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Shifting the SFA Treatment Paradigm

Global thought leaders discuss
the ELUVIA DES IMPERIAL Trial
results and its influence on
treatment decisions



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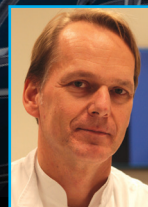
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Shifting the SFA Treatment Paradigm

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IMPERIAL 12-Month Full Cohort and Long Lesion Sub-Study Results

Sustained drug-release in the SFA drives superior results.

BY WILLIAM A. GRAY, MD | IMPERIAL PRINCIPAL INVESTIGATOR



Coronary drug-eluting stents (DES) with both paclitaxel and limus drugs have demonstrated successful long-term clinical outcomes for patients, with single-digit reintervention rates at 1 year. While the limus family of drugs have been particularly successful in coronary stenting, two major clinical trials studying limus-eluting stents in the superficial femoral artery (SFA) failed to show clinical efficacy. The SIROCCO study evaluated a sirolimus-eluting version of the SMART stent (Cordis, a Cardinal Health company),¹ and the STRIDES study evaluated an everolimus-eluting version of the Dynalink stent (Abbott Vascular).² Neither study was able to show a statistically significant difference between the limus-eluting stents and their respective bare-metal counterparts.

Conversely, paclitaxel, which works by inhibiting cell proliferation and migration, has demonstrated safety and efficacy in the coronary arteries as well as the SFA. The randomized controlled trial for the Zilver PTX DES (Cook Medical) showed an 18% difference in primary patency between the Zilver PTX arm versus the bare-metal stent (BMS) arm.³ Additionally, the RANGER-SFA, LEVANT, and IN.PACT trials demonstrated the efficacy of paclitaxel-coated balloons over PTA in the SFA.⁴⁻⁶

RESTENOSIS IN THE SFA

The treatment of disease in the SFA presents a considerable challenge due to the unique mechanical forces in this vessel bed and the high degree of severe calcium and occlusions. Based on the clinical literature, smooth muscle cell proliferation can occur for up to 100 days or longer, and the final phase of restenosis can last for well beyond 1 year.⁷

Unlike disease in the coronary arteries, where restenosis usually peaks within 3 to 6 months, restenosis tends to peak later in the SFAs, usually between 9 to 12 months. The experience with peripheral first-generation nitinol BMS was disappointing, with 1-year primary patency rates well below 80%, far less than patency rates observed in the coronary arteries.

THE ZILVER PTX DRUG-COATED STENT

The Zilver PTX stent is a paclitaxel drug-coated stent, which received FDA approval in 2012. This stent does not have a polymer or carrier, so the drug is simply applied to the stent. It has a 3 $\mu\text{g}/\text{mm}^2$ dose of paclitaxel, which upon implantation is immediately released during the first few days and remains in the vessel wall up to 56 days in preclinical testing.⁸ The Zilver PTX stent is well-studied and has demonstrated improved patency and target lesion revascularization (TLR) rates over its BMS counterpart, with a 12-month primary patency rate of 82.7% in the Zilver PTX randomized controlled trial.³ The Zilver PTX stent has a 5-year primary patency rate of 66.4% versus a percutaneous transluminal angioplasty (PTA) primary patency rate of 43.4%, demonstrating a durable patency effect with antiproliferative therapy that improves outcomes.⁹

THE ELUVIA DRUG-ELUTING STENT

With the design of the Eluvia Drug-Eluting Stent System, Boston Scientific sought to improve upon existing clinical outcomes, targeting low single-digit reintervention rates and more durable long-term outcomes for patients. The Eluvia Drug-Eluting Stent represents a novel approach to the treatment of diseased femoropopliteal arteries as the first and only technology designed to sustain drug release beyond 1 year to match the restenotic process in the SFA (Figure 1). The stent platform is designed to withstand the mechanical forces of the SFA, balancing optimal strength and fracture resistance, while providing a uniform scaffolding for drug delivery. The polymer is a fluorinated polymer, which was intentionally designed to deliver optimized drug transfer with the lowest possible drug dose. The paclitaxel release is highly targeted to the lesion with virtually no drug lost downstream. Its safety has been studied in over 100,000 patients in clinical trials and implanted in over 20 million vessels commercially.¹⁰ The polymer allows the 0.167 $\mu\text{g}/\text{mm}^2$ paclitaxel dose drug delivery to be tuned to sustain drug release beyond 1 year.

THE IMPERIAL CLINICAL TRIAL PROGRAM

The IMPERIAL trial represents the first head-to-head

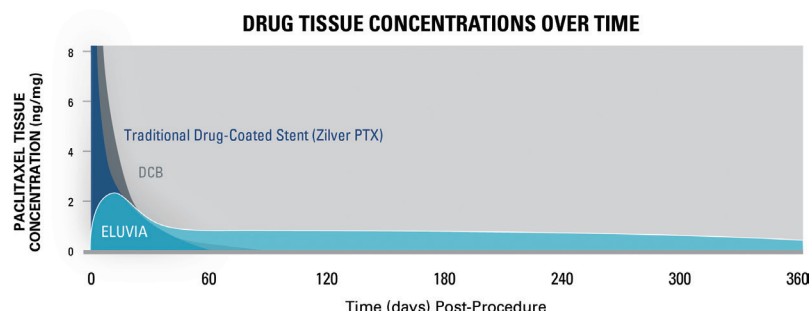


Figure 1. Comparison of drug release over time between Zilver PTX, DCBs, and Eluvia. Eluvia is designed to sustain drug release to match when restenosis peaks in the SFA.

trial comparing two antiproliferative stents in the SFA. The IMPERIAL randomized cohort is a global prospective single-blind multicenter randomized controlled trial comparing Boston Scientific's Eluvia Drug-Eluting Vascular Stent to Cook Medical's Zilver PTX drug-coated stent (2:1 randomization). The randomized cohort enrolled 465 patients across 64 sites around the world. Eligible patients had chronic, symptomatic lower limb ischemia and de novo or restenotic lesions up to 140 mm in length in the native SFA and/or proximal popliteal artery (PPA). As prespecified in the Statistical Analysis Plan, once both primary endpoints were met, a post-hoc superiority analysis could be performed. The IMPERIAL trial also included a single-arm 50-patient long lesion sub-study evaluating safety and effectiveness of Eluvia in lesions 140 to 190 mm in length (clinicaltrials.gov identifier NCT02574481).

The average lesion length in the IMPERIAL randomized cohort was 87 mm in the Eluvia arm and 82 mm in the Zilver PTX arm. In the Eluvia arm, 40% of the lesions were severely calcified, 31% were total occlusions, and 84% extended into the distal portion of the SFA and/or PPA. In the Zilver PTX arm, 32% of the lesions were severely calcified, 30% were total occlusions, and 78% extended into the distal portion of the SFA and/or proximal popliteal artery. There were no statistically significant differences in terms of patient or lesion characteristics between the two study arms.

SUPERIOR RESULTS IN THE FIRST HEAD-TO-HEAD DES SFA TRIAL

Eluvia demonstrated superiority in primary patency over Zilver PTX in the prespecified post-hoc analysis.¹¹ The Kaplan-Meier estimated primary patency rates were 88.5% versus 79.5%, respectively ($P = .0119$). IMPERIAL reported a 4.9% major-adverse event rate in the Eluvia arm and a 9% rate in the Zilver PTX arm ($P = .0975$), most of which were comprised of TLR rates at 1 year

in both arms. Patients in the Eluvia arm underwent half as many TLRs compared to those in the Zilver PTX arm (4.5% versus 9%, $P = .0672$). Both arms of the study reported strong patient outcomes, with 85.8% of the patients presenting with no or minimal claudication at 12 months in the Eluvia arm compared to 84.5% in the Zilver PTX arm, but at a cost of twice the reintervention rate in the Zilver PTX arm to achieve these outcomes. Baseline clinical improvement was sustained at 12 months in 89.6% of the Eluvia patients and 83.1% of the Zilver PTX patients.¹²

CONSISTENT RESULTS INDEPENDENT OF LESION LENGTH

In the long lesion cohort of the IMPERIAL trial, Eluvia demonstrated an 87.9% primary patency rate in lesions with a mean length of 162.8 mm (Figure 2). This patient group also had lesion characteristics of 70% moderate/severe calcium, nearly a third total occlusions, and 76% extended into the distal portion of the SFA and/or PPA. Freedom from major adverse events was observed at 93.5% at 12 months with a TLR rate of 6.5% (Table 1).¹³ These results with Eluvia completely counter the notion that as lesion length and complexity increases, stent patency decreases. These data are consistent with the results from the smaller independent Münster registry, which observed an 87% primary patency rate at 12 months in a highly complex patient population with 80% chronic total occlusions, 48% critical limb ischemia, and an average lesion length of 200 mm.¹⁴

The IMPERIAL trial is a landmark trial that advances the peripheral vascular space and provides the physician

Long Lesion Sub-Study Results: Kaplan-Meier Primary Patency Rate

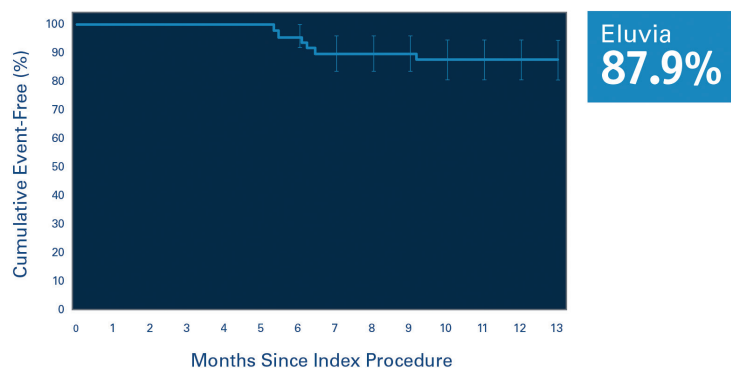


Figure 2. In the long lesion sub-study of the IMPERIAL trial, Eluvia demonstrated an 87.9% primary patency rate (by Kaplan-Meier estimate) in lesions with a mean length of 162.8 mm.

INSIGHTS ON THE DATA WITH AN IMPERIAL PRINCIPAL INVESTIGATOR

With Prof. Stefan Müller-Hülsbeck, MD, EBIR, FCIRSE, FICA, FSIR | IMPERIAL Co-Principal Investigator



As the lead Principal Investigator for the MAJESTIC trial and Co-Principal Investigator for IMPERIAL, what were your initial reactions to the IMPERIAL results?

Prof. Müller-Hülsbeck: The results were excellent.

My expectations, which were based on the encouraging 1-year data from MAJESTIC, were met for primary patency and rate of freedom from TLR. I felt somewhat relieved that a larger study population achieved excellent data with a polymer-coated DES.

Why is it important for the endovascular community to have a head-to-head trial comparing two DES technologies?

Prof. Müller-Hülsbeck: Having a head-to-head comparison of two available devices is something new that the interventional community has been waiting for. Comparing an established DES like Zilver PTX with the new Eluvia DES technology is outstanding, because convincing 5-year Zilver PTX data have already been published. Having more robust data from a head-to-head comparison might strengthen the acceptance of this technology in general when there is a need for an implant such as a self-expanding stent or DES.

Eluvia demonstrated superiority over Zilver PTX in IMPERIAL. How should physicians performing endovascular procedures think about this superiority data when making device decisions?

Prof. Müller-Hülsbeck: Physicians must keep in mind that all trial data are collected under ideal "trial conditions," meaning dedicated inclusion and exclusion criteria need to be fulfilled before the study device is allowed to be used; all patients are under more controlled follow-up, including stricter drug regimens; and last but not least, all participating physicians are well trained to serve as investigators in the trial. That means data are obtained under optimized conditions, which strengthens the results reached.

However, statistical calculations for device safety and efficacy necessitate a minimum number of included subjects to draw any conclusions on the results, so the device performance is impressive. IMPERIAL showed that both available DES technologies provide good patient outcomes, but Eluvia performed better in terms of primary patency and 50% lower

TLR rates. This might influence future decision making, meaning current Zilver PTX users may switch to Eluvia, and first-time potential users of DES technology will probably choose Eluvia from the beginning.

What are your thoughts on Eluvia's performance in IMPERIAL (88.5% primary patency), based on the very challenging lesion characteristics studied (40% severe calcium in the Eluvia arm and nearly a third chronic total occlusions)?

Prof. Müller-Hülsbeck: My preference in cases that need a stent is rather clear: implant a DES, ideally Eluvia. Doing the best for our patients is the goal. Since seeing the results of the first-in-human MAJESTIC trial, I believed that all lesions that need scaffolding should receive a DES such as Eluvia. Now seeing the results from IMPERIAL, this vision may come true. Calcium and chronic total occlusions shouldn't hinder us from using an Eluvia stent.

"Leave nothing behind" has become a popular saying in the endovascular space. However, Eluvia demonstrated a TLR rate of just 4.5% in IMPERIAL. Do you believe that outcome could cause some physicians to rethink a leave-nothing-behind strategy, when a DES provides such excellent TLR rates?

Prof. Müller-Hülsbeck: "Leave nothing behind" should still be a considered strategy, because a nitinol scaffold may not be appropriate for some patients. If a stentless strategy fails, we still have the option to implant a scaffold, or simply to repeat a leave-nothing-behind intervention. Stenting in all cases is not appropriate; however, many stents are still used because there is a strong need, and these cases should be privileged with a DES rather than a BMS. The promising results from IMPERIAL may liberalize stent usage, but this decision will ultimately be influenced by reimbursement, which varies from country to country.

How might the IMPERIAL data affect your SFA treatment algorithm moving forward?

Prof. Müller-Hülsbeck: I believe that if there is a need for an implant, all implants should be DES. This may be the end of the BMS era for femoropopliteal disease treatment. ■

Table 1. Safety Results from IMPERIAL Long Lesion Sub-Study

	Eluvia (n=50)
12-month MAE	6.5%
All Causes of Deaths at 1 Month	0.0%
Target Limb Major Amputation	0.0%
Target Lesion Revascularization	6.5%
Stent Thrombosis	0.0%

6.5% TLR
in 162.8 mm Lesions

community with level 1 clinical evidence to help make clinical and device treatment decisions. It sets a new standard for clinical evidence moving forward.

DRUG-ELUTING THERAPIES IN PRACTICE

Antiproliferative therapies such as DESs and drug-coated balloons (DCBs) have demonstrated proven results in the SFA. We know they work. But how do we decide which therapy to use when and where? That question still needs to be answered. However, the patient populations studied in DCB trials represent primarily TASC A/B lesions, < 10 cm, and less calcification. Historical SFA stenting studies are typically inclusive of patient populations with more complex lesions and a high degree of calcification. Currently, interventionalists' treatment algorithms typically start with vessel prep using a PTA balloon. If the result is optimal, then for shorter, simpler (TASC A and B) lesions, one might consider first-line therapy to be a DCB. If the result is suboptimal following PTA, a DES would be an appropriate treatment option.

The current available clinical data for long, highly calcified lesions seems to skew in favor of DES. Data from Dr. Fabrizio Fanelli demonstrated that the severity of calcification may impact DCB efficacy.¹⁵ As noted in the IMPERIAL long lesion sub-study results, Eluvia has demonstrated a 12-month patency of 87.9% in average lesion lengths of 162.8 mm and 70% moderate to severe calcium.¹³

Today, technologies not only need to prove safety and efficacy, but total cost and overall value to the health care system must also be evaluated. With the progressive nature of peripheral artery disease, multiple reinterventions on the same patient becomes an expensive enterprise. Treating restenosis is often not an easy task, requiring multiple modalities depending on the location and nature of restenosis. Antiproliferative therapies greatly improve the reintervention rates not only at 12 months, but also provide durable results long-term. Balancing durable improved clinical outcomes with time spent in the lab during the procedure should be

taken into consideration when evaluating the total value of a therapy. Mean procedure time for Eluvia was 57 minutes in the IMPERIAL trial. Eluvia has demonstrated consistent, reproducible results across multiple data sets in patients with claudication and critical limb ischemia, as well as short and long lesion lengths. A DES like Eluvia aims to provide patients with improved clinical outcomes and gives physicians an effective tool to help minimize costly reinterventions while keeping the procedure simple and efficient. ■

1. 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.
2. 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.
3. 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.
4. Steiner S, Willfort-Ehringer A, Sievert H, et al. 12-month results from the first-in-human randomized study of the Ranger paclitaxel-coated balloon for femoropopliteal treatment. *JACC Cardiovasc Interv.* 2018;11:934-941.
5. Rosenfield K, Jaff MR, White CJ, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med.* 2015;373:145-153.
6. Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation.* 2015;131:495-502.
7. Forrester JS, Fishbein M, Helfant R, Fagin J. A paradigm for restenosis based on cell biology: clues for the development of new preventive therapies. *J Am Coll Cardiol.* 1991;17:758-769.
8. Zilver PTX [brochure]. PI-NAM-11365-EN-201402. Bloomington, IN: Cook Medical.
9. Dake MD, Ansel GM, Jaff MR, et al. Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. *Circulation.* 2016;133:1472-1483.
10. Total global sales of the PROMUS (Boston Scientific) and XIENCE (Abbott) series of stents since 2007. Data on file at Boston Scientific Corporation.
11. Gray AW, Keirse K, Soga Y, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet.* 2018 Sept 24. pii: S0140-6736(18)32262-1. doi: 10.1016/S0140-6736(18)32262-1. [Epub ahead of print]
12. Gray AW. IMPERIAL: a randomized trial of drug-eluting stents for treatment of femoropopliteal artery lesions. Presented at: 30th annual Transcatheter Cardiovascular Therapeutics (TCT) scientific symposium 2018; September 21-25, 2018; San Diego, California.
13. Gray AW. 1-year outcomes for Eluvia in long lesions: IMPERIAL long lesion substudy. Presented at: Vascular Interventional Advances (VIVA); November 5-8, 2018; Las Vegas, Nevada.
14. Bisdas T, Beropoulos E, Argyriou A, et al. 1-year all-comers analysis of the Eluvia drug-eluting stent for long femoropopliteal lesions after suboptimal angioplasty. *JACC Cardiovasc Interv.* 2018;11:957-966.
15. 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.

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A Roundtable Discussion on Results From the First Head-to-Head DES SFA Trial: IMPERIAL

A multidisciplinary panel of PAD experts discuss the impact on patient care and the health care system and how these results may shift current treatment algorithms.

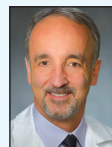
WITH MICHAEL R. JAFF, DO; GARY M. ANSEL, MD, FACC; WILLIAM A. GRAY, MD; STEVE HENAO, MD, FACC, FACS; AND ROBERT A. LOOKSTEIN, MD

MODERATOR



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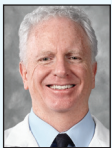
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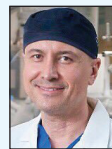
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I'm joined here by an illustrious panel to talk about the results that were recently presented and published about the IMPERIAL trial^{1,2}—arguably, the most impactful modern endovascular trial we have seen in our collective careers. This was a study that randomized head-to-head in a 2:1 ratio, the Eluvia drug-eluting stent (Boston Scientific Corporation) to the Zilver PTX drug-eluting stent (Cook Medical) in patients with claudication and superficial femoral artery (SFA) and popliteal artery disease. This study was designed to show noninferiority of the Eluvia stent to Zilver PTX with a secondary prespecified post hoc analysis to look at superiority. This study very clearly showed that not only did Eluvia meet the noninferiority endpoint, but it achieved superiority for efficacy and safety in the post hoc analysis.

In my view, this study completely changes what vascular disease clinical trials need to be in the future. This first head-to-head peripheral drug-eluting stent (DES) trial gives us an answer and allows us to make decisions. From an administrative standpoint, the fact that you can take a device and have similar patient outcomes with 50% fewer repeat interventions positively affects cost, comfort to patients, and reassurance to practitioners. This is truly a game-changing study.

—Michael R. Jaff, DO

Dr. Jaff: Dr. Gray, because you were the presenter and lead author on this trial, I would love to hear your thoughts on the magnitude of this study—how well it was done and what you think are the key points.

Dr. Gray: The trial is unique in several ways, and the first is the device. This is the first truly paclitaxel-eluting stent. The Zilver PTX stent has paclitaxel on it, but the drug doesn't really elute—it delivers a payload, and then because of the residence of paclitaxel in tissue and its lipophilicity, there is a time period where paclitaxel is still present. That has clearly shown to be effective. Zilver PTX has robust data against percutaneous transluminal angioplasty and bare-metal stents (BMSs), and it has data out to 5 years, so there is nothing wrong with that device.

Eluvia sought to improve on that. We see rates of restenosis in the SFA actually peak between 6 and 12 months

in peripheral vascular disease, so it made sense to try to extend the life of the paclitaxel into that zone of restenosis.

The durable polymer coating is the same one that is used in the PROMUS coronary DES (Boston Scientific Corporation), which has been studied in tens of thousands of patients. With this device's configuration, it could use approximately 1/20th of the magnitude of paclitaxel load compared to Zilver PTX and still get long-term elution into the tissue and residence.

The trial design was unique. At the time the trial was being conceived, the standard of care could have been considered percutaneous transluminal angioplasty or BMS, but to Boston Scientific's credit, they chose to go up against what was the only stent on the market at the time that had antiproliferative therapy and go head-to-head.

For Eluvia, the efficacy endpoints were clearly superior. Safety endpoints were noninferior but with a strong trend

Table 1. 12-Month Safety Results

	Eluvia	Zilver PTX	p-value
12-month MAE	4.9%	9.0%	0.0975
All Causes of Deaths at 1 Month	0.0%	0.0%	Undefined
Target Limb Major Amputation	0.3%	0.0%	1.0000
Clinically-driven TLR	4.5%	9.0%	0.0672
Stent Thrombosis	1.7%	4.0%	0.1956

toward safety on stent thrombosis—less than half the rate of stent thrombosis and target lesion revascularization (TLR) in Eluvia compared to Zilver PTX (Table 1). This is a home run all the way around and I think it will change the landscape and requirements for proof going forward in peripheral artery disease (PAD).

Dr. Lookstein: I would echo Dr. Gray's sentiment that this is a complete game changer. I think we're entering an era when we're going to demand comparative effectiveness data. Level 1 evidence has been desperately needed in our clinical practice to allow us to make clinical decisions for our patients, so this is a milestone for PAD therapy. We now have a powerful message of superiority of Eluvia over Zilver PTX.

Dr. Jaff: What do you think about patients who were included in this study compared to standard bare-nitinol stent trials or drug-coated balloon (DCB) trials? Were there patient characteristics that made the trial tougher or easier?

Dr. Ansel: It is interesting to look at the Zilver PTX database, which had an average lesion length of a little more than 4 cm in their trial. In IMPERIAL, we're talking about 8-cm lesions or longer, with a lot of chronic total occlusions (CTOs) and calcification—a much more challenging baseline population compared to the typical trial.

Dr. Jaff: When we think back to the early days of vascular device trials, most of the patients included in IMPERIAL would have been selected out. More than 60% of these patients had moderate-to-severe calcification, and a third had CTOs. These were beyond 8-cm lesions. They were not straightforward cases.

Dr. Jaff: We are all accustomed to looking at Kaplan-Meier curves in vascular trials that show excellent results at the 365-day mark. But often, there appears to be quite a bit of step off early

after that 365-day endpoint. The Kaplan-Meier curves from this trial might tell a different story. How might that play out?

Dr. Ansel: When you don't see that drop off, that's a game changer, because then you can depend on the numbers you're getting. That really tells you about the durability both in terms of patency and the lack of need for reintervention.

Dr. Gray: I can't think of another trial where there hasn't been that window 30 days before and 30 days after the 365-day mark. That's when we measure duplex and see binary restenosis, even if the patient is asymptomatic and has not had a TLR. The separation of the curves occurred in this trial at 6 months and were flat out to 12 months. Even after being measured, we didn't see any more binary restenosis of any measurable amount. I can't recall that ever happening in my experience. Does anybody else here?

Participants: No.

Dr. Jaff: It raises the question, what is it about this device? Of course, everyone will want to see 2-year, 3-year, and 5-year outcomes. But going into this study, what about the device gave you a degree of confidence about the outcome?

Dr. Lookstein: The MAJESTIC trial was a single-cohort study looking at feasibility of the implant, which showed incredible data at 1 year and now published out to 3-year follow-up with unbelievably low rates of TLR and very high rates of primary patency at 12 months.³ It was an incredible foundation to have the confidence to initiate a head-to-head comparative effectiveness trial (Table 2).

IMPACT FOR PATIENTS

Dr. Jaff: Do these results have the same degree of potential impact on patients as it does on physicians?

Dr. Henao: Patients are getting very sophisticated about their care and the implants they receive. In our practice, many patients take the time to do their

Table 2. Eluvia Clinical Study Results

	IMPERIAL RCT	IMPERIAL Long Lesions	MAJESTIC	Münster Registry
Study design	RCT, multicenter, global	Single arm, multicenter, global	Single arm, multicenter	Single-center registry
N (Eluvia)	309	50	57	62
Lesion length (mm)	86.5 ± 36.9	162.8 ± 34.7	70.8 ± 28.1	200 ± 120
12-month primary patency rate*	88.5%	87.9%	96.4%	87%
Severe calcification (%)	40%	28%	65%	42%†
Total occlusions (%)	31%	32%	46%	79%

Abbreviations: RCT, randomized controlled trial

*Kaplan-Meier estimate at 12 months.

†Moderate and severely calcified.

homework on what exactly they may receive. Looking at this head-to-head comparison will show the remarkable difference: a 9% improvement on efficacy and half the rate of revascularization of Zilver PTX, which was the gold standard until now. I think it puts patients at ease knowing that they're going to have a more durable result with an Eluvia stent.

Dr. Jaff: Because this is a more modern trial, the clinical endpoints actually show whether the patient got better. This study included surveys like the Walking Impairment Questionnaire and the 6-minute walk test. Those results were comparable in the two arms of the trial, which is great. Could you tease out the information that makes the difference here?

Dr. Gray: All of those measures improved after the intervention and were sustained to 12 months, which is very pleasing and obviously accrues to the patient's benefit.

What is not present in those data is the number of revascularizations it requires to maintain quality at 12 months. That is an artifact of the way we report data in SFA trials—it's a mandate by the FDA. We're reporting data at 12 months, not through 12 months, so we have to really understand what it took to get there. What it took was twice the number of TLRs in the Zilver PTX group as compared to Eluvia.

Not only is this a patient benefit, because clearly patients don't want to come back for reintervention, but we are in a time when we are looking at our cost per episodic care. It may be that we will extend that episode

out to a year, and primary care physicians will choose the lowest cost providers. Reintervention is a very expensive enterprise. Again, it is hard to overstate the importance of this trial.

PAD TREATMENT ALGORITHM

Dr. Jaff: Are we getting closer to an algorithm for the treatment of patients with claudication and SFA disease?

Dr. Lookstein: I think we would all agree we're in an era where antiproliferative therapy for the SFA is standard of care. It's what we would want for our family. The data have been best in class across the board, whether it's antiproliferative therapies on balloons or stents. Physicians who are using plain balloons or BMSs need to be provoked as to why they are ignoring the overwhelming amount of evidence.

Beyond that, I think we're learning in the United States that DCBs are not ideal for every patient. There's clearly anatomic and physiologic subsets that do not allow that technology to perform as well as we would hope. In distinction, we now have a trial that has looked at lesions with severe calcification and CTOs and it's performing incredibly well. We are very close to being able to make recommendations about which form of antiproliferative therapy is best for which patients. There's much more work to be done, but we're clearly moving in the right direction of using level 1 evidence to make our decisions.

Dr. Ansel: At OhioHealth, we've actually taken it one step further. Our vascular dashboard includes

the percentage use of drug-eluting or drug-based technology in the femoropopliteal region, so the whole section is now graded on this metric. We have a guideline for treatment of femoropopliteal disease and it is, without a doubt, drug-based because we feel very strongly that reducing reinterventions should be the cornerstone—maybe not for every patient, but for the vast majority. We want to make sure interventionalists are seeing what the percentage of drug usage is in the femoropopliteal region.

Dr. Lookstein: I don't think 5 years ago we could have had the conversation about whether this should be incorporated to society guidelines, but I think now that we have two DES trials, which is the standard for guideline incorporation, it is very close to the time when we should be making recommendations on what we consider as appropriate care for our patients.

Dr. Henao: We participate in the Vascular Quality Initiative, and every case has a log that describes a TASC II A, B, C, or D lesion. We have proposed our own algorithm. If it's a TASC A or B lesion, it's probably reasonable, based on the data, to proceed with a DCB. TASC C and D lesions can be treated with a DCB and a stent. I certainly see the IMPERIAL results as changing that particular slice of the algorithm in a major way because we all have a fiduciary responsibility to cut down those three or four DCBs and the number of nitinol stents that we put in.

It should be noted that there was no atherectomy or aggressive vessel prep in this trial. This was putting the stents in and getting terrific results. That is a true algorithm eraser or modifier.

LOOKING AHEAD

Dr. Jaff: What's the next head-to-head trial you'd like to see to help advance the discussion about treatment algorithm?

Dr. Gray: The long lesion subset (14 to 19 cm) will also help us.⁴ For the moderately complex to highly complex lesions, you're likely to use combination therapy—vessel prep and a stent. The next level of research starts to look at some of that. Do you now need a trial of Eluvia versus a DCB plus a stent programmatically? I think there will be challenges to DCB usage in more complex lesions when you have Eluvia data like these.

Dr. Henao: If we're on the topic of antiproliferatives, I think the question on everyone's mind and the one that I still get asked by patients: "Is there a difference

between DCBs?" If there was a head-to-head study of all the FDA-approved DCBs, it would be quite enlightening.

Dr. Ansel: I'd like to get to the real-world lesions that are longer and even more calcified. I would like to see a DES versus DCB with bailout stenting because that's real-world practice. I want a look at those patency rates a few years out to get an episode of care and see where that's going to go. That will help the everyday practitioner make those decisions.

Dr. Lookstein: In addition to that, I would like to see that trial performed with a look at procedure time, cost, and adverse events. Any additional technology that's added to the equation increases the procedure time and likelihood of an adverse event, and it takes its toll not only on the patient but on the provider.

Dr. Gray: I agree, I think the ancillary assessment of what's going on around the procedure is very important. When you have a trial like this with such a low adverse event rate, improving on that and proving superiority is going to be tough. If you wanted to incorporate a trial with atherectomy and complex lesions, or DCB with bailout stenting, you can do that, but I think the best you're going to prove is noninferiority. You can't run a trial big enough to prove superiority or show a treatment effect that's meaningful. The next trial is hampered by the success of this trial. It's a real conundrum for folks who want to look at an alternative therapy to Eluvia because Eluvia performed so well in this study.

Dr. Jaff: It does raise an interesting challenge, and certainly, if you're the one writing the check and putting your product at risk for the results of a trial, it's a pretty high bar to set. I think this is a unique moment in time for us in the vascular space. It's a time to celebrate that the clinical trial bar has been raised to a point that we all can be proud of. I think the results of this trial show, without question, that not only is this device noninferior to Zilver PTX, but at 1 year, it's superior to Zilver PTX. It's a safe device. It offers great clinical improvement with fewer TLRs, so theoretically, a lower total episode of cost. It's an exciting time to be practicing in the vascular field. ■

1. Gray AW, Keirse K, Soga Y, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet*. 2018 Sept 24; pii: S0140-6736(18)32262-1. doi: 10.1016/S0140-6736(18)32262-1. [Epub ahead of print]

2. Gray AW. IMPERIAL: a randomized trial of drug-eluting stents for treatment of femoropopliteal artery lesions. Presented at: 30th annual Transcatheter Cardiovascular Therapeutics (TCT) scientific symposium 2018; September 21-25, 2018; San Diego, California.

3. Müller-Hülsbeck S, Keirse K, Zeller T, et al. Long-term results from the MAJESTIC trial of the Eluvia paclitaxel-eluting stent for femoropopliteal treatment: 3-year follow-up. *Cardiovasc Intervent Radiol*. 2017;40:1832-1838.

4. Gray AW. 1-year outcomes for Eluvia in long lesions: IMPERIAL long lesion substudy. Presented at: Vascular Interventional Advances (VIVA); November 5-8, 2018; Las Vegas, Nevada.

Discussing the IMPERIAL Data in Practice

Two vascular experts share their reactions to hearing the results of the first head-to-head peripheral DES trial.

WITH YANN GOUËFFIC, MD, PhD, AND ANDREW HOLDEN, MBChB, FRANZCR, EBIR

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What were your initial reactions to the IMPERIAL results?

Prof. Gouëffic: My first reaction to IMPERIAL was regarding the robustness of the trial. The methodology of this randomized controlled trial, recently published in *The Lancet*, is very well designed and with few biases.¹ The noninferiority and superiority analyses are well described prior to the beginning of the study. IMPERIAL achieves its objectives, showing noninferiority and superiority of a polymer-based paclitaxel-eluting stent (Eluvia, Boston Scientific Corporation) over a polymer-free paclitaxel-coated stent (Zilver PTX, Cook Medical). The difference of patency between both groups is quite large (nearly 10%) and significant (Figure 1). We can also note a significant difference in terms of target lesion revascularization (TLR), nearly a two-fold TLR decrease in favor of the Eluvia stent.

Dr. Holden: I was impressed with both drug-eluting stent (DES) platforms; each one performed extremely well in a challenging lesion cohort with a significant incidence of moderate to severe calcification and chronic total occlusion. The performance of the Eluvia stent was obviously particularly impressive.

Why is it important for the endovascular community to have a head-to-head trial comparing two DES technologies?

Dr. Holden: Boston Scientific should be congratulated for initiating and performing this head-to-head trial. In the current cost-sensitive environment, statistically powered trials that directly compare treatment strategies is exactly what physicians, patients, and health funders need.

Prof. Gouëffic: Physicians have huge expectations for drug-eluting devices to improve outcomes for endovascular treatment of femoropopliteal lesions. Despite promising results for drug-coated balloons (DCBs), there remains a need for scaffolding. Intraoperative angiography to assess DCB results is not so easy to analyze, and physicians tend to use bailout stenting to avoid unsatisfactory results. Moreover, in a real-world setting, femoropopliteal lesions are more complex than typically observed in trials, so bailout stenting increases considerably. Thus, the endovascular community has interest in the ability to use DESs for a femoropopliteal lesion to prevent intimal hyperplasia, recoil, and remodeling.

Since 2011, Zilver PTX has undergone the only randomized controlled trial to assess a paclitaxel-coated stent for femoropopliteal lesions. In that study, Zilver PTX, a polymer-free paclitaxel-coated stent, was compared to plain balloon angioplasty. In 2018, balloon angioplasty is no longer the standard of care for femoropopliteal lesions, and consequently head-to-head comparison between drug-eluting technologies is expected. Interventionalists are expecting data to make a choice between devices.

Eluvia demonstrated superiority over Zilver PTX in IMPERIAL. How should physicians performing

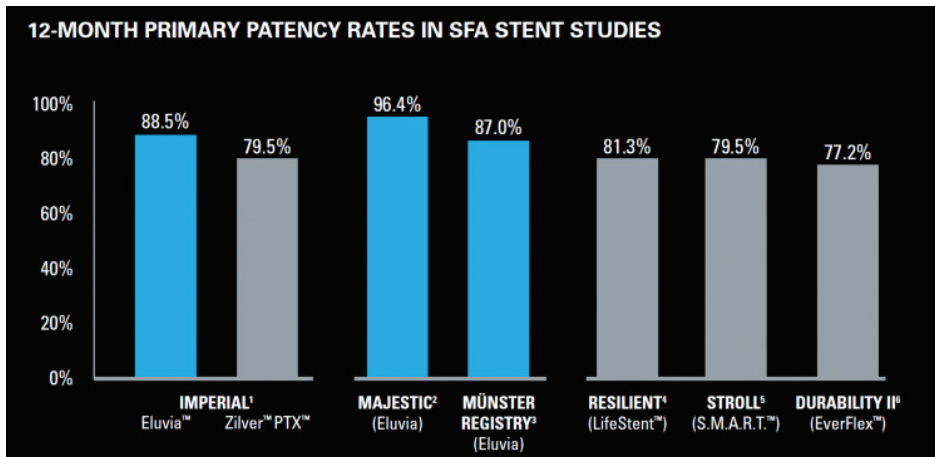


Figure 1. Patency rates were significantly higher with Eluvia across trials.

endovascular procedures think about this superiority data when making device decisions?

Prof. Gouëffic: Head-to-head trials should be helpful for vascular interventionalists. IMPERIAL provides evidence that a sustained-release polymer-based DES is superior to a polymer-free drug-coated stent, which helps physicians make a choice between the two stents. However, IMPERIAL does not establish an algorithm by itself. More evidence is required to define the indications of using bare-metal stents (BMSs), DCBs, and DESs for femoropopliteal lesions.

Also, according to the inclusion and exclusion criteria of IMPERIