Supplement to

Sponsored by Cook Medical

Endovascular TODAY

November 2014

THE RISE OF PERIPHERAL DRUG ELUTION


Gary Ansel, MD


John Phillips, MD

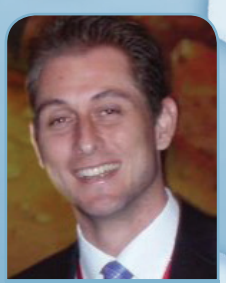

John R. Laird, MD

How to incorporate drug-coated balloons and drug-eluting stents into your practice.


Ehrin J. Armstrong, MD


William A. Gray, MD


George L. Adams, MD


Konstantinos Katsanos, MD


Louis L. Nguyen, MD


Rebecca E. Scully, MD


Marc Bosiers, MD


Koen Deloose, MD

Note: Physician authors were not paid for their contributions to this supplement.

CONTENTS

Drug Elution, Data, and Decisions

What the data tell us about how to integrate drug-eluting technology into our daily practice.

BY GARY ANSEL, MD, AND JOHN A. PHILLIPS, MD

The use of drug-eluting technology has been studied and subsequently utilized for the treatment of peripheral vascular disease for over a decade. Specific to the superficial femoral and popliteal arterial segment during this time interval, investigators have conducted many trials for both drug-coated balloons (DCBs) and drug-eluting stents (DES). The Zilver PTX DES (Cook Medical) is the first drug-eluting technology to be approved in the United States. The 5-year data were presented at the VIVA 2014 meeting and demonstrated stable patency with superiority over both percutaneous transluminal angioplasty (PTA) and bare-metal stents (BMS). More recent randomized controlled datasets have been presented for DCBs in the LEVANT 2 and IN.PACT SFA trials. Both trials have demonstrated that safety and 1-year effectiveness of these DCBs are superior to plain old balloon angioplasty. However, durable longer-term results for DCBs are yet to be demonstrated.

Currently, it may not be fully apparent how physicians should incorporate DES and DCBs into their daily interventional practice. To this end, what do the latest well-designed trials tell us about each technology, and more importantly, what do the data suggest about how we should incorporate these devices into our practice? For this discussion, we focus on three pivotal trials and, based on the latest level-1 clinical evidence supplemented by real-world registries, deduce how we should initially implement DCBs and DES into everyday practice. In this article, we do not address the use of stent grafts (which have demonstrated superiority over BMS and equivalency to prosthetic open bypass), atherectomy (which has no randomized datasets but growing registry data), nor open surgical bypass.

ZILVER PTX DATA

The Zilver PTX trial is the largest and only randomized and controlled peripheral endovascular device trial with 5-year follow-up data. There is an abundance of peer-reviewed data demonstrating the safety and effectiveness of this device. Importantly, most of the data are centered around the typical pivotal patency, utilizing a duplex PSVR (peak systolic velocity ratio) of 2.0. For this discussion, we will limit the scope to published or presented 1- and 4-year data for primary patency and target lesion revascularization (TLR).

With respect to 1-year patency, primary Zilver PTX stenting demonstrated statistically significant superiority to optimal PTA, and provisional Zilver PTX stenting

TABLE 1. ZILVER PTX 12-MONTH RESULTS ACROSS TRIALS*

	Zilver PTX RCT (Zilver PTX arm only: United States, Japan, Germany)	Zilver PTX Single-Arm Study (European Union, Korea, Canada)	Zilver PTX Japan PMS (Japan)
Number of patients	236	787	907
PSVR	2.0	2.0	2.4
12-month primary patency	84.4%	82.8%	84.8%
Freedom from TLR at 12 months	91.6%	89.5%	91.4%

**Data adapted from Yokoi Y.[1]*
Abbreviations: PMS, postmarketing surveillance; RCT, randomized controlled trial.

was superior to BMS use.[2] Zilver PTX also demonstrated superior TLR rates when compared to either optimal PTA or when comparing provisional Zilver PTX stenting to the use of BMS.[2]

Additionally, the paclitaxel drug effect of Zilver PTX was sustained through 4 years. Four-year data from the Zilver PTX trial demonstrated a 75% primary patency rate compared to a 57.9% patency rate for patients who underwent provisional BMS placement in the study. This represents a 41% reduction in 4-year restenosis, favoring DES over BMS placement.[3] Furthermore, freedom from TLR was 83.2% for Zilver PTX compared to 69.4% of patients who were treated with standard care (BMS or successful PTA).[3] The data from the Zilver PTX randomized controlled trial are supported by large, single-arm registry studies conducted in Europe and Japan. Dr. Hiroyoshi Yokoi recently presented data from the Japan post-market study with a 12-month freedom from TLR rate of 91.7% (Table 1).[1] The 5-year Zilver PTX data were presented at VIVA 2014, and the results were generally consistent with the 4-year results.

DCB TRIAL RESULTS AT A GLANCE

LEVANT 2 Trial

On October 10, 2014, the US Food and Drug Administration approved the Lutonix paclitaxel DCB (Bard Peripheral Vascular, Inc.) for use in the United States. The primary composite safety endpoint for Lutonix was noninferiority to PTA (Table 2). For the primary effectiveness endpoint, utilizing duplex scan evaluation with a PSVR of 2.5, Lutonix demonstrated superior 12-month patency rates to PTA using Kaplan-Meier estimates (73.5% vs 56.8%). However, when using the VIVA criteria (PSVR = 2.0), which is typical of most pivotal trials for primary patency assessment, there is no significant difference between Lutonix and PTA ($P = 0.13$).[4]

The Lutonix freedom from TLR dataset demonstrated no significant difference with balloon angioplasty alone at 12 months. It should be noted that there were a couple of unique aspects to this trial design that may have affected the TLR result. First, trial prescreening involved assessment of the lesion's response to predilation and excluded patients who did not respond favorably, thereby resulting in PTA patency rates that were much higher than what has been seen in most pivotal trials. Additionally, for the first time, investigators were blinded during follow-up, which may have lowered TLR rates.[4] Despite the lower-than-expected patency rates, Lutonix's results did show a favorable trend over PTA on several endpoints, suggesting that there is a benefit conferred from the paclitaxel coating.

IN.PACT SFA II

On April 5, 2014, Prof. Gunnar Tepe presented the 12-month data from the IN.PACT SFA II trial at the Charing Cross meeting in London (Table 3).[5] This randomized controlled trial compared the In.Pact Admiral DCB (Medtronic, Inc.) to standard PTA, with results suggesting significant patency and clinical benefits when using the In.Pact DCB. Both the 12-month primary patency rates and the 12-month clinically driven TLR rates for In.Pact were superior to PTA. Follow-up was not blinded, but nonetheless, the patency data suggest that there is in fact a significant drug effect with the In.Pact balloon when compared to standard PTA. Although the In.Pact DCB data appear more promising than that of Lutonix, comparing the two trials is fraught with bias, especially as they had different blinding during follow-up. The In.Pact DCB awaits US Food and Drug Administration approval and is presently an investigational devices in the United States. We are eager to learn more about the device datasets as more peer-reviewed information becomes available.

One-year TLR data from the initial 655 patients in the ongoing IN.PACT Global trial were recently presented at the 2014 Transcatheter Therapeutics meeting in Washington, DC. This outside-the-United States, core-lab-adjudicated (core lab patency only for long lesions

TABLE 2. LEVANT II TRIAL DATA FOR LUTONIX

	Lutonix	Control PTA	*P* Value
Primary composite safety endpoint (freedom from perioperative death and 12-month index limb amputation [above and below the ankle], index limb reintervention and index limb-related death)	83.9%	79%	0.005
12-month primary patency (Kaplan-Meier, PSVR = 2.5)	73.5%	56.8%	< 0.001
12-month primary patency (PSVR = 2.0)	53.2%	45%	0.13*
Total TLR at 12 months	12.3%	16.8%	0.208*

**No statistically significant difference.*

TABLE 3. IN.PACT SFA II TRIAL DATA FOR IN.PACT ADMIRAL			
	In.Pact Admiral	**Control PTA**	***P* Value**
Primary safety composite	95.7%	76.6%	< 0.001
12-month primary patency (Kaplan-Meier, PSVR = 2.4)	89.8%	66.8%	< 0.001
Clinically driven TLR at 12 months	97.5%	79.3%	< 0.001

and chronic total occlusions), global DCB registry has a planned enrollment of 1,500 patients. The TLR rate for the 655 patients who were evaluable at the 1-year time point was an impressive 8.7%. This low TLR rate is consistent with the randomized trial and is certainly in line with the impressively low TLR rate seen in the randomized trial.

DATA GAPS AND TRIAL DIFFERENCES BETWEEN DCB AND DES

Before we determine what the data tell us about how to incorporate drug-eluting devices into our practice, there are several gaps between DCB data and DES data that must be acknowledged. The first gap is in long-term follow-up. Although all three of the previously mentioned main trials are planned for 5-year follow-up, only the Zilver PTX DES has long-term results available to support its sustained effectiveness. The Lutonix and In.Pact DCBs have only presented non-peer-reviewed 1-year data. Previous studies, such as the SIROCCO II trial (DES) and the THUNDER trial (DCB), demonstrated continued late lumen loss, and this possibility must be considered when physicians evaluate DCB technology as it becomes more widely available.

There are also critical differences in trial design that must be factored in as we consider how and when to use drug-eluting technology. Perhaps the most important difference between the two DCB trials and the DES trials is that these two DCB trials perform screening via standard PTA. In both LEVANT 2 and IN.PACT SFA II, if the lesion did not respond well to the initial predilatation with balloon angioplasty to provide the investigator a reasonable assurance that the lesion would not require stenting, then that patient was not randomized to the control or treatment arm. Because these patients failed the initial screening angioplasty, they were considered a "screen fail" and were not placed in the study or the final results.

Although in this trial design it makes sense to eliminate confounding variables in order to more easily discern the effectiveness of the drug on the balloon, it significantly distorts the ability to generalize effectiveness endpoints to a wider population. For example, when looking at the IN.PACT trial, the PTA patency at 12 months was 66.8% for all PTA. When looking across several trials, the 12-month patency numbers for PTA tend to be much lower because an initial PTA failure was tracked as failed PTA (Table 4). The process of screening lesions may contribute to the significantly higher standalone patency numbers for DCBs by effectively eliminating suboptimal PTA results that would typically require stenting from the trial. This fact becomes even more apparent when looking at the proportion of severely calcified lesions in the three trials (Table 5).

Although the definition of calcification is variable, the Zilver PTX trial appears to have included significantly more calcified lesions than the DCB trials. If accurate, this is an important point because it is becoming increasingly apparent that calcification may be a significant issue that impacts the overall effectiveness of DCBs in real-world lesions. Fanelli et al noted this limitation of DCBs in the conclusion of a recently peer-reviewed publication.[8] To quote the authors, "Calcium represents a barrier to optimal drug absorption. Circumferential distribution seems to be the most influencing factor with the worst effect noticed in 360° calcium presence."[8] The issue of calcification certainly raises other questions, as well. The reported provisional stenting rate in the two major DCB trials varied but was relatively low. Will these stenting rates hold up in real-world lesions? The IN.PACT Global

TABLE 4. TWELVE-MONTH PATENCY RESULTS FOR PTA*				
	Zilver PTX RCT (PTA arm)	**RESILIENT RCT (PTA arm)**	**Viabahn PMA IDE Study (PTA arm)**	**IN.PACT SFA II RCT (PTA arm)**
12-month primary patency for PTA	32.7%	36.7%	40%	66.8%

**Data adapted from Cook Medical, Laird JA et al, Gore & Associates, and Tepe G.[1,5-7]*
Abbreviations: IDE, investigational device exemption; RCT, randomized controlled trial; PMA, premarket approval.

TABLE 5. SEVERE CALCIFICATION IN DRUG-ELUTING DEVICE TRIALS*

	Zilver PTX RCT	IN.PACT SFA II	LEVANT 2
Severe calcification	37.3%	8.1%	10.4%

**Data adapted from Cook Medical, the Department of Health & Human Services, and Tepe G.[1,4,5]*
Abbreviations: RCT, randomized controlled trial.

trial reported an almost 25% provisional stenting rate for a relatively modest average lesion length of 12 cm. Interventionists can still expect to commonly utilize bail-out stenting for many modest-to-complex lesions, adding to the overall cost of a procedure.

The last significant gap is head-to-head data to directly compare the effectiveness of the two drug-eluting modalities in a variety of lesion types. In order to better understand the relative effectiveness of DCBs and DES in the superficial femoral artery (SFA), a head-to-head comparison of the two technologies is needed. Prof. Dierk Scheinert is conducting the REAL PTX study. This study will randomize patients with femoropopliteal disease to either a DCB or DES. This trial is significant, as it will represent the first direct comparison of DCBs to DES in the SFA and will provide even more insight into when to choose a DCB versus DES for treating SFA disease.

Although the DCB and DES trials give us confidence in the ability of drug-eluting devices to fight intimal hyperplasia, they do not answer every question. In light of the previously mentioned data gaps and the differences in trial designs, what can the data really tell us about how we should incorporate drug-eluting devices into our daily practice? The following sections describe what we believe are the five key considerations when deciding whether to use a DCB or DES to deliver paclitaxel to the SFA (see the *5 Considerations for Choosing a Drug-Eluting Modality* sidebar).

5 CONSIDERATIONS FOR CHOOSING A DRUG-ELUTING MODALITY

1. DES and DCB have demonstrated superiority to their bare counterparts.
2. A significant number of "real-world" SFA lesions require stenting.
3. DCB + BMS has not been shown to equal DES results.
4. The effectiveness of DCBs for calcified lesions is still unknown.
5. Long-term data are essential to fully assess new technologies.

1. DES and DCB Have Demonstrated Superiority to Their Bare Counterparts

Zilver PTX demonstrated superiority to BMS through 5 years. The In.Pact and Lutonix DCBs both demonstrated superior patency to standard PTA balloons through 1 year. All three of these trials were randomized and core lab adjudicated, which should give physicians confidence in choosing these drug-eluting devices over their bare counterparts. In general, the use of technologies that have not demonstrated patency benefit over bare ballooning or stenting should be relegated to niche usage, and high-volume usage of other technologies should be scrutinized.

2. A Significant Number of "Real-World" SFA Lesions Require Stenting

One may favor balloons over stents with the hope of "leaving nothing behind." However, we know that stents are used in 70% of SFA cases in the United States.[9] We expect that stenting (either primary or bailout) will be performed at a rate that correlates with lesion complexity, even with the use of DCBs. Balloons and stents both have a role in treating peripheral artery disease, and as such, physicians will need to generate data to help clearly delineate "optimal therapy." Ultimately, choosing a DCB or DES is heavily influenced by lesion morphology and lesion location, and these lesion factors are unlikely to change when adding a drug to a balloon or stent.

3. DCB + BMS Results Have Not Been Shown to Equal DES Results

Dosing is different for each device, and in the case of DCBs, the use of excipients add another potentially confounding variable. DCB effectiveness may not be a class effect, and each product will need to be evaluated and compared. There are no reliable SFA data that prove that DCB + BMS provides comparable results to a DES alone. In fact, some coronary data suggest that DCB + BMS is not equivalent to DES alone.[10] More research is needed to understand the impact that different drug formulations and delivery methods have on outcomes. Finally, just as 5-year results have been the cornerstone for evaluating surgical therapy, DCBs will now need to demonstrate similar or improved durability to the currently available DES.

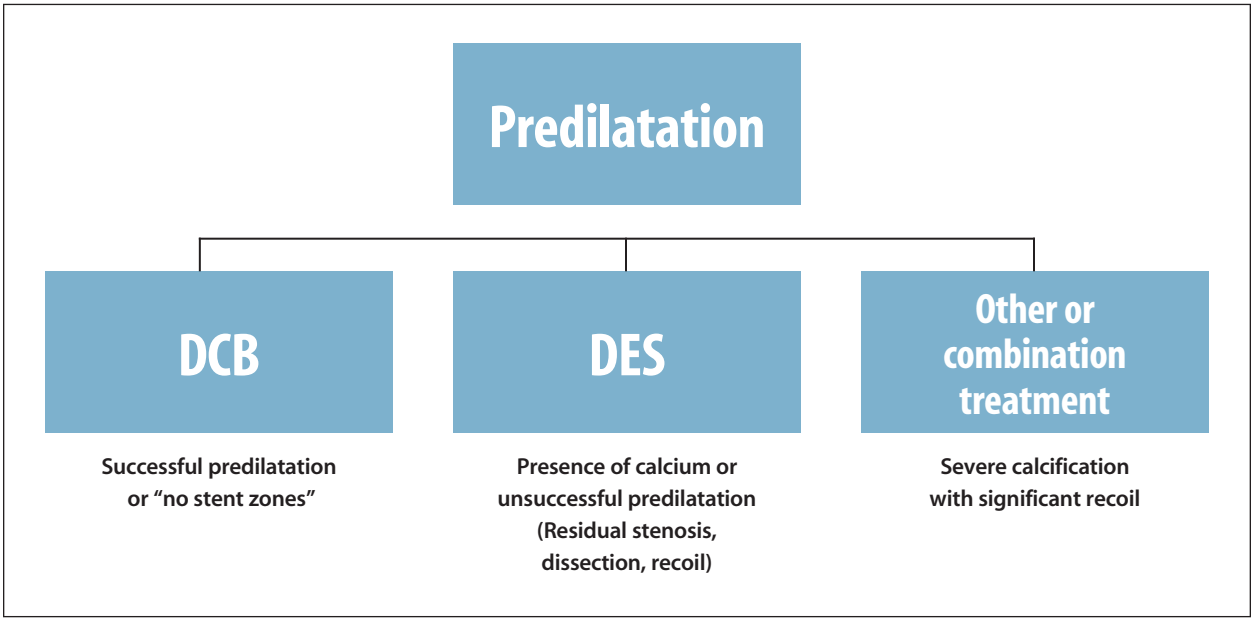


Figure 1. Choosing a drug-eluting modality for SFA lesions.

4. The Effectiveness of DCBs for Calcified Lesions Is Still Unknown

One cannot underestimate the potential significance of this factor when considering a DCB or DES for treating SFA lesions. Further, the work of Fanelli et al should give us pause when considering DCB use for heavily calcified lesions.

5. Long-Term Data Are Essential to Fully Assess New Technologies

Perhaps one of the greatest challenges and most important factors in treating SFA disease is long-term effectiveness. We know that there are several modalities that provide acute success. The real challenge is avoiding restenosis and maintaining long-term patency in the SFA. Zilver PTX has proven long-term effectiveness with few stent fractures and 5 years of level-1 evidence. Although DCBs are promising, they are still early in their level-1 evidence. More time is needed to determine the long-term effectiveness of DCBs, and head-to-head data are needed to determine when to utilize one technology versus another.

CHOOSING A DRUG-ELUTING MODALITY FOR SFA LESIONS IN 2015

Ultimately, recent trials have made it apparent that drug-eluting devices outperform their bare counterparts. However, when incorporating these devices in light of the recent randomized controlled trial results, the remaining gaps in the DCB data, and the differences in drug-eluting device trials, there remains a critical question: How should we incorporate DCBs and DES into everyday practice? We suggest that the approach should be a relatively simple one (Figure 1).

For All Lesions, Predilate First

Whether you are leaning toward using a DCB or DES, perform predilatation with plain old balloon angioplasty in every case. Predilatation is required in the instructions for use for DCBs and is optional and at the discretion of the physician for DES. We also know that vessel preparation can lead to more successful results.

Successful Predilatation May Suggest a "Leave Nothing Behind" Strategy

If the lesion responds well to predilatation (ie, lack of moderate-to-severe calcification, residual stenosis, flow-limiting dissection, or significant recoil), consider using a DCB.

Suboptimal Predilatation Suggests a DES Strategy

If the lesion does not respond well to predilatation due to significant dissection, or if the lesion has moderate-to-severe calcification but can be adequately dilated, choose a DES.

Suboptimal Predilatation With Severe Calcification or Significant Recoil

Whether one should use debulking/scoring technology with spot stenting (particularly with a more crush-resistant woven nitinol stent), with or without DCB or DES

with Zilver PTX is up for debate. Pending actual data, the operator should choose the most appropriate method that will (in their mind) lead to the greatest luminal gain and durability.

All Patients Should Have Aggressive Risk Factor Modification and Medical Therapy

Mild symptoms should not be treated with a device, and a walking program and medical therapy should be considered if doubling the walking for the patient will be adequate. Although drug technology is improving short- and long-term results, all procedures have some risks, and appropriate procedural indications continue to be recognized. ■

Gary Ansel, MD, is Director, Center for Critical Limb Care, Riverside Methodist Hospital in Columbus, Ohio; and Assistant Clinical Professor of Medicine, Department of Internal Medicine, University of Toledo Medical Center in Toledo, Ohio. He is paid by Cook Medical for speaking, consulting, and physician education. Dr. Ansel may be reached at garyansel@aol. com.

John A. Phillips, MD, is with OhioHealth Heart & Vascular Physicians in Columbus, Ohio.

Neither Dr. Ansel nor Dr. Phillips were paid for writing this article.

1. Yokoi Y. Postmarket surveillance study of paclitaxel-eluting nitinol stents for treating femoropopliteal artery disease in japan: 12-month results. Presented at EuroPCR 2013; May 21–24, 2013; Paris, France.
2. Cook Medical. Zilver PTX United States Instructions for Use. Available at https://www.cookmedical.com/data/IFU_PDF/IFU0093-4.PDF. Accessed October 20, 2014.
3. Ansel G. Zilver PTX randomized trial of paclitaxel-eluting stents for femoropopliteal artery disease: 4-year results. Presented at VIVA 2013; October 8, 2013; Las Vegas, NV.
4. Department of Health & Human Services. Bard Lutonix 035 drug coated balloon PTA catheter. FDA Executive Summary. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM400614.pdf. Accessed October 20, 2014.
5. Tepe G. IN.PACT SFA randomized trial of In.Pact admiral DCB vs. PTA for the treatment of atherosclerotic lesions in the SFA and/or PPA 1-year primary outcomes. Presented at Charing Cross 2014; April 5–8, 2014; London, UK.
6. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery. twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv. 2010;3:267-276.
7. Gore Medical. Instructions for Use for Gore Viabahn endoprosthesis. Available at http://www.goremedical.com/resources/dam/assets/20019563.pdf. Accessed October 20, 2014.
8. Fanelli F, Cannavale A, Gazzetti M, et al. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. Cardiovasc Intervent Radiol. 2014;37:898-907.
9. Millennium Research Group. US Markets for Peripheral Vascular Devices 2014. Available at http://www.mrg.net/Products-and-Services/Syndicated-Report.aspx?r=RPUS11PV13. Accessed October 20, 2014.
10. Buszman PP, Tellez A, Afari M, et al. Stent healing response following delivery of paclitaxel via durable polymeric matrix versus iopromide-based balloon coating in the familial hypercholesterolaemic swine model of coronary injury. EuroIntervention. 2013;9:510-516.

An Overview of Superficial Femoral Artery Stenting

The history, data, and latest advancements in stenting of the SFA and popliteal arteries.

BY JOHN R. LAIRD, MD, AND EHRIN J. ARMSTRONG, MD


During the past decade, multiple technologies have been developed for treatment of superficial femoral artery (SFA) atherosclerotic disease, including balloon angioplasty, bare-nitinol self-expanding stents, drug-eluting nitinol stents, and drug-coated balloons. Although many endovascular treatment options exist, nitinol stents remain a mainstay of SFA therapy.[1] This article reviews the historical development of SFA stent technologies, with an emphasis on recent advances and data supporting the use of stents in the SFA and popliteal arteries.

SUPERIORITY OF SFA STENTS OVER BALLOON ANGIOPLASTY

The Vienna Absolute study was the first randomized study to show superiority of primary stenting over balloon angioplasty for the treatment of moderate-length SFA lesions.[2] In that study, patients were randomized 1:1 to a Dynalink* or Absolute* stent (Abbott Vascular) versus balloon angioplasty. At 1 year, primary patency was significantly higher for patients treated with a stent (63% vs 37%). However, other randomized studies conducted with the Luminexx stent (Bard Peripheral Vascular) failed to show a benefit of stent placement for shorter-length (mean, 40 mm) SFA lesions.[3] At the same time, concerns regarding a high prevalence of stent fracture in the SFA using early generation self-expanding stents limited the broad application of stents to the femoropopliteal segment.[4]

The RESILIENT trial was the second major randomized trial to show superiority of primary stent placement over balloon angioplasty for the treatment of moderate-length SFA lesions.[5] Patients were randomized 2:1 to placement of a LifeStent (Bard Peripheral Vascular) versus balloon angioplasty. At 12 months, the primary patency rate was significantly higher for patients randomized to primary stent placement based on both intention-to-treat analysis (81% vs 36%) and as-treated analysis (80% vs 61%). The stent fracture rate was only 3% at 1 year. At 3-year follow-up, patients randomized to primary stent placement also had significantly higher freedom from target lesion revascularization (TLR) in the intention-to-treat group (75.5% vs 41.8%).[6] These results provided significant evidence in support of primary stenting to treat moderate-length SFA lesions with modern stent designs.

REGISTRY STUDIES OF SFA STENTS

After completion of early, randomized studies of nitinol self-expanding stents versus balloon angioplasty, the majority of subsequent studies have consisted of registry data supporting the incremental improvement of new-generation stents. These studies have, in general, been based on the VIVA objective performance goals in the SFA and have shown excellent rates of primary patency, as well as extremely low stent fracture rates when compared to earlier stent designs.[7] In most cases, reports of these registries have led to US Food and Drug Administration approval of an SFA-specific indication for these stents (Table 1).

Two of the more recent registries highlight improvements in outcomes with newer-generation self-expanding stents. The SUMMIT study was a prospective, multicenter registry of the Epic* stent (Boston Scientific Corporation), which is a laser-cut nitinol self-expanding stent that contains radiopaque tantalum markers at the proximal and distal ends.[8] At 1-year of follow-up, the binary restenosis rate was 15.7%, with a freedom from TLR rate of 92%. Among patients with available x-rays, there were no stent fractures at follow-up.

The COMPLETE SE multicenter trial studied use of the Complete SE stent (Medtronic, Inc.), which has an

*These devices are investigational or not indicated for use in the SFA in the United States.

TABLE 1. REGISTRY STUDIES OF NITINOL SELF-EXPANDING STENTS IN THE SFA

Stent Name	Study Name	Lesion Length (mm)	% CTO	Primary Patency Rate at 1 Year	TLR Rate at 1 Year	Stent Fracture Rate at 1 Year
Conformexx*	FACT	59	35%	77%	7.4%	NR
EverFlex	Durability I	96	40%	72%	21%	8%
EverFlex	Durability II	89	38%	67%	14%	0.4%
Supera	SUPERB	79	NR	86%	10%	0 %
Supera	Supera SFA Registry	90	30%	85%	NR	NR
Supera	Popliteal Registry	58	48%	88%	7%	0%
Supera	Supera 500	126	53%	84%	NR	NR
Epic*	SUMMIT	69	30%	84%	8%	0%
SMART	Stroll	77	24%	82%	12%	2%
Complete SE	Complete SE trial	61	30%	73%	8%	0%
Misago*	Misago 2	64	38%	88%	10%	3%

Abbreviations: CTO, chronic total occlusion; NR, not reported.
Adapted with permission from Aghel A, Armstrong EJ. Exp Rev Cardiovasc Ther. *2014;12:833–842.*[1]

offset crown design that may minimize crown interaction during flexion.[9] At 1 year, the primary patency rate was 72.6%, with a clinically driven TLR rate of only 8.4%. No fractures were observed, although determination was difficult in some cases due to deployment in heavily calcified lesions.

Based on these recent registry studies, current-generation nitinol self-expanding stents have improved rates of primary patency, with low to zero rates of stent fractures and improved patient-reported outcomes.

RECENT DEVELOPMENTS IN SFA STENTS

SFA stent technologies continue to undergo significant improvement with a goal toward increased durability and conformability in the SFA and popliteal arteries with better long-term patency. The Supera stent (Abbott Vascular) is a recently approved stent with a novel woven design that results in improved flexibility, increased radial strength, and resistance to fracture. The SUPERB study reported a primary patency rate of 86% in the pivotal registry data submitted for US Food and Drug Administration approval.[10]

Other stent designs under investigation include the Tigris* stent (Gore & Associates), which has a nitinol wire frame with ePTFE coating and interconnecting ePTFE linking regions; the SMART Flex* stent (Flexible Stenting Solutions, acquired by Cordis Corporation), which has helical strut bands and flex bridges that provide flexibility while maintaining longitudinal integrity; and the BioMimics 3D* stent (Veryan Medical), which has a helical design that may promote laminar flow. This new generation of flexible stents may provide increased conformability and continue to improve outcomes of femoropopliteal stenting.

DRUG-ELUTING STENTS IN THE SFA

Initial studies of drug-eluting stents (DES) in the SFA were hampered by lack of clinical benefit compared to non-DES. These early DES included both sirolimus-eluting and everolimus-eluting designs using an earlier-generation stent platform.[11,12] Subsequently, a paclitaxel-eluting stent has shown significant benefit in the SFA in comparison to both balloon angioplasty and placement of a bare-nitinol self-expanding stent. The Zilver PTX (Cook Medical) is a nitinol scaffold stent with a polymer-free coating that elutes paclitaxel. In the ZILVER PTX study, patients were randomized to placement of a paclitaxel-eluting Zilver stent versus balloon angioplasty; a second arm of the study randomized patients to Zilver PTX versus bare-metal stenting in cases of acute failure of balloon angioplasty.[13] At 1 year, the primary patency rate was 83% in the DES group and 32% for the PTA group. In the secondary randomization, 12-month primary patency with Zilver PTX was superior to Zilver BMS (89.9% vs 73%). These results support the superiority of the Zilver PTX stent over balloon angioplasty and an additional benefit of drug elution compared to Zilver without the drug coating.

Based on these results, DES provide significant promise for improving patency and long-term outcomes among

**These devices are investigational or not indicated for use in the SFA in the United States.*

patients with femoropopliteal occlusive disease. Further refinement of drug-eluting technology and application to new stent scaffolds and balloon technologies will significantly improve the outcomes of endovascular interventions in the SFA. ■

John R. Laird, MD, is Professor of Medicine and Medical Director of the Vascular Center, University of California Davis Medical Center in Sacramento, California. He has disclosed that he is a consultant/advisory board member for Abbott Vascular, Bard Peripheral Vascular, Boston Scientific, Covidien, and Medtronic, and receives research support from W.L. Gore. Additionally, he is paid by Cook Medical for speaking. Dr. Laird may be reached at (916) 734-2028; john.laird@ucdmc.ucdavis.edu.

Ehrin J. Armstrong, MD, is Associate Professor of Medicine at the Division of Cardiology, University of Colorado School of Medicine in Aurora, Colorado. He has disclosed that he is a consultant/advisory board member for Spectranetics, Abbott Vascular, and Pfizer. Dr. Armstrong may be reached at ehrin.armstrong@gmail.com.

Neither Dr. Laird nor Dr. Armstrong were paid for writing this article.

1. Aghel A, Armstrong EJ. Recent advances in self-expanding stents for use in the superficial femoral and popliteal arteries. Exp Rev Cardiovasc Ther, 2014;12:833-842.
2. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. New Engl J Med. 2006;354:1879-1888.
3. Krankenberg H, Schluter M, Steinkamp HJ, et al. Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the Femoral Artery Stenting Trial (FAST). Circulation. 2007;116:285-292.
4. Schlager O, Dick P, Sabeti S, et al. Long segmental SFA stenting – the dark sides: in-stent restenosis, clinical deterioration, and stent fractures. J Endovasc Ther. 2005;12:676-684.
5. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. Circ: Cardiovasc Interv. 2010;3:267-276.
6. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation vs balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: three-year follow-up from the RESILIENT randomized trial. J Endovasc Ther. 2012;19;1-9.
7. Rocha-Singh K, Jaff MR, Crabtree TR, et al. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Cathet Cardiovasc Interv. 2007;69;910-919.
8. Werner M, Piorkowski M, Thieme M, et al. SUMMIT registry: one-year outcomes after implantation of the EPIC self-expanding nitinol stent in the femoropopliteal segment. J Endovasc Ther. 2013;20:759-766.
9. Laird JR, Jain A, Zeller T, et al. Nitinol stent implantation in the superficial femoral artery and proximal popliteal artery: twelve-month results from the Complete SE multicenter trial. J Endovasc Therapy. 2014;21:202-212.
10. Supera Periperal Stent System. Available at http://www.abbottvascular.com/static/cms_workspace/pdf/ifu/peripheral_intervention/eIFU_Supera.pdf. Accessed September 23, 2014.
11. Duda SH, Bosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. J Endovasc Therapy. 2006;13;701-710.
12. Lammer J, Bosiers M, Zeller T, et al. First clinical trial of nitinol self-expanding everolimus-eluting stent implantation for peripheral arterial occlusive disease. J Vasc Surg. 2011;54:394-401.
13. Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. Circ: Cardiovasc Interv. 2011;4:495-504.

Zilver PTX for Simple and Challenging Lesions

How I integrate this versatile tool into my lower extremity practice.

BY WILLIAM A. GRAY, MD

The host of devices available to the interventionist to address the management of their patients with superficial femoral artery disease—associated with either claudication or limb threat—are myriad and, occasionally, confusing. Relatively new to the scene, and a welcome addition, is the first drug-eluting stent with dedicated outcome data and US Food and Drug Administration approval for use in the SFA/popliteal territories, Zilver PTX (Cook Medical). It also represents the first antiproliferative device in any form and the first drug-device combination for the lower extremities. Accordingly, the application of this advancement in certain patient subsets warrants careful consideration in order to maximize both patient outcomes and cost effectiveness.

APPLICATIONS FOR ZILVER PTX

Although nonrandomized, the prospective global registry data may both inform and support the physician decision to use Zilver PTX in a variety of situations at their discretion.

Given that there is a cost differential between Zilver PTX and other commercially available devices (eg, PTA), one might consider several different strategies for its use. One approach might be to use a less-costly device as initial therapy and to use the Zilver PTX as a second-line treatment should restenosis occur. This seems reasonable in the simple, short lesion where most device choices are likely to be associated with good long-term patency. With this said, we must recognize that level-1 data collected as part of the Zilver PTX randomized study showed superiority for Zilver PTX when compared to both percutaneous transluminal angioplasty with or without provisional stenting. In complex or lengthy lesions, where a prosthesis is required to maintain acute patency and long-term patency is challenged, the choice of Zilver PTX as primary therapy may be more cost effective, especially if follow-up is extended to 2 years and repeat interventions—possibly multiple and including surgical bypass—are avoided.

> … we have been very impressed with the clinical effectiveness of the Zilver PTX thus far, consistent with randomized and registry data collected on Zilver PTX and noting only infrequent failures.

Another potential strategy for shorter, less-complex lesions with the recent introduction of drug-coated balloons in the United States is to predilate the lesion with a standard bare balloon and then assess the vessel's response and make a determination whether balloon angioplasty will be sufficient or if a scaffold will be necessary to address any apparent recoil or dissection. If angioplasty appears to be successful, one may select a drug-coated balloon. However, if a scaffold is necessary, the placement of Zilver PTX has demonstrated long-term, durable outcomes.

Beyond the complexity of the lesion being treated as a determinant of device selection, the clinical scenario may also be helpful in the choice of devices. Specifically, patients presenting with critical limb ischemia and multilevel disease involving the femoropopliteal segment may not only tend to be less tolerant of vessel failure in general but may also benefit from sustained patency in their femoropopliteal segment given the poor infrapopliteal patency rates. Thus, a multilevel patient with a wound can have direct in-line flow to their foot to the associated wound subsequent to a revascularization, heal the wound, and should their infrapopliteal vessel fail subsequently—which is a reasonable likelihood—they have nevertheless now been converted from a multilevel to a single-level patient who may be less predisposed to develop a recurrent critical limb or wound reformation.

ZILVER PTX IN OUR PRACTICE

In our lab, we use Zilver PTX in a manner similar to what has previously been described and, importantly,

have adjusted our expectations of long-term patency appropriate to the lesion and patient complexity being undertaken. This was accepted by our implanting physicians as a reasonable approach in patient selection. Although we have not yet completed formal data analysis of the 1-year outcomes in these challenging lesions and patients, we have been very impressed with the clinical effectiveness of the Zilver PTX thus far, consistent with randomized and registry data collected on Zilver PTX and noting only infrequent failures. We look forward to developing a more formal survey of Zilver PTX in our clinical environment using the aforementioned paradigm. ■

William A. Gray, MD, is Associate Professor of Medicine at Columbia University Medical Center in New York, New York. He has disclosed that he is paid by Cook Medical for speaking. Dr. Gray may be reached at wg2131@cumc.columbia.edu.

Dr. Gray was not paid for writing this article.

DCBs in the United States

The use of drug-coated balloons is creating a paradigm shift in the treatment of peripheral arterial disease by preventing restenosis and leaving nothing behind.

BY GEORGE L. ADAMS MD, MHS, AND O JESSE MENDES, BA


Restenosis is the proverbial Achilles' heel of peripheral endovascular treatment. Modalities focused on inhibiting neointimal hyperplasia, specifically drug-coated balloons (DCBs), have resulted in a paradigm shift in the treatment of peripheral arterial disease (PAD). To date, utilization of DCBs in the United States has been limited to enrollment in four ongoing clinical trials: three superficial femoral artery (SFA) trials (LEVANT 2,[1] IN.PACT SFA II,[2] and Lutonix SFA In-Stent Restenosis[3]) and one below-the-knee (BTK) trial (Lutonix BTK[4]).

Each of these trials has specific inclusion and exclusion criteria (Table 1) influencing the PAD population treated. Regarding SFA treatment, many endovascular specialists believe that a "leave nothing behind" concept is important in this vascular bed. The SFA, like no other artery in the body, has multiple forces that influence its movement, including extension, contraction, torsion, compression, and flexion.[5] Although modern stent designs have made stent fractures a rare occurrence, there is still a chance that these forces may compromise the integrity of a stent, leading to stent fracture and ultimately stent

> Although these drug delivery devices have shown promise, long-term data are still needed. Unlike the Zilver PTX drug-eluting stent, none of the DCBs have long-term randomized controlled trial data.

TABLE 1. UNITED STATES CLINICAL TRIAL OVERVIEW

Trial Name	Target	Lesion	Rutherford Category	Outflow	Exclusion Criteria
LEVANT 2	• Femoropopliteal artery • 4–6 mm in diameter	• De novo or nonstented restenotic • ≤ 15 cm	2–4	One patent native outflow artery	• Severe calcium • Renal failure or CKD • No adjunctive treatment modality
IN.PACT	• SFA • 4–7 mm in diameter	• De novo or nonstented restenotic lesions • 70%–99% stenosis ≥ 4 cm and ≤ 18 cm • 100% ≤ 10 cm	2–4	Adequate outflow	• Severe calcium • CKD • No adjunctive treatment modality
Lutonix ISR	• Femoropopliteal artery • 4–6 mm in diameter	• ≥ 50% bare-nitinol stent restenosis • 4–18 cm	2–4	One patent native outflow artery	• Grade 4–5 stent fracture • No adjunctive treatment modality
Lutonix BTK	• Above-the-ankle tibial lesions • 2–4 mm in diameter	De novo or nonstented restenotic	4–5	NA	CKD

Abbreviations: CKD, chronic kidney disease; N/A, not applicable.

occlusion.[5] Additionally, stents make the artery rigid, inhibiting the natural undulant flow of blood and possibly resulting in reocclusion.[5] The DCB allows a paradigm shift in the treatment of de novo SFA stenosis by not leaving a stent behind but also in preventing restenosis.

LEVANT 2[1] and IN.PACT[2] focus on a specific patient population—those with predefined native SFA lesions. Patients whose lesions are > 18 cm and/or extend into the popliteal region, critical limb ischemia (Rutherford 5 and 6[6]), severely calcified vessels, and/or those with chronic kidney disease are excluded from these SFA trials.

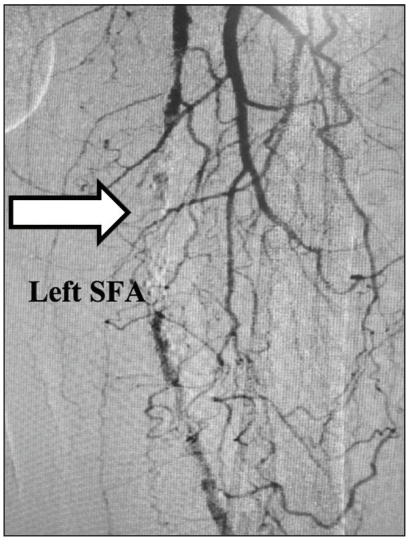


Figure 1. The left SFA preintervention.

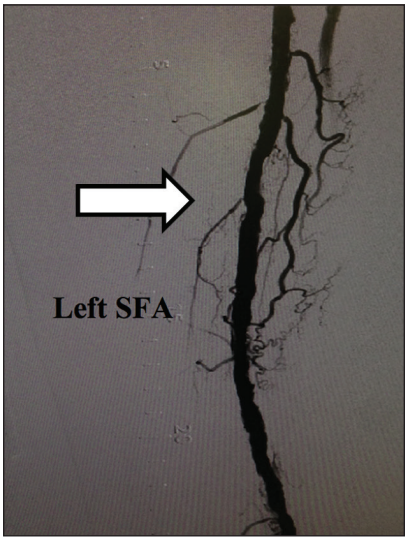


Figure 2. The left SFA postintervention with a DCB.

CASE 1

An 81-year-old man with a history of hypertension, hyperlipidemia, coronary artery disease, and diabetes was complaining of left lower extremity claudication. The ankle-brachial index of his left lower extremity was 0.54. He was found to have an occluded left SFA (Figure 1) and underwent successful percutaneous intervention with a DCB. Postintervention, his pain resolved, and 26-month duplex ultrasound confirmed that the vessel has remained patent (Figure 2).

CASE 2

A 65-year-old woman with a history of dyslipidemia, tobacco use, and PAD (left SFA stent placed 11 months earlier) presented with left lower extremity claudication. An angiogram showed in-stent reocclusion (Figure 3), and she was treated with a DCB. Currently, the vessel is widely patent at 3 months postintervention (Figure 4).

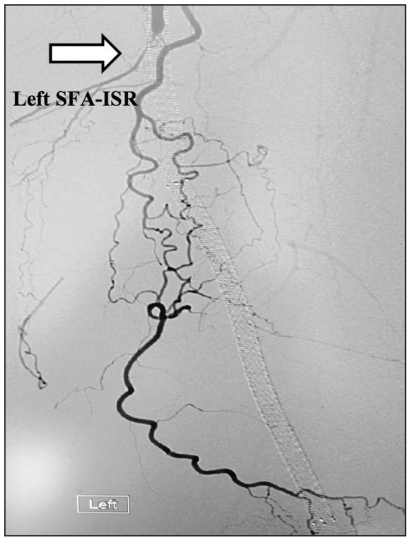


Figure 3. Preintervention image from a patient in the SFA-ISR trial.

Figure 4. The 3-month postintervention imaging.

The importance of inflow patency on outflow patency is well recognized, as is the importance of outflow patency on inflow.[9,10] Even with this knowledge, many endovascular specialists continue to avoid tibial and pedal interventions. BTK interventions are challenging because these vessels are considerably smaller (1–4 mm), heavily calcified, commonly have chronic total occlusions, and are typically located far from the access site.[7,11] Additionally, tools and techniques for BTK interventions have historically lagged behind those for above-the-knee interventions. In the United States, tools and techniques for BTK interventions are rapidly evolving for immediate technical success.[12] However, there has been a void for devices focused on long-term vessel patency. The DCB may provide that answer.

CASE 3

A 61-year-old woman with coronary artery disease, diabetes, hyperlipidemia, and hypertension presented with a nonhealing ulcer of the left great toe. She underwent endovascular intervention of the left anterior tibial artery (Figure 5) with a DCB and showed immediate technical success. She remained patent on duplex ultrasound at 8 months posttreatment. The wound healed 3 weeks postintervention (Figure 6).

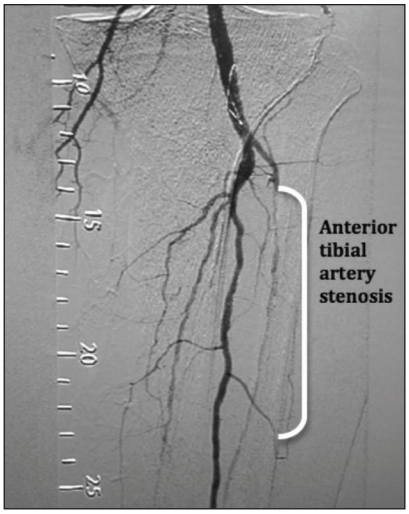


Figure 5. Preintervention imaging of the anterior tibial artery stenosis.

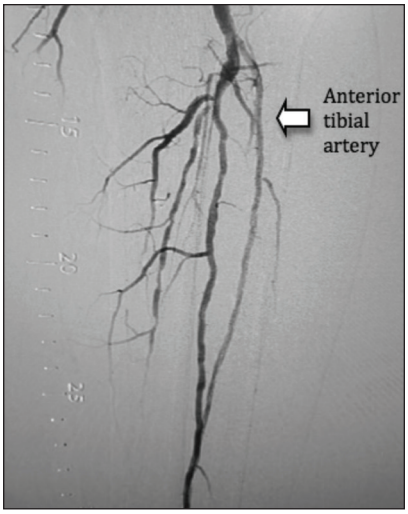


Figure 6. Postintervention result showing the patent anterior tibial artery.

Endovascular specialists in the United States are rapidly adopting drug-eluting technologies with the hope of improving long-term outcomes.[12] Devices are evolving to meet this need and currently include DCBs, drug-eluting stents, and direct drug delivery. Although these drug delivery devices have shown promise, long-term data are still needed. Unlike the Zilver PTX drug-eluting stent (Cook Medical), none of the DCBs have long-term randomized controlled trial data. Rather than being a stand-alone treatment, drug-eluting devices may be used in concert with other modalities to improve their performance. For example, with medial calcification, antineoproliferative agents may be inhibited from reaching the media and adventitia of the artery. Modification of the calcified artery by atherectomy may improve drug delivery with a DCB and improve the overall outcome.[13] Thinking outside the box is crucial for the development of future devices and techniques to address this population in need.

CONCLUSION

As an American endovascular specialist, drug-eluting technology is changing the way we practice. The concept of leaving nothing behind by using a DCB is an ideal concept embraced by many. However, there will be times, as shown in the previously mentioned clinical trials, when either a flow-limiting dissection or recoil occurs after vessel preparation (prolonged balloon inflation or possible future use of atherectomy). Many times, this is secondary to intra-arterial or medial calcium. As a result, the best strategy would be the marriage of a scaffold and drug elution (ie, a drug-eluting stent). The Zilver PTX drug-eluting stent is currently available and utilized in the United States, with compelling randomized outcomes data in the SFA.[14] Drug-eluting technologies will continue to evolve to address different patient pathologies, thus allowing for a truly personalized approach. ■

George L. Adams MD, MHS, is with Rex Health Care, University of North Carolina Health System in Raleigh, North Carolina. He is paid by Cook Medical for speaking, consulting, and physician education and is also a paid consultant for Medtronic and Bard. Dr. Adams may be reached at george.adams@rexhealth.com.

O Jesse Mendes, BA, is a graduate student in Physiology at the University of North Carolina at Chapel Hill in North Carolina. He has disclosed that he has no financial interests related to this article.

Neither Dr. Adams nor Mr. Mendes were paid for writing this article.

1. C. R. Bard. Moxy Drug Coated Balloon vs Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries (LEVANT 2). ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/record/NCT01412541. Accessed September 2014.
2. Medtronic Endovascular. IN.PACT Admiral Drug-Eluting Balloon vs Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery (SFA) and Proximal Popliteal Artery (PPA) (INPACT SFA II). ClinicalTrials.gov website. http://clinicaltrials.gov/show/NCT01566461. Accessed September 2014.
3. C. R. Bard. Lutonix Drug Coated Balloon vs Standard Balloon Angioplasty for Treatment of Femoropopliteal In-Stent Restenosis (SFA ISR). ClinicalTrials.gov website. http://clinicaltrials.gov/show/NCT02063672. Accessed September 2014.
4. C. R. Bard, Bard Ltd. Lutonix DCB Versus Standard Balloon Angioplasty for Treatment of Below-The-Knee (BTK) Arteries. ClinicalTrials.gov website. http://clinicaltrials.gov/show/NCT01870401. Accessed September 2014.
5. Arena FJ. Arterial kink and damage in normal segments of the superficial femoral and popliteal arteries abutting nitinol stents—a common cause of late occlusion and restenosis? A single-center experience. J Invasive Cardiol. 2005;17:482-486.
6. Weinberg I. Arterial disease: Rutherford classification. Vascular medicine: angiologist. Available at http://www.angiologist.com/arterial-disease/rutherford-classification. Accessed September 2014.
7. Kraitzer A1, Kloog Y, Zilberman M. Approaches for prevention of restenosis. J Biomed Mater Res B Appl Biomater. 2008;85:583-603.
8. Gallino Mahler F, Probst P, Nachbur B. Percutaneous transluminal angioplasty of the arteries of the lower limbs: a 5 year follow-up. Circulation. 1984;70:619-623.
9. Davies MG, Saad WE, Peden EK, et al. Impact of runoff on superficial femoral artery endoluminal interventions for rest pain and tissue loss. J Vasc Surg. 2008;48:619-626.
10. Al Mahameed A. Peripheral arterial disease. Cleveland Clinic for Continuing Education website. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/peripheral-arterial-disease. Accessed September 2014.
11. El-Sayed HF. Retrograde pedal/tibial artery access for treatment of infragenicular arterial occlusive disease. Methodist Debakey Cardiovasc J. 2013;9:73-78.
12. Gray WA, Granada JF. Drug-coated balloons for the prevention of vascular restenosis. Circulation. 2010;121:2672-2680.
13. Cioppa A, Stabile E, Popusoi G, et al. Combined treatment of heavy calcified femoro-popliteal lesions using directional atherectomy and a paclitaxel coated balloon: one-year single centre clinical results. Cardiovasc Revasc Med. 2012;13:219-223.
14. Ansel G. The Zilver PTX randomized trial of paclitaxel-eluting stent for femoropopliteal disease: 4-year results. Presented at: Vascular Interventional Advances (VIVA) 2013; October 8-11, 2013; Las Vegas, Nevada.

DES and DEB Use in Europe

As devices develop and longer follow-up data become available, one thing is certain: It's a drug-eluting world, all right.

BY KONSTANTINOS KATSANOS, MSc, MD, PhD, EBIR

The femoropopliteal artery is the most common site of disease in patients with peripheral vascular disease and is typically characterized by increased and often aggressive vascular restenosis after endovascular treatments.[1] Drug-coated balloons (DCBs) and drug-eluting stents (DES) have emerged as the latest and most promising development in the fight against neointimal hyperplasia in the peripheral arteries.

However, before discussing the base of evidence underpinning the use of DES and DCBs, one needs to understand the rationale and key principles of percutaneous angioplasty and endovascular treatments in general. Each patient requires a customized treatment plan depending on baseline comorbidities, anatomy and morphology of the disease, and above all, clinical symptoms. Intermittent claudication is fundamentally a benign condition that limits lifestyle, contrary to critical limb ischemia, which necessitates more aggressive revascularization to avoid limb loss and is often related to limited life expectancy akin to a malignancy.[2] During the last decades, the armamentarium of percutaneous balloon angioplasty has evolved from primitive Dottering catheters to sophisticated miniaturized equipment able to (1) cross the lesion, (2) debulk the plaque, (3) dilate the vessel, (4) scaffold the lumen, and (5) apply antirestenotic drugs. Hence, each individual treatment will employ a series of the aforementioned tasks with the aim to maximize acute luminal gain followed by a durable patency result.

DCBs address only the last task, whereas DES address the tasks of both scaffolding the vessel after balloon angioplasty and drug elution to inhibit restenosis, albeit at the expense of a permanent metal implant. Soon after the failure of the SIROCCO and the STRIDES trials, which employed -olimus agents,[3,4] paclitaxel has become the mainstream drug to fight neointimal hyperplasia in the femoral artery. In a recent network meta-analysis of 16 randomized controlled trials comprising > 2,500 patients, we have shown that paclitaxel-coated balloons and paclitaxel-eluting stents offer the best long-term results in the femoropopliteal artery by significantly reducing the incidence of restenosis and target lesion revascularization by approximately 50%.[5] The base of evidence supporting DCB currently includes nine randomized trials with > 1,000 patients and 1 to 2 years of follow-up. DES in the femoral artery is supported by an RCT, the ZILVER-PTX trial, with 479 patients and 5 years of follow-up in the latest update.[6]

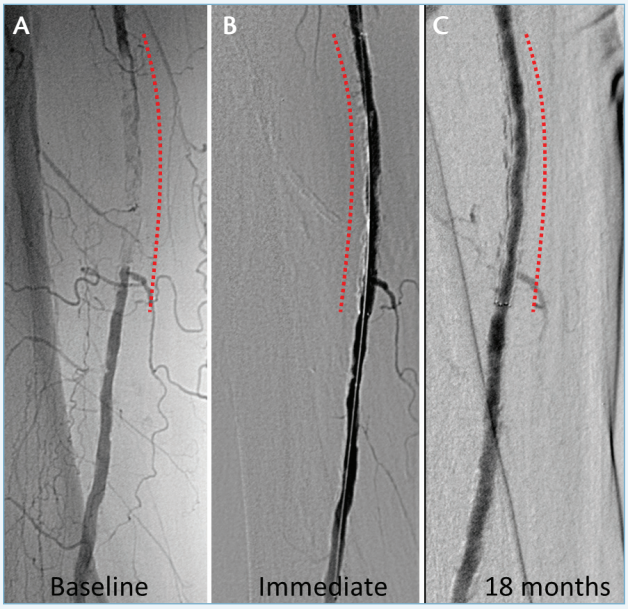
Each patient requires a customized treatment plan depending on baseline comorbidities, anatomy and morphology of the disease, and above all, clinical symptoms.

On the basis of the previous rationale and evidence, DCBs are best suited for short, noncalcified lesions in patients of younger age who are suffering from lifestyle-limiting claudication with the aim to inhibit vascular restenosis. On the other hand, stents are associated with significantly higher immediate technical success compared to balloon angioplasty.[5] Hence, DES are quite suitable for more complex lesions. As a glimpse to the future, bioabsorbable DES that may combine the best of both worlds (ie, scaffold the vessel and inhibit restenosis, but without a permanent implant) are already paving the way from the bench to the clinic.

Currently, adoption of DCBs and DES in Europe is gradually increasing. However, variations of paclitaxel pharmacokinetics, differing results in the magnitude

CASE REPORT

This is an illustrative case study of paclitaxel-eluting Zilver PTX stent (Cook Medical) placement in a typical patient with critical limb ischemia (CLI). The patient presented with long-segment, heavily calcified, mid-superficial femoral artery (SFA) total occlusion (A). Heavy vessel calcification is the most common cause of suboptimal balloon angioplasty outcomes due to plaque recoil and significant residual stenosis. The immediate completion angiogram showed a well-expanded 6- X 100-mm Zilver PTX stent with normal intimal coverage (B). At 18 months, angiographic follow-up showed no evidence of vascular restenosis (C), which was actually performed for diagnostic purposes because the patient developed CLI in the contralateral leg.



of paclitaxel effectiveness, the need for drug carriers or excipients, and above all, the increased costs associated with these new devices have been a barrier to mainstream use. In Europe in particular, conservative health care models and complicated reimbursement policies within a cost-sensitive economic environment have further impeded the use of paclitaxel stents and balloons in the periphery. Of note, clinical- and cost-effectiveness has been shown for both DCB and DES with the application of budget-impact modeling or probabilistic cost-benefit analyses.[7,8] In brief, the significant reduction of repeat angioplasty events (TLR) is expected to materialize in significant cost savings for the health care providers in the future despite the higher up front investment in patient care (price premium of drug balloons and stents). Whatever the future holds, it is definitely a drug-eluting one. ■

Konstantinos Katsanos, MSc, MD, PhD, EBIR, is a Consultant Vascular & Interventional Radiologist, Guy's and St. Thomas' Hospitals, NHS Foundation Trust, Department of Imaging Sciences & Biomedical Engineering, King's College, London. He stated that over the last 2 years, he has been a proctor for Medtronic-Invatec and has received honoraria for lectures by Cook and Gore. Dr. Katsanos may be reached at Konstantinos.Katsanos@gstt.nhs.uk.

Dr. Katsanos was not paid for writing this article.

1. Norgren L, Hiatt WR, Dormandy JA, et al; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45(suppl S):S5-67.
2. Lumsden AB, Davies MG, Peden EK. Medical and endovascular management of critical limb ischemia. J Endovasc Ther. 2009;16(2 suppl 2):II31-62.
3. Duda SH, Bosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. J Endovasc Ther. 2006;13:701-710.
4. Lammer J, Bosiers M, Zeller T, et al. First clinical trial of nitinol self-expanding everolimus-eluting stent implantation for peripheral arterial occlusive disease. J Vasc Surg. 2011;54:394-401.
5. Katsanos K, Spiliopoulos S, Karunanithy N, et al. Bayesian network meta-analysis of nitinol stents, covered stents, drug-eluting stents, and drug-coated balloons in the femoropopliteal artery. J Vasc Surg. 2014;59:1123-1133.e8.
6. Dake MD, Ansel GM, Jaff MR, et al; Zilver PTX Investigators. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. J Am Coll Cardiol. 2013;61:2417-2427Published online ahead of print April 10, 2013. Erratum in: J Am Coll Cardiol. 2013;62:666.
7. De Cock E, Sapoval M, Julia P, et al. A budget impact model for paclitaxel-eluting stent in femoropopliteal disease in France. Cardiovasc Intervent Radiol. 2013;36:362-370.
8. Kearns BC, Michaels JA, Stevenson MD, Thomas SM. Cost-effectiveness analysis of enhancements to angioplasty for infrainguinal arterial disease. Br J Surg. 2013;100:1180-1188.

The Costs and Benefits of Medical Innovation

Looking beyond prices and assessing the true value of new technologies.

BY LOUIS L. NGUYEN, MD, MBA, MPH, AND REBECCA E. SCULLY, MD


Throughout history, innovation and medicine have gone hand in hand. A number of major advances come to mind: vaccines, anesthesia, antibiotics, imaging, and organ transplantation. Each represents a pivotal turning point in health care and an abrupt divergence in our understanding of disease. Such innovations are remarkable, not only for the impact they have had on improving health and longevity, but also in their rarity. Indeed, the majority of innovation is incremental rather than disruptive. They build on previous work and make small steps toward improvement. An example is consumer electronics, where innovation and competition have resulted in smaller, cheaper, and more high-performance gadgets.

THE RISE OF HEALTH CARE COSTS

It is not surprising that novel innovations come at a cost. Health care is currently 18% of the US GDP, and medical technology an estimated 6% of health care expenditures in the United States. The initial high prices of new products reflect the costs of development, both for the featured product as well as the many related products that never actually made it to use in patients. These prices also reflect prevailing market forces, including available substitutes and market share.

In most industries, technological innovation results in greater benefit at a decreased price to the consumer. What makes medicine somewhat unique is that the opposite is sometimes true. Many advancements in technology seemingly result in increased prices and greater health care expenditures. For example, Soliris (Alexion Pharmaceuticals), a monoclonal antibody to treat paroxysmal nocturnal hematuria costs $409,500 a year. Elaprase (Shire Plc), a drug to treat Hunter syndrome, which is a congenital metabolic disorder that affects approximately 500 Americans, costs $375,000 annually. These high prices can partially be explained by the magnitude of the potential market. Developmental costs are easier to recoup for products with broad application, rather than a narrow user market, as exemplified by drugs/devices that treat rare diseases. The fact that physicians and patients are relatively insulated from costs due to third-party reimbursement for health care services also contributes to high prices.

> If we ignore the benefits of innovation for short-term cost gains, we risk stifling innovation and jeopardizing future gains in health, longevity, and quality of life for patients and society.

BENEFITS OF INNOVATION

Innovators are protected by patents, allowing them exclusive rights to manufacture and market their products in return for public disclosure. Although this exclusivity is often seen as a source of rising health care costs, the economic balance between being an initial innovator and those who later benefit from the discovery does not always favor the innovator. There are many examples of innovations that do not return significant economic benefits until after the product becomes a public good and an experienced manufacturer or distribution organization brings the product to the full market.

Although most would agree that cost controls are needed, their implementation remains a topic of much debate. The health care systems in many other countries, such as the National Health System in the United Kingdom, use cost-effectiveness research to help guide budgetary and coverage decisions. United States governmental health care agencies, however, have been reluctant to use cost-effectiveness research. Notably, the Patient-Center Outcomes Research Institute, established by the Affordable Care Act, currently does not

fund research proposals for cost-effectiveness research, a decision at least in part driven by the politically negative association with cost-based evaluation and the specter of "death panels."

Even in its current form, cost-effectiveness research can fail to capture the entire benefit of new innovations. The value of medical innovations, including new drugs, devices, or processes, is typically measured by direct effect over a short period of time. Using vascular stents as an example, one might track vessel patency and the need for reinterventions. These outcomes are then compared with the costs of the stent, as measured by the acquisition costs from the perspective of the payer. Although somewhat more readily captured, these data represent just a small component of the potential benefit of successful treatment. To continue our example with vascular stents, the patient who has successful peripheral revascularization may return to work earlier, improve his or her cardiopulmonary function with increased walking, and may enjoy greater social integration by being able to participate in activities. Society itself may benefit from a more mobile person who is able to be productive at work and does not rely on assistance for ambulation. From the patient's perspective, these are the true benefits of revascularization. In addition, innovations often spur further advances and spinoff technologies, exponentially increasing the value of advances, but also being rarely accounted for in current models of cost effectiveness.

PENNY-WISE AND POUND-FOOLISH?

Although medical innovation and technology have been a major factor in the improvement of health care throughout history, shortsighted purchasing policies and limited investment in innovation and innovators have the potential to derail this process. Attention to cost is crucial in controlling health care expenditures, but decisions based on price alone fail to capture the true benefit of innovation. Investment in technology, appropriate endpoints in cost-effectiveness research, and support for innovators is vital to the continued advancement of health care technology. If we ignore the benefits of innovation for short-term cost gains, we risk stifling innovation and jeopardizing future gains in health, longevity, and quality of life for patients and society. ■

Louis L. Nguyen, MD, MBA, MPH, is Associate Professor of Surgery, Brigham & Women's Hospital, Harvard Medical School in Boston, Massachusetts. He has disclosed that he has no financial interests related to this article. Dr. Nguyen may be reached at llnguyen@partners.org.

Rebecca E. Scully, MD, is a resident in General Surgery, Brigham & Women's Hospital in Boston, Massachusetts. She has disclosed that she has no financial interests related to this article.

Neither Dr. Nguyen nor Dr. Scully were paid for writing this article.

DES Versus Bypass for Femoropopliteal Disease

Should the current data on drug-eluting devices cause surgeons to reconsider when to use bypass?

BY MARC BOSIERS, MD, AND KOEN DELOOSE, MD


Vascular surgeons have more options for treating femoropopliteal disease available today than ever before. Whereas other physician specialties only have to consider the appropriateness of medical, exercise, and endovascular therapies for treating their patients, the vascular surgeon also has to consider bypass surgery. Good-quality randomized data comparing different endovascular options have significantly increased over the past decade. Among the different endovascular options, percutaneous transluminal angioplasty (PTA) and stenting are the most common and would have been considered standard care not too long ago.

The emergence of drug-coated balloons and drug-eluting stents, however, are now showing superiority to their bare counterparts. In the IN.PACT SFA trial, the In.Pact Admiral drug-coated balloon (Medtronic, Inc.) demonstrated superiority to a standard, bare PTA balloon catheter.[1] In the Zilver PTX randomized controlled trial, the Zilver PTX stent (Cook Medical) demonstrated superiority to both PTA and bare-metal stents (BMS).[2] These trials have given physicians great confidence in using drug-eluting devices over their bare counterparts.

A largely unanswered question, however, is how drug-eluting devices compare to bypass. Data comparing percutaneous coronary intervention/drug-eluting stents to coronary artery bypass grafting in the coronary arteries suggest that target lesion revascularization (TLR) rates are higher with percutaneous coronary intervention/drug-eluting stents, but the risk of stroke is higher with coronary artery bypass grafting.[3,4] Unfortunately, substantial data comparing femoropopliteal bypass to superficial femoral artery (SFA) drug-eluting stents are lacking.

In the BASIL trial, bypass was compared to PTA. For the first 2 years of follow-up, there was no difference between PTA and bypass; but after 2 years, bypass showed more durable results.[5] Although the trial provided some insight into the performance of bypass compared to PTA, it is greatly limited for drawing conclusions about choosing modern SFA treatment options. The evidence comparing drug-eluting therapies to bypass is far from complete, but there is some evidence available to help surgeons re-examine their treatment philosophies and consider whether they should make any adjustments to how they approach treatment selection for SFA lesions. This article examines how drug-eluting SFA stents compare to three forms of bypass: "endovascular bypass" (polytetrafluoroethylene stent grafts), synthetic bypass, and vein bypass.

> When considering performance in randomized trials, safety issues, and the cost of each device, a strong hypothesis may be formed in favor of Zilver PTX.

ZILVER PTX VERSUS ENDOVASCULAR BYPASS

Although femoropopliteal stent grafts are not technically a mode of bypass, some vascular surgeons choose them based on their perceived similarities to synthetic bypass. The most widely used femoropopliteal stent graft is the Viabahn endoprosthesis (Gore & Associates). Currently, there are no head-to-head data comparing Zilver PTX to the Viabahn device, but there are some good randomized data for each device. From these data, we may be able to formulate hypotheses about which device to choose.

The Viabahn device was randomized against BMS in two different trials: the VIBRANT trial and, most recently, the VIASTAR trial. In the VIBRANT trial, the first-generation Viabahn device did not demonstrate a difference in patency when compared to BMS (24.2%

vs 25.9% at 3 years, respectively). However, the second-generation Viabahn fared better than the first-generation device. In the VIASTAR trial, Viabahn showed an improvement in patency to a BMS at 24 months (63.3% vs 41.4%).[6] That said, the primary patency results were somewhat dampened by the secondary patency rates and freedom from TLR rates. Viabahn showed no significant improvement over BMS for secondary patency (89.7% vs 88.8%) and no significant improvement in freedom from TLR at 24 months (76.1% vs 68.4%).[6] Regardless of which device generation is used, the benefit of Viabahn over BMS appears to be marginal.

In the Zilver PTX randomized trial, the Zilver PTX device showed significant improvement over both optimal PTA and BMS, cutting both restenosis and reinterventions by nearly half. At 2 years, Zilver PTX showed a 46% reduction in restenosis (83.4% vs 63.1%).[2] Further, Zilver PTX demonstrated a 53% reduction in reinterventions at the 2-year mark (89.1% vs 76.7%).

In addition to considerations of effectiveness, one must consider safety factors, as well. Thrombosis can be a challenge for permanently implanted devices. However, Zilver PTX showed a 2.3% thrombosis rate through 2 years compared to the BMS rate of 3.6%.[7] Further, a scan of the literature shows that a thrombosis rate of 2% to 5% is typical for bare-metal SFA stents and that Zilver PTX is within that range. Although Viabahn has shown modest acute thrombosis rates, it has not fared as well in terms of late stent thrombosis. In the Viabahn 25-cm study, Gore reports that the latest generation of Viabahn has a 12-month thrombosis rate of 15.5%.[8] In one physician-initiated study, thrombosis rates through 12 months were reported to be at 17%.[9] Further, that same study reports that 12% of patients undergoing Viabahn placement presented with acute limb ischemia.

When considering performance in randomized trials, safety issues, and the cost of each device, a strong hypothesis may be formed in favor of Zilver PTX.

ZILVER PTX VERSUS SYNTHETIC BYPASS

Before assessing differences between an endovascular device trial to a surgical bypass trial, one must account for the historically different definitions of patency between the two. Importantly, one should take note that bypass patency is not the same as endovascular patency. In an endovascular trial, such as the Zilver PTX randomized trial, patency is often measured in a binary fashion and is determined by the patient's peak systolic velocity ratio (PSVR) relative to the PSVR threshold set in the trial design (usually 2.0 or 2.4). By contrast, bypass is assessed simply by observing the flow through the bypass: either it is open or closed.

In a recent prospective study, Deloose et al found that 11% of those considered to be patent by classic vascular definitions were restenosed when using an endovascular standard of binary restenosis at a PSVR of 2.4.[10] Therefore, comparing patency between surgical and endovascular trials handicaps any endovascular therapy (especially if a more conservative PSVR of 2.0 is used).

Although there are no completed trials directly comparing Zilver PTX to bypass, data from various randomized controlled trials can help formulate hypotheses about which one might perform better (Table 1). A selective scan from 2005 to 2010 of trials that include bypass primary patency showed a 12-month primary patency rate of between 70% and 80%.[11] For the Zilver PTX randomized trial, single-arm study, and Japanese postmarket surveillance study, the 12-month primary patency rates for Zilver PTX ranged from 80% to 90%. A comprehensive literature review of bypass trials from 1966 to 2002 shows that the 2-year patency rate for synthetic bypass was 67%.[12] Results from the Zilver PTX randomized trial show that the primary patency rate at 2 years was 83.4%. It will be interesting to see how the 5-year patency rate for Zilver PTX compares to the 5-year patency rates for synthetic bypass.

Obviously, the most reliable method of comparison would be to randomize patients to either bypass or Zilver PTX in the same trial. By conducting a head-to-head comparison of Zilver PTX to bypass in the same trial, the patency bias that was previously discussed will be eliminated. That is why this author has initiated the ZILVERPASS study. The study will include two arms with a 1:1 randomization to either Zilver PTX or synthetic

TABLE 1. COMPARISON OF PATENCY RATES BY PROCEDURAL MODALITY

Treatment Type	2-Year Patency	4-Year Patency	5-Year Patency
Synthetic bypass	67%	NA	49%
Vein bypass	80%	NA	69%
Zilver PTX	83%	75%	NA (data will be reported later this year)

Abbreviation: NA, not available.

bypass. Further, as previously noted, the definition of patency will be the same for both arms, giving us one of the best comparisons of Zilver PTX to synthetic bypass to date. The trial is currently in the process of enrolling, and we look forward to seeing these data, which will inform treatment options for vascular surgeons.

ZILVER PTX VERSUS VEIN BYPASS

For most vascular surgeons, vein bypass is the gold standard for treating the femoropopliteal segment. But given the aforementioned differences between how patency is measured for a surgical bypass trial and an endovascular trial, comparisons can be difficult to assess. Nonetheless, there are some data available to again help us formulate hypotheses about the relative effectiveness of femoropopliteal bypass compared to SFA drug-eluting stents.

The same comprehensive literature review of bypass trials from 1966 to 2002 (as previously mentioned) shows the 2-year patency rate for vein bypass at 80%.[12] Results from the Zilver PTX randomized trial demonstrated a 2-year primary patency rate of 83%. From the same literature review of multiple bypass trials, the aggregated 5-year patency rate for vein bypass was 69%. The 4-year primary patency rate for Zilver PTX was 75%. We look forward to the publication of the 5-year Zilver PTX RCT data.

The ZILVERPASS study, comparing head-to-head bypass versus Zilver PTX for above-the-knee long femoropopliteal lesions, will shed new light on how the next long overdue revision of the TASC classification should be handled. ■

Marc Bosiers, MD, is Chief of Surgery at AZ Sint-Blasius in Dendermonde, Belgium. He stated that he has no financial interests related to the article. Dr. Bosiers may be reached at marc.bosiers@telenet.be.

Koen Deloose, MD, is a vascular surgeon at AZ Sint-Blasius in Dendermonde, Belgium. He stated that he has no financial interests related to the article.

Neither Dr. Bosiers nor Dr. Deloose were paid for writing this article.

1. IN.PACT SFA one-year results: Drug-eluting balloon outperforms angioplasty with lower reintervention rates and superior patency. Charing Cross website. http://www.cxvascular.com/cx-latest-news/cx-latest-news/cx-2014-audience-recognises-the-impact-of-drug-eluting-balloons. Accessed September 15, 2014.
2. Dake MD, Ansel GM, Jaff MR, et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. J Am Coll Cardiol. 2013;61:2417-2427.
3. Athappan G, Patvardhan E, Tuzcu ME, et al. Left main coronary artery stenosis: a meta-analysis of drug-eluting stents versus coronary artery bypass grafting. JACC Cardiovasc Interv. 2013;6:1219-1230.
4. Al Ali J, Franck C, Filion KB, Eisenberg MJ. Coronary artery bypass graft surgery versus percutaneous coronary intervention with first-generation drug-eluting stents: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv. 2014;7:497-506.
5. Conte MS. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia. J Vasc Surg. 2010;51(5 suppl):69S-75S.
6. Lammer J. Endovascular treatment of TASC C and D lesions in the SFA 2 year data of the VIASTAR trial. Presented at ISET 2014; January 18–22, 2014; Miami Beach, FL.
7. Zilver PTX Instructions for Use. Cook Medical website. https://www.cookmedical.com/data/IFU_PDF/IFU0093-4.PDF. Accessed September 15, 2014.
8. Instructions for Use for Gore Viabahn endoprosthesis. Gore Medical website. http://www.goremedical.com/resources/dam/assets/20019563.pdf. Accessed September 15, 2014.
9. Johnston PC, Vartanian SM, Runge SJ, et al. Risk factors for clinical failure after stent graft treatment for femoropopliteal occlusive disease. J Vasc Surg. 2012;56:998-1006.
10. Deloose K, Bosiers M, Callaert J, et al. Evaluation of primary patency in surgical bypasses using the endovascular approach. Presented at Eastern Vascular Society 26th Annual Meeting; September 13–15, 2012; Pittsburgh, PA. Available at http://meeting.easternvascular.org/abstracts/2012/p17.cgi. Accessed September 15, 2014.
11. Bosiers M. Does Zilver PTX DES yield better results than an open bypass? Presented at Controversies & Updates in Vascular Surgery; January 23–25, 2014; Paris, France.
12. Klinkert P, Post PN, Breslau PJ, van Bockel JH. Saphenous vein versus PTFE for above-knee femoropopliteal bypass. A review of the literature. Eur J Vasc Endovasc Surg. 2004;27:357-362.