Drug-Eluting Peripheral Stent was comparable to that seen in prior published endovascular studies of similar patient populations. Furthermore, this study was designed to contribute to a multi-study pool of more than 1000 Zilver PTX patients to provide broad clinical data and to establish the rate of potentially rare (device- or drug-related) adverse events with reasonable precision.

A total of 787 patients were enrolled at 30 sites. The study entry criteria were similar to the randomized study with the exception that there was no limitation on lesion length or the number of lesions treated per patient (up to 4 Zilver PTX Drug-Eluting Peripheral Stents could be used per patient) and the inclusion of lesions with in-stent restenosis was allowed. The study follow-up schedule included clinical assessment at pre-discharge and at 1, 6, 12, and 24 months, and ultrasound imaging and stent X-rays at pre-discharge and at 6 and 12 months. Telephone contact was scheduled for 3, 9, and 18 months. Clinical follow-up was available for 740 patients at 12 months and 500 patients at 24 months at the time of data analysis.

Demographics
Patient medical history included a high incidence of diabetes (36%, 285/787), hypercholesterolemia (58%, 458/787), hypertension (80%, 627/787), and past or current smoking (80%, 632/787). A total of 1722 Zilver PTX Drug-Eluting Peripheral Stents were implanted in 900 lesions during the study procedure, with more than 60% of patients being treated with at least 2 stents. Lesions treated in the study had a mean length of 100 ± 82 mm with 25% of lesions > 14 cm in length (224/900), 38% (345/900) classified as total occlusions, and 24% (219/900) having been previously treated, including 130 lesions that had been previously stented. **NOTE:** Lesions > 14 cm in length and previously stented lesions are outside of the approved indication for use.

Results
The 6-month event-free survival (EFS) rate for patients with a Zilver PTX Drug-Eluting Peripheral Stent was 97.4%, a rate superior to the prospectively defined objective performance criterion of 75% EFS ($p < 0.01$). EFS was 89.0% at 12 months and 79.3% at 24 months. Similarly, freedom from TLR was 89.3% at 12 months and 80.5% at 24 months.

Secondary outcomes were also favorable. Specifically, primary patency (conservatively defined as a PSV ratio < 2.0) was 83.0% at 12 months, and clinical and functional status measures (i.e., Rutherford classification, ABI, walking scores, and quality of life scores) improved significantly from pre-procedure to 12 months. Stent fractures were detected in 1.5% of stents (22/1432) at 12 months

The results from the Zilver PTX single arm study provide supporting evidence confirming the safety of the Zilver PTX Drug-Eluting Peripheral Stent for the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries.

COMBINED ANALYSIS of RANDOMIZED and SINGLE ARM STUDIES
The combined randomized and single arm studies include more than 1000 patients treated with more than 2000 Zilver PTX Drug-Eluting Peripheral Stents.

Stent integrity and the potential for rare adverse events were evaluated in this combined group of patients receiving Zilver PTX Drug-Eluting Peripheral Stents, including patients with long lesions treated with overlapped stents. Event-free survival at 12 months was 90.4% for the primary Zilver PTX group in the randomized study and 89.0% in the single arm study. Primary patency at 12 months was also similar between the two studies at 82.7% for the primary Zilver PTX group in the randomized study and 83.0% in the single arm study. These similar results demonstrate the complementary and supportive nature of the two studies. Whereas the randomized study was the pivotal study supporting safety and effectiveness and enrolled moderate length lesions, the single arm study provides additional clinical evidence supporting safety in a broader patient population.

Regarding stent integrity, high resolution radiographs demonstrated that 98.6% of stents remained free from stent fracture at 12 months (1863/1889), for a stent fracture rate of 1.4% (Table 17).

Table 17: Stent integrity at 12 months

# of Stents Visualized by X-ray	# of Stents with No Fracture	# of Stents with Stent Fracture	12-month Stent Integrity Rate	12-month Stent Fracture Rate
1889	1863	26*	98.6%	1.4%

* 3 Type I (single strut fracture), 5 Type II (multiple strut fractures resulting in complete transection of the stent, without displacement of stent segments, 4 Type III (multiple single strut fractures), 14 Type IV (multiple strut fractures resulting in displacement of segments of the stent).

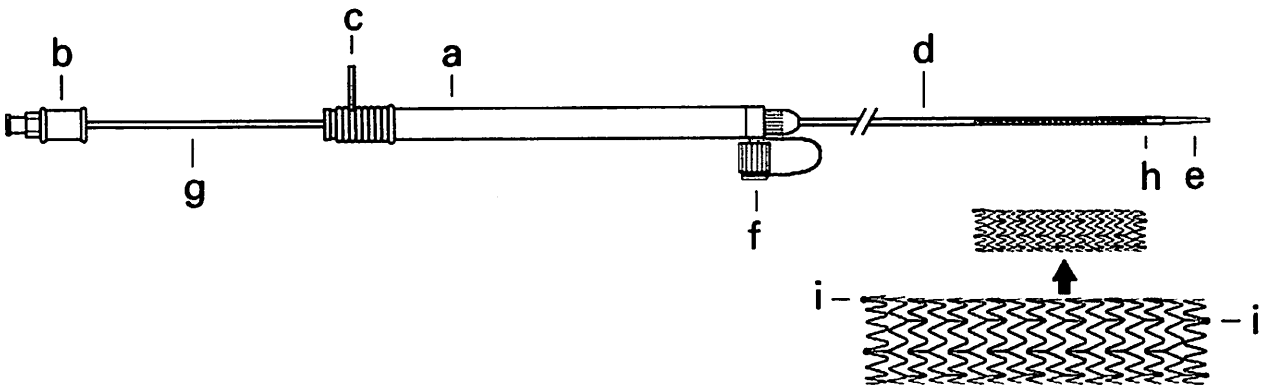
Importantly, 17 of the 26 stents with fractures (65%) were associated with quantifiable stent elongation during the implant procedure, including 11 (79%) of the Type IV fractures.

Regarding potential rare adverse events, there were no reported drug or hypersensitivity reactions attributed to the paclitaxel drug coating or the nitinol stent; the majority of reactions (21/33) were attributed to the antiplatelet medications ticlopidine or clopidogrel. Neutropenia was reported for 3.6% (2/56) of patients receiving bare Zilver stents (after

provisional stenting in the PTA control group) and for 0.4% (4/1092) of patients receiving Zilver PTX Drug-Eluting Peripheral Stents (all Zilver PTX Drug-Eluting Peripheral Stent patients from combined randomized and single arm studies). None of the rare cases of neutropenia were determined to be due to the paclitaxel coating on the Zilver PTX Drug-Eluting Peripheral Stent or to participation in the study. The incidence of adverse events with a potential to be related to particulate matter (i.e., embolism distal to the study vessel and blue toe syndrome) was low for patients receiving bare Zilver (1.8%, 1/56) or Zilver PTX Drug-Eluting Peripheral Stents (0.6%, 7/1092), and was not increased for patients receiving a Zilver PTX Drug-Eluting Peripheral Stent. The low rate of stent thrombosis through 24 months was not increased for patients receiving a Zilver PTX Drug-Eluting Peripheral Stent (3.4%, 37/1092) compared to patients receiving a bare Zilver stent (3.6%, 2/56), and was also consistent with previous femoropopliteal stenting outcomes reported in the literature. These results, including more than 1,000 patients and 2,000 Zilver PTX Drug-Eluting Peripheral Stents, provide additional evidence supporting the safety of the polymer-free PTX® coating and of the Zilver PTX Drug-Eluting Peripheral Stent.

PRODUCT RECOMMENDATIONS

Placement of this vascular stent requires advanced skills in interventional vascular procedures. The following instructions will give technical guidance, but do not obviate formal training in the use of the device.



a. Handle
b. Hub
c. Safety Lock
d. Delivery System: Outer Sheath
e. Tip of Delivery System Inner Catheter
f. Side-arm Flushing Port
g. Metal Cannula
h. Radiopaque Markers on the Delivery System
i. Gold Radiopaque Markers

Figure 6

Multiple Stent Placement

If placements of multiple stents are required in a patient, to cover the length of the lesion, the following recommendations should be considered:

- In relation to the lesion site, the distal area of narrowing should be stented first, followed by the proximal locations (i.e., a second stent should be placed proximally to the previously placed stent).
- Stents placed in tandem must overlap to allow for complete coverage of the lesion.
- The effect of implanting more than four 10 x 80 mm Zilver PTX Drug-Eluting Peripheral Stents (i.e., a maximum drug coating quantity of approximately 3 mg paclitaxel) in a patient has not been clinically evaluated.

INSTRUCTIONS FOR USE

Stent Sizing

1. Determine the proper stent size after complete diagnostic evaluation. The stent deployment must be performed under fluoroscopic control. Measure the length of the target lesion to determine the length of the stent required. Allow for the proximal and distal aspects of the stent to cover the entire target area.

NOTE: The Zilver PTX Drug-Eluting Peripheral Stent is designed not to shorten upon deployment. Bench testing has shown that on average, the stent length increases from pre-deployment to post-deployment by approximately 2.5%.

The stent is recommended for use in above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 7 mm.

Measure the diameter of the reference vessel (proximal and distal to the lesion) and use the LARGEST reference diameter as your basis for choosing the appropriate stent size.

The stent size should be selected so that the unconstrained stent diameter is at least 1 mm larger than the reference vessel diameter and no more than 2 mm larger than the reference vessel diameter.

Introduction of the Stent

1. Gain access to the site using a 6.0 French (2.0 mm) or larger introducer sheath.
2. To ensure adequate support of the system, introduce the extra or ultra stiff 0.035 inch (0.89 mm) wire guide through the introducer sheath across the distal segment of the target lesion.
3. Predilatation before stent placement is optional and at the discretion of the physician.

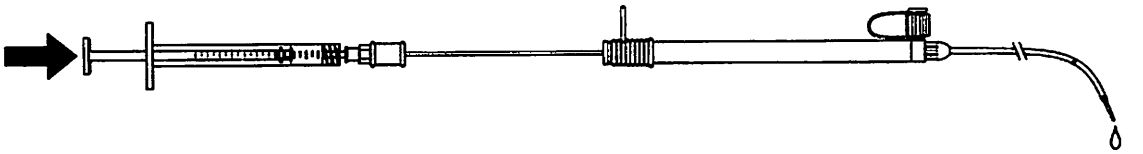


Figure 7

4. Immediately before placing the stent delivery system into the body, use the 1 ml syringe included in the inner package to flush the wire guide lumen with saline through the hub. (Figure 7)

   Use the 1 ml syringe to flush the delivery system with saline through the side-arm flushing port. Flush only until a few drops of saline exit the distal tip, between the delivery system inner catheter and outer sheath. (Figure 8).

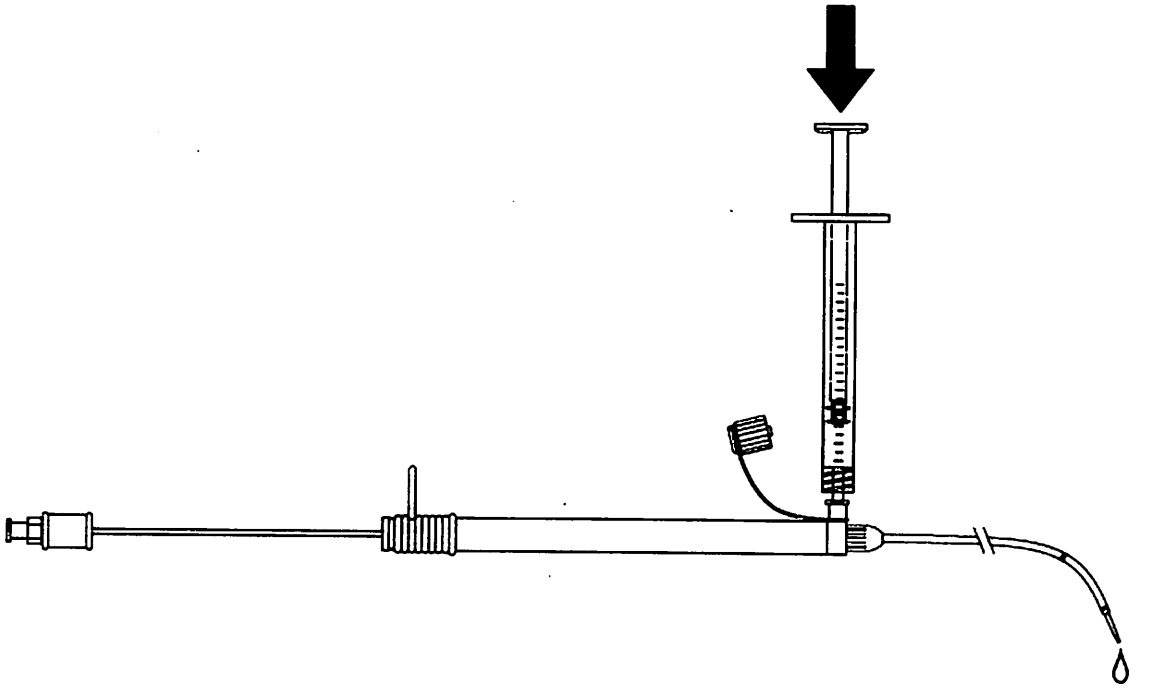


Figure 8

5. Under fluoroscopy, advance the delivery system over the wire guide through the introducer sheath until the distal gold radiopaque markers on the stent are beyond the target lesion site (Figure 9).

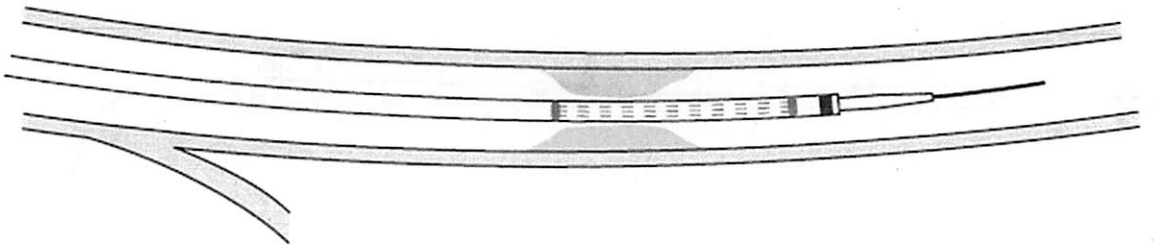


Figure 9

Alignment of the Stent

1. Before stent alignment, it is important to:
    a. Straighten the proximal part of the delivery system as much as possible (Figure 10)
    b. Remove any slack in the delivery system
    c. Keep the handle in a stable position.

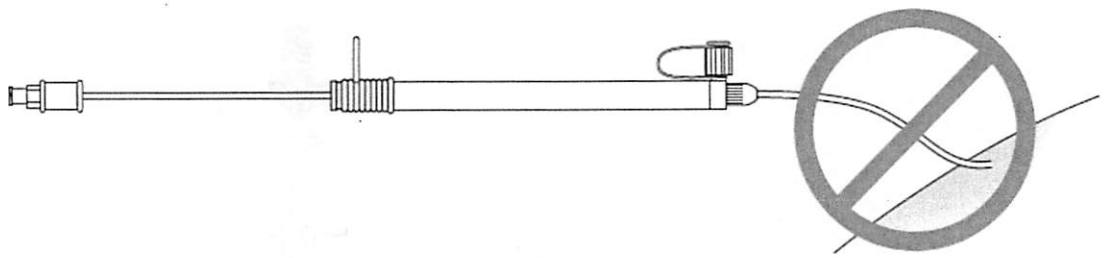


Figure 10

2. The stent alignment must be performed under fluoroscopic control.

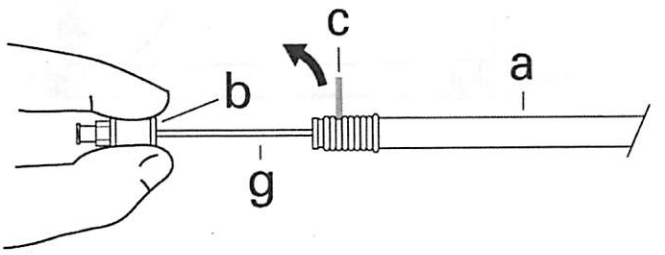


Figure 11

3. Remove the red safety lock (**c**) while holding the hub (**b**) on the metal cannula (**g**) steady. (Figure 11)

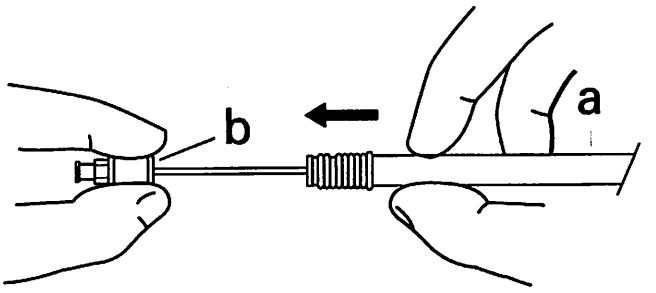


Figure 12

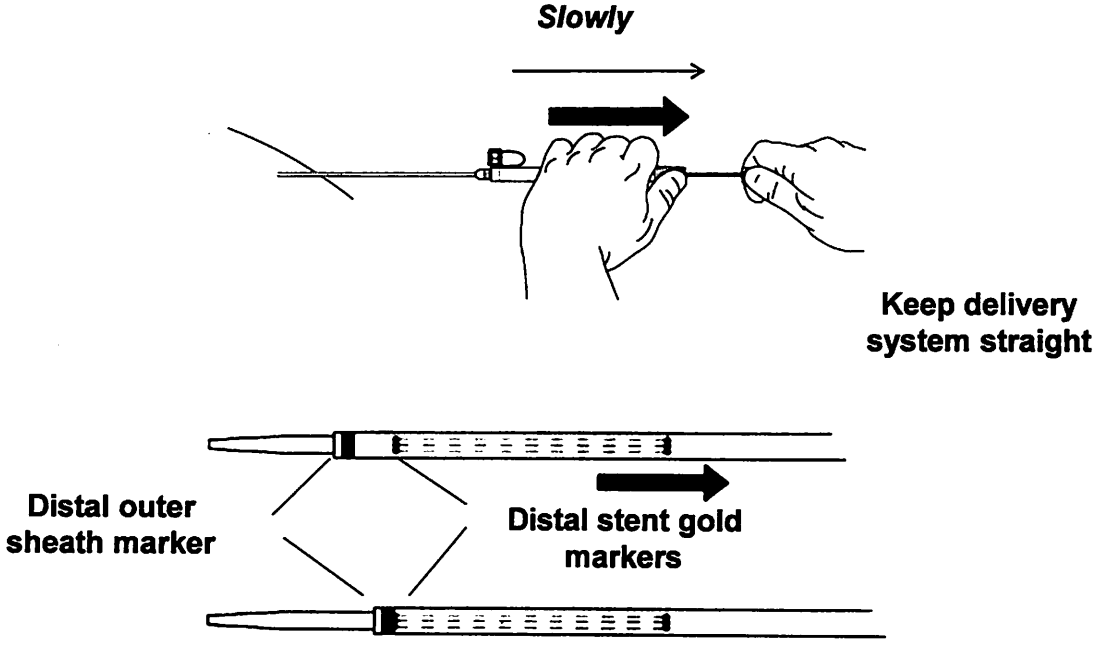


Figure 13

4. Hold the hub (**b**) steady. <u>As deployment begins, be prepared for some resistance</u>. Slowly pull the handle (**a**) toward the hub (**b**) (Figure 12) until the distal outer sheath marker overlaps the distal stent gold markers. (Figure 13)

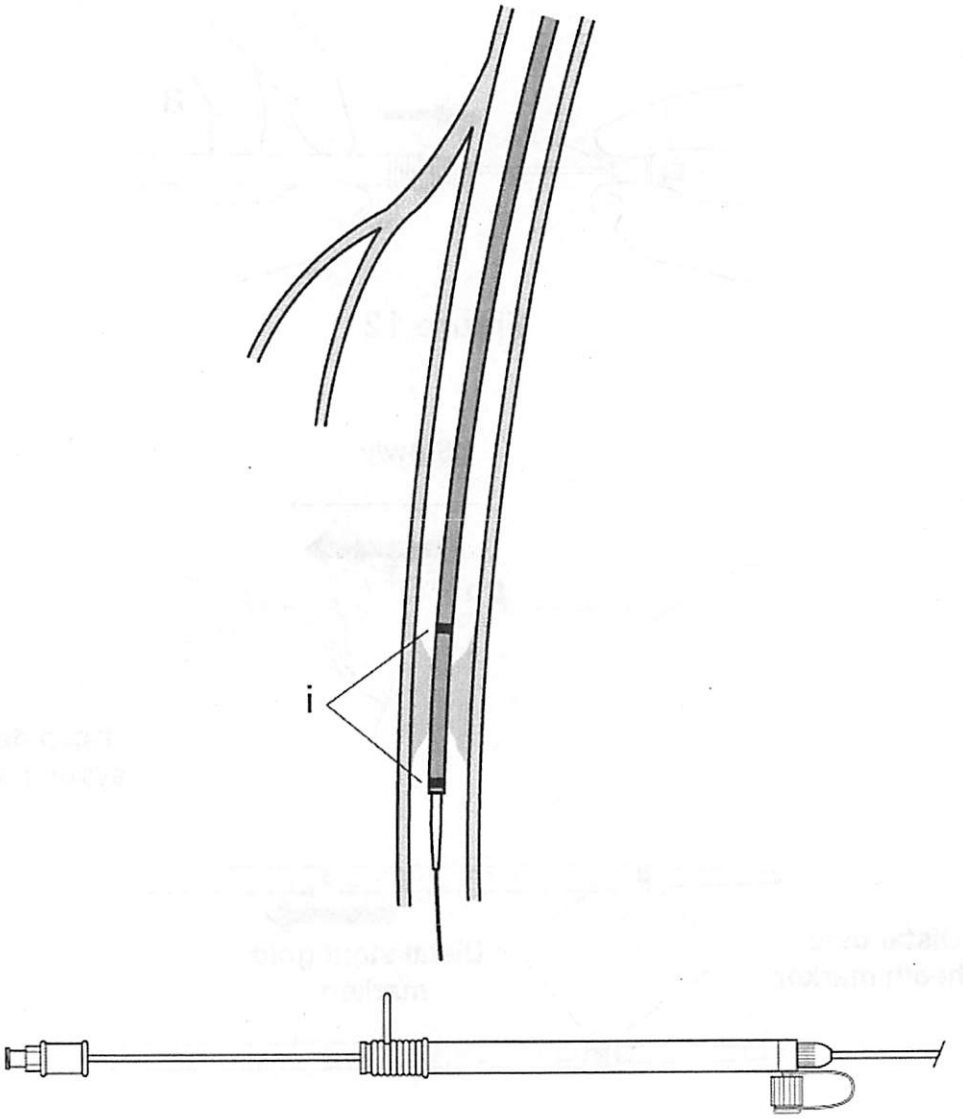


Figure 14

5. Align the radiopaque stent markers (i) to the desired position. (Figure 14) The stent should now be ready to be deployed.

Deployment of the Stent

1. Before stent deployment, it is important to:
    a. Straighten the proximal part of the delivery system as much as possible (Figure 15)
    b. Remove any slack in the delivery system
    c. Keep the handle in a stable position.

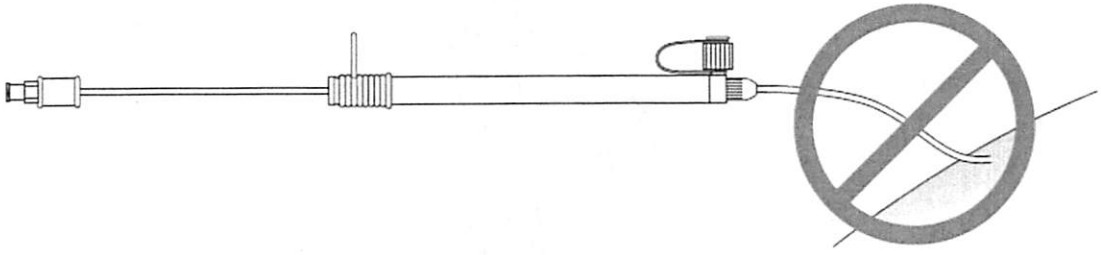


Figure 15

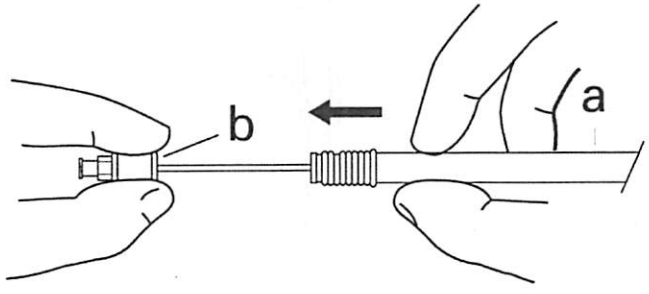


Figure 16

2. Hold the hub (**b**) steady. The stent will be deployed as you pull the handle (**a**) toward the hub (**b**). (Figure 16)

   NOTE: The majority of stent fractures in clinical studies were associated with stent elongation ≥ 10% at deployment. Therefore, care should be taken to hold the hub (**b**) stationary and to remove any slack in the introducer catheter to ensure the stent is not stretched or compressed lengthwise during deployment (i.e., so that the stent is deployed to its proper length). Before the stent deploys, slight movement may occur, so confirm that the stent markers are still aligned to the desired position. Reposition if necessary before deploying. Full deployment of the stent length will occur when the distal end of the sheath has been retracted past the proximal part of the stent.

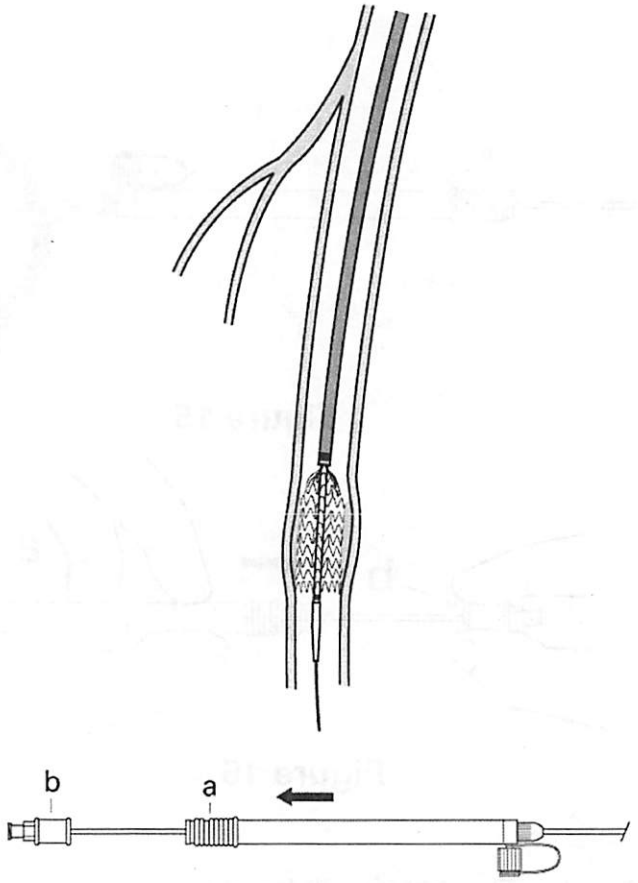


Figure 17

3. As deployment occurs, continue sliding the handle (**a**) toward the hub (**b**) in a slow, smooth and consistent fashion. (Figure 17) Once good wall apposition has been achieved by the distal 1-2cm of the stent, watch the proximal stent markers to ensure they remain stationary - this indicates that there is no compression or elongation of the stent.

   NOTE: Once stent deployment has begun, the stent must be fully deployed. Repositioning of the Zilver PTX Drug-Eluting Peripheral Stent is not possible since the delivery system's outer sheath cannot be re-advanced over the stent once deployment begins. Refer to the **Multiple Stent Placement** section of these Instructions For Use for information on missed lesions.

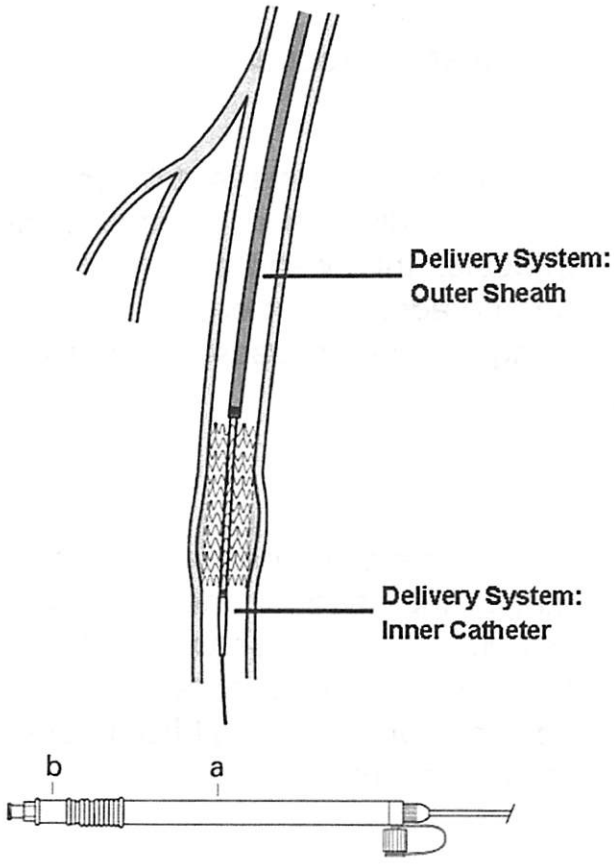


Figure 18

4. The stent is fully deployed when the handle (**a**) reaches the hub (**b**). (Figure 18)

Post Stent Deployment

1. Remove the delivery system.

   NOTE: If resistance is met during the withdrawal of the inner catheter through the stent, re-advance the outer sheath over the inner catheter to its pre-deployment position. Withdraw the system in this position.

2. Perform an arterial angiogram to verify full deployment of the device. If incomplete expansion exists within the stent at any point along the lesion,

post-deployment balloon dilatation (standard PTA) can be performed at the discretion of the physician.

3. Remove the wire guide and introducer sheath from the patient.
4. Close the entry wound as appropriate.

NOTE: Flow restrictions remaining after stent deployment (e.g., residual proximal or distal stenosis or dissection, or poor distal outflow) may increase the risk of stent thrombosis. Inflow and outflow should be assessed at procedure completion and additional measures considered (e.g., additional PTA, adjunctive stenting, or distal bypass) if necessary to maintain good inflow and outflow.

HOW SUPPLIED

Supplied sterilized by ethylene oxide gas in an outer non-sterile foil pouch and inner peel-open package. Intended for one-time use. Sterile if inner 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.

Use By

Single Use

Date of Manufacture

Lot Number

Keep away from direct sunlight

Keep Dry

Consult IFU

Attention See IFU

Sterilized using Ethylene oxide

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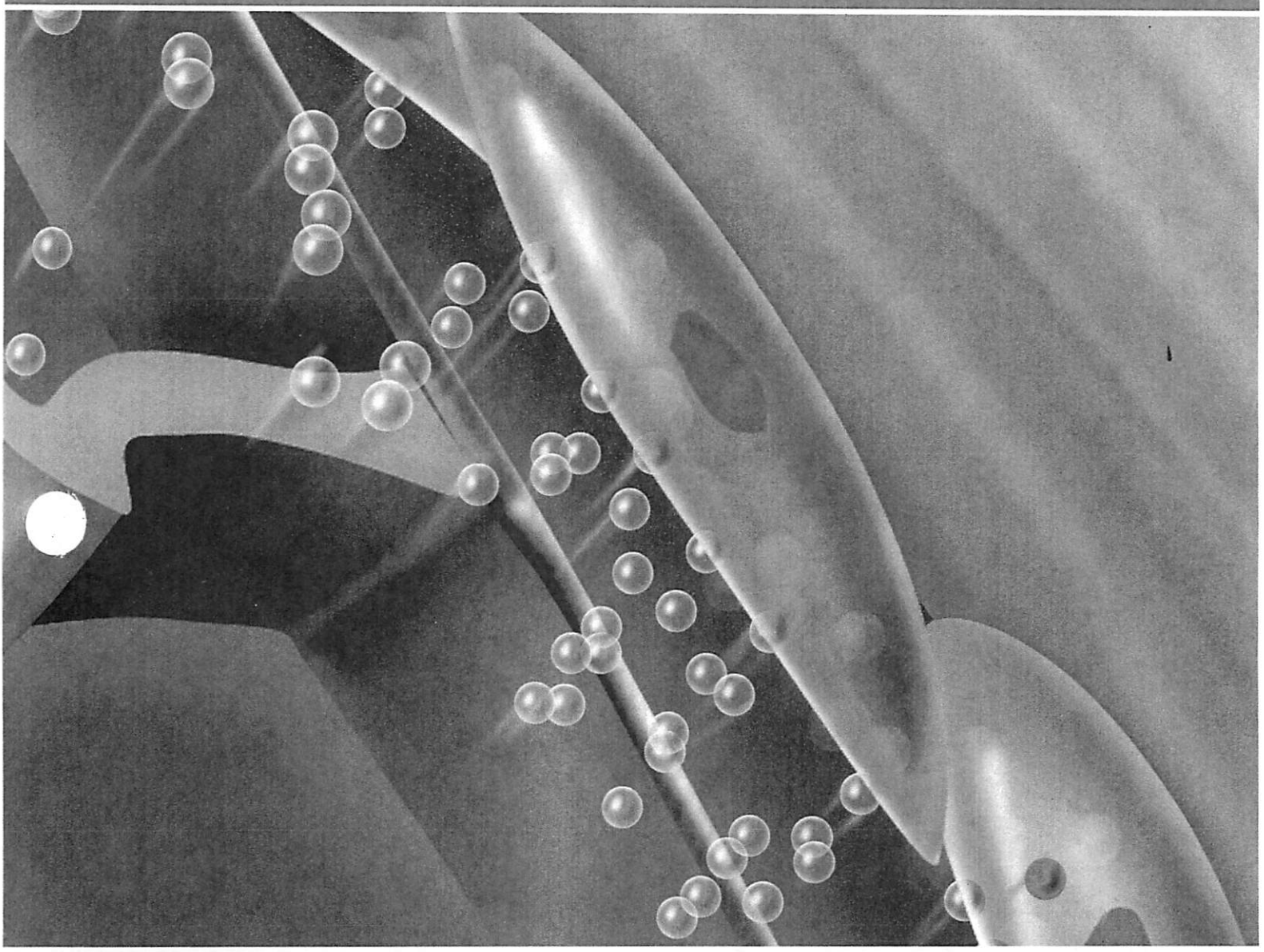
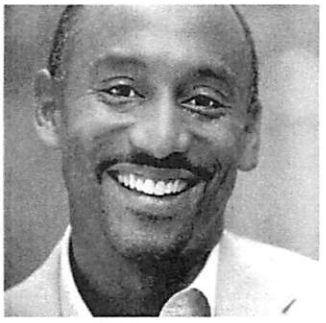
DRUG-ELUTING STENT



PATIENT GUIDE



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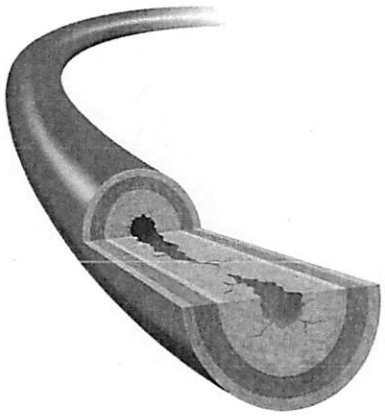


Peripheral arterial disease

Peripheral Arterial Disease

What is peripheral arterial disease?

Peripheral arterial disease, known as PAD, affects more than 30 million people worldwide every year. This serious, under-diagnosed disease is similar to coronary artery disease in that it develops when cholesterol levels and scar tissue build up, causing the arteries to narrow and restrict blood flow. The difference is that PAD affects arteries outside the heart.

Untreated, PAD can lead to difficulty in walking and, in its most severe stage, gangrene leading to leg amputation. Also, people who have PAD often have arterial blockages in other parts of the body and are therefore at greater risk of suffering a heart attack or stroke.

Who is at risk?

While **peripheral arterial disease** can strike anyone, it is most common in people over the age of 65. Up to 20 percent of all adults over the age 65 are affected by PAD.

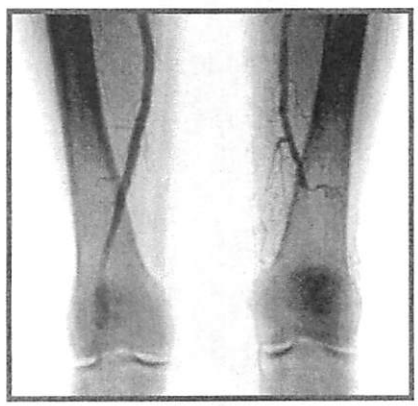
Artery during normal function

The most common risk factor for PAD is smoking. According to the University of Maryland, smoking increases the risk of PAD by two to five times. The American Heart Association says that on average smokers are diagnosed with PAD 10 years earlier than nonsmokers.

Diabetes is also a leading risk factor for PAD. People with Type 2 diabetes have three to four times the normal risk of PAD. Other risk factors include:

- Obesity
- High blood pressure
- Lack of exercise
- Family history of atherosclerosis (hardening of the arteries)
- High cholesterol

What are the symptoms of PAD?



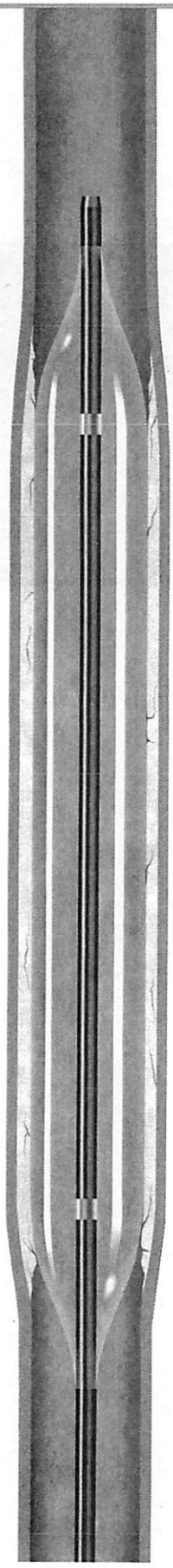
Many people with PAD do not exhibit any warning signs. In fact, only 33 percent of those diagnosed with PAD have any symptoms at all. Those who do have severe symptoms often mistake them for signs of aging.

The most common symptom of PAD is leg pain that occurs when walking, but disappears during rest. Other symptoms include:

- Numbness or weakness in the legs
- Aching pain in the feet or toes while at rest
- Ulcers or sores in the leg or foot that don't heal
- Cold legs or feet
- Skin-color changes in the legs or feet

How is PAD diagnosed?

Unfortunately, many cases of PAD go undiagnosed because the symptoms are often mistaken for signs of aging. One way to determine whether someone could be suffering from PAD is an ankle-brachial index (ABI) test. The ABI test measures the blood pressure at the ankle and at the arm. A comparison of the two blood pressure readings can point to problems. Specifically, a blood pressure that is lower in the ankle than in the arm implies a blockage in the artery between the heart and the leg. Other tests used to diagnose PAD include ultrasound, X-ray, **angiography** and magnetic resonance imaging **angiography** (MRA).



Treatment of PAD

The first-line treatment for PAD consists of lifestyle changes, such as smoking cessation, exercise and lowering blood pressure and cholesterol. These changes can help to slow the progression of PAD and decrease the likelihood of a heart attack or stroke. Lifestyle changes are often made in combination with the use of certain drugs—such as antiplatelet therapy to inhibit blood clotting, statins to reduce cholesterol, and ACE inhibitors to lower blood pressure. In a minority of patients, however, lifestyle changes and drug therapy are not enough to prevent PAD progression. For these patients, **angioplasty,** stenting or surgery may be necessary.

Angioplasty

Angioplasty is a nonsurgical procedure that widens narrowed or blocked peripheral arteries. In an **angioplasty** procedure, a **catheter** with a deflated balloon is inserted into the narrowed segment of the artery. The balloon is inflated to open the artery; the balloon is then deflated and the **catheter** is withdrawn.

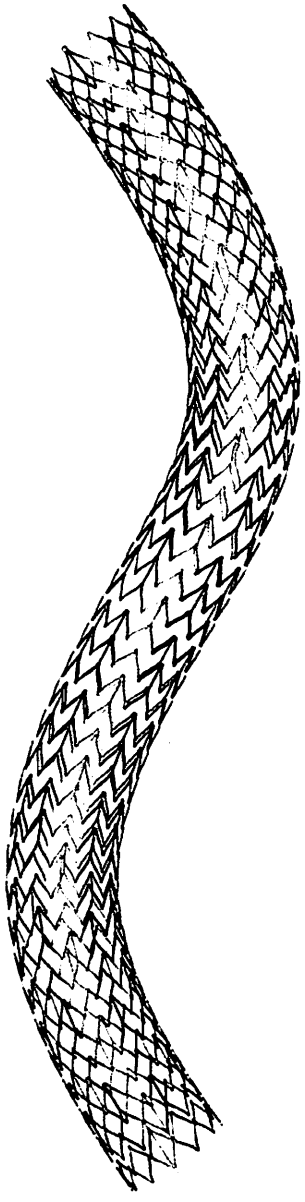
In other cases, a **stent**—a tubular metal device that acts as a scaffold—is placed in the narrowed segment of the artery. The **stent,** in an unexpanded form, is delivered via a **catheter** to the correct place. The **stent** expands and stays in place to keep the artery open after the **catheter** is withdrawn.

Restenosis

In many cases, patients who have been treated with balloon **angioplasty** and stenting experience a re-narrowing, or **restenosis,** of the artery over time. This is partly because the body tries to heal the injury to the vessel that occurs when the balloon is inserted and inflated. During the healing process, excess tissue may grow over the **stent** causing the vessel to narrow again. Statistics show that 30 to 60 percent of patients will suffer from a re-narrowing of arteries over time, making a repeat intervention necessary.

Bypass surgery

Bypass surgery is typically reserved for patients whose anatomy is not appropriate for less invasive catheter-based treatment and for whom lifestyle changes don't work. Surgery involves sewing a vein from another part of the body or an artificial blood vessel above and below the blocked area to detour blood flow around the blockage. Surgery has additional risks, however, particularly for patients who suffer from other disorders such as heart disease, high blood pressure or diabetes.



Your Zilver PTX Stent

Drug-coated stents

A **drug-coated stent** is a metal **stent** that has been coated with a medicinal substance intended to prevent re-narrowing of the artery. Clinical data demonstrate that the Zilver PTX stent is effective in preventing re-narrowing of the artery and can help patients who suffer from PAD.

The Zilver PTX paclitaxel-eluting stent

The Zilver PTX paclitaxel-eluting stent is a nitinol **stent** coated with the drug **paclitaxel.**

What is paclitaxel?

Paclitaxel is the active component of Taxol,* a drug that is used as an anti-cancer agent. **Paclitaxel** is also used on **stents** used in the heart to reduce the risk of re-narrowing of the artery. It is intended to limit the response of the blood vessel so excess tissue growth that could cause re-narrowing of the vessel does not occur.

The Zilver PTX **stent** uses a very small amount of **paclitaxel,** which is applied directly to the vessel wall.

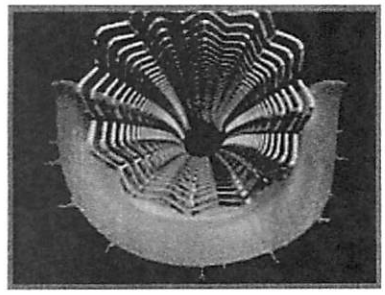
Who should not receive a Zilver PTX stent?

- Patients with blockages of their artery that will not allow the physician to properly inflate the **angioplasty** balloon or place the **stent.**
- Patients with bleeding disorders.
- Women who are pregnant, breast-feeding or plan to become pregnant in the next five years should not receive a Zilver PTX **stent.** There is the possibility that **paclitaxel** will be excreted in human milk, which could result in an adverse reaction in the nursing infant.

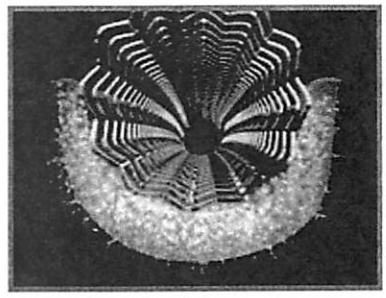
* Taxol is a registered trademark of Bristol Myers Squibb Company.

What are the potential adverse events that may be associated with a Zilver PTX stent?

- Allergic reaction to anticoagulant and/or antithrombotic therapy or contrast medium
- Allergic reaction to nitinol
- Atheroembolization (Blue Toe Syndrome)
- Arterial **aneurysm**
- Arterial rupture
- Arterial thrombosis
- **Arteriovenous fistula**
- Death
- **Embolism**
- **Hematoma**/hemorrhage
- Hypersensitivity reactions
- Infection
- Infection/abscess formation at access site
- **Ischemia** requiring intervention (bypass or amputation of toe, foot, or leg)
- **Pseudoaneurysm** formation
- Renal failure
- **Restenosis** of the stented artery
- **Stent** embolization
- Stent malapposition
- Stent migration
- Stent strut fracture
- Vessel perforation or rupture
- Worsened **claudication**/rest pain



PTX **paclitaxel**-eluting stent placed in affected vessel



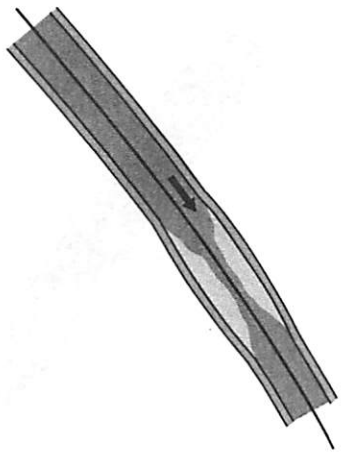
The drug **paclitaxel** is intended to keep the blood vessel from re-narrowing

Potential adverse events, not described previously, may be unique to the **paclitaxel** drug coating, and include:

- Allergic/immunologic reaction to the drug coating
- **Alopecia**
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- **Hematologic dyscrasia** (including leukopenia, neutropenia, thrombocytopenia)
- **Hepatic enzyme** changes
- Histologic changes in vessel wall, including inflammation, cellular damage or **necrosis**
- **Myalgia/Arthralgia**
- **Myelosuppression**
- Peripheral **neuropathy**

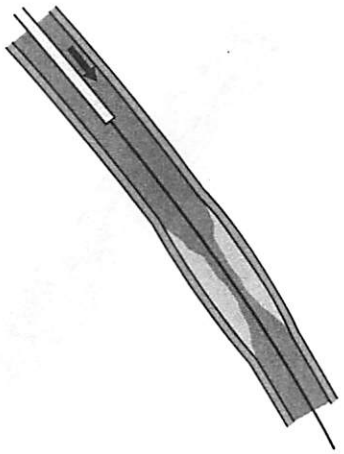
You may want to ask your physician about the potential for each of these risks in your specific situation.

The Angioplasty and Stenting Procedure



Before the procedure

Your doctor will explain how to prepare for your **angioplasty** and **stenting** procedure before you are admitted to the hospital. You may be asked to avoid eating or drinking anything after midnight on the night before the procedure. You may also be asked to take aspirin or other medication for a few days prior to the procedure to thin your blood and prevent clots from forming.

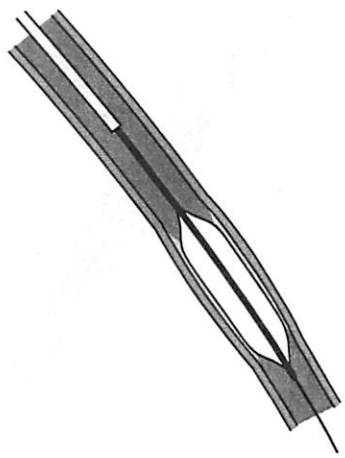


During the procedure

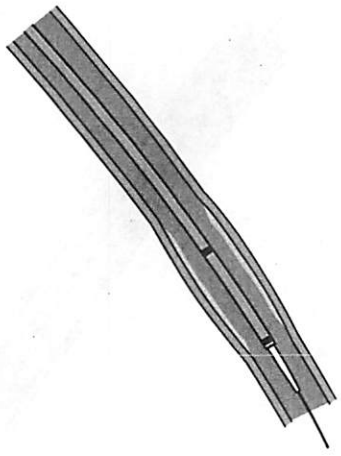
Your **angioplasty** and **stenting** procedure will take place in the hospital, in a catheterization lab. Although you may be given a sedative to help you relax, you will be awake during the procedure. This will allow you to follow your doctor's instructions to move, cough or breathe as needed.

Your doctor will be accessing your artery through your groin. The access area will first be shaved, swabbed with antiseptic and numbed with a local anesthetic. Your doctor will then make a small incision in your skin and gain access to your artery with a needle.

A wire guide will be inserted through the needle and advanced to the part of your artery that contains the blockage. The doctor will then insert an **introducer sheath** over the wire guide into your artery, and a balloon **catheter** will be advanced through the **introducer sheath** to the site of the blockage. The balloon will be inflated briefly, widening the blocked artery.



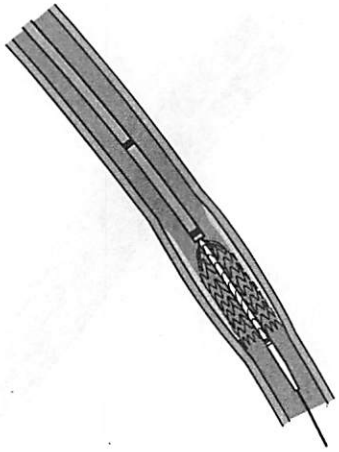
After the artery has been widened, the doctor will deflate the balloon and remove the balloon **catheter**. He or she will then advance a delivery **catheter** containing the PTX **stent** to the area of the artery where the balloon previously was. When the **stent** is positioned in the right spot, the doctor will unsheath it, allowing it to expand against the walls of your artery. The doctor will then remove the **catheter** and wire guide, leaving the **stent** in place. The **introducer sheath** may also be left in place for a few hours while you are monitored.



After the procedure

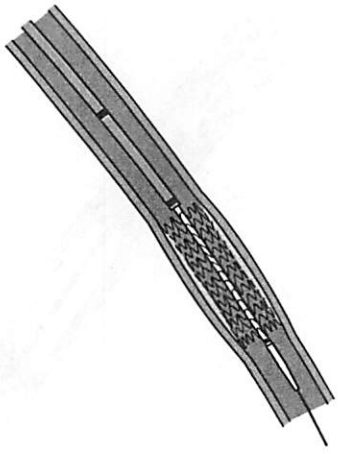
When your procedure is finished, you will be moved to a recovery area. You may feel some discomfort, which can be relieved with pain medicine. Your blood pressure and heart rate will be monitored closely. Your doctor and the standard protocol of the hospital where your procedure was performed will determine when you are allowed to go home.

Frequently Asked Questions



1. What is a stent?

A **stent** is a metal tube used to keep the artery open. The Zilver **stent** is made of nitinol, an alloy of nickel and titanium. This blend of metals was discovered in 1965. It has super-elastic properties that help it maintain its shape, even after it is crushed many times. The **stent** is compressed into a plastic tube so that it can be passed into your artery. The **stent** is placed across the blockage, where it is released and expands to the size of your artery.



2. What is a drug-coated stent?

A **drug-coated stent** is simply a **stent** with drug on it. **Drug-coated stents** have recently become widely used for the arteries of the heart. The **drug-coated stents** used in the heart have reduced the occurrence of blockages after the **stents** are in place. Zilver PTX clinical trials confirmed that **drug-coated stents** help to keep the leg arteries from becoming blocked again.

3. What is paclitaxel?

Paclitaxel (păk'lĭ-tăk'səl) is a natural product that was discovered in 1967. It originally came from the bark of the Pacific yew tree. **Paclitaxel** reacts with cells in several ways. One is that it keeps cells from dividing. The cells cannot divide because **paclitaxel** keeps the microtubules (which are like muscles in your cells) from pulling the cell apart to form two new cells. Too much cell division is known to happen often after your artery has been treated, sometimes causing it to become blocked again. Thus, by preventing cell division, **paclitaxel** may keep your artery from becoming blocked again.

Since cancer cells divide rapidly and since **paclitaxel** keeps cells from dividing, it is sometimes given to treat cancer (e.g., ovarian or breast cancer). The drug to treat cancer is called Taxol. Taxol includes **paclitaxel** and an oil to make the drug easy to inject. When Taxol is given to treat cancer, the dose is large and the drug goes throughout the entire body, which may cause side effects. The PTX **stent** was designed to reduce the chances of such side effects because the **paclitaxel** amount on the **stent** is small, does not contain the oil found in Taxol and is given locally from the **stent** to your artery.

4. How much paclitaxel is on the stent?
The **stent** carries only 1/1300 to 1/200 the amount of **paclitaxel** given in a single cancer treatment.

5. Where do the stent and the drug go after the doctor puts them in my body?
The doctor puts the **stent** across the blockage in the artery. The **stent** remains in that place in your artery for the rest of your life. The wall of your artery absorbs the drug from the **stent**. A small portion of the drug may get carried away by the blood flowing through your artery.

Glossary

Alopecia - Baldness; absence of hair from the skin areas where it is normally present.

Aneurysm - A sac formed by localized dilation of the wall of an artery, a vein or the heart.

Angiography - A method of taking X-rays after injection of contrast dye.

Angioplasty - A catheter-based treatment to open narrowed or blocked arterial vessels.

Arteriovenous fistula - An abnormal or artificial connection between an artery and vein.

Arthralgia - Pain in a joint.

Catheter - A hollow, flexible tube used to access parts of the body, such as arterial vessels.

Claudication - Condition marked by pain, tension and weakness of legs induced by walking, and the disappearance of all discomfort when at rest. This condition is caused by a narrowing of the arteries in the legs.

Drug-coated stent - A stent with a drug coating that is intended to prevent the vessel from re-narrowing.

Embolism - The sudden obstruction of an artery by a clot or any foreign material formed or introduced elsewhere in the circulatory system and carried to the site of blockage by the bloodstream.

Hematologic Dyscrasia - An abnormal condition in the composition of blood.

Hematoma - A localized collection of extravasated blood, usually clotted, in an organ, space or tissue.

Hepatic Enzyme - A protein secreted by the liver that promotes or accelerates a chemical change in other substances.

Introducer sheath - A tube that is inserted into the body to provide access and allow delivery of other devices.

Ischemia - Lack of blood in an area of the body due to an obstruction or constriction of a blood vessel.

Myalgia - Muscular pain.

Myelosuppression - Bone marrow suppression.

Necrosis - The morphological changes indicative of cell death caused by progressive enzymatic degradation; it may affect groups of cells or part of a structure or an organ.

Neuropathy - A functional disturbance or pathological change in the peripheral nervous system; sometimes limited to noninflammatory lesions as opposed to those of neuritis.

Paclitaxel - A drug derived from the Pacific yew tree which prevents cell division.

Peripheral arterial disease - A condition that develops when cholesterol levels and scar tissue build up, causing arteries to narrow and restrict blood flow.

Pseudoaneurysm - False aneurysm; dilation or tortuosity of a vessel, giving the appearance of an aneurysm.

Restenosis - The re-narrowing of a vessel.

Stent - An expandable metal tube that is used to keep a vessel open.

COOK MEDICAL INCORPORATED
P.O. Box 4195, Bloomington, IN 47402-4195 U.S.A.
Phone: 812.339.2235, Toll Free: 800.457.4500, Toll Free Fax: 800.554.8335

COOK (CANADA) INC.
111 Sandiford Drive, Stouffville, Ontario, L4A 7X5 CANADA
Phone: 905.640.7110, Toll Free: 800.668.0300

WILLIAM A. COOK AUSTRALIA PTY. LTD.
Brisbane Technology Park, 12 Electronics Street, Eight Mile Plains
Brisbane, QLD 4113 AUSTRALIA, Phone: +61 7 38 41 11 88

WILLIAM COOK EUROPE ApS
Sandet 6, DK-4632, Bjaeverskov, DENMARK, Phone: +45 56 86 86 86

www.cookmedical.com

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Cook recommends that the patient register the MR conditions disclosed in this patient ID card with the MedicAlert Foundation. The MedicAlert Foundation can be contacted in the following manners:

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

Phone: 888.633.4298 (toll free) or
209.668.3333 from outside the US

Fax: 209.669.2450

Web: www.medicalert.org

- MR image quality may be compromised if the area of interest is within the lumen or within approximately 5 mm of the position of the stent.
- A patient with this stent can be scanned safely after placement under the following conditions:
  - Static magnetic field of 1.5 Tesla or 3.0 Tesla
  - Spatial magnetic gradient of 1600 Gauss/cm or less
  - Normal operating mode: Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of scanning or less.

Attach Label

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47404 U.S.A.
812.339.2235

William Cook Europe ApS
Sandet 6, DK-4632
Bjaeverskov, Denmark
+45 56 86 86 86

William Cook Australia Pty. Ltd.
95 Brandl Street Eight Mile Plains,
QLD 4113 Australia
+61 7 38 41 11 88

Cook Ireland Ltd.
O'Halloran Road, National Technology Park
Limerick, Ireland
+353 613 34440

MRI information on back side.

Patient Name _____ Implant Date _____

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Implanting Physician _____

Implanting Physician Phone # _____

Follow-up Physician _____

Follow-up Physician Phone Number _____

Product Catalog # _____

Because unforeseen variations in patient anatomy or scanners may increase risk, the MRI facility should allow prompt intervention if necessary.

INSTRUCTIONS

Please carry this card at all times and show it to any medical personnel who may be treating you.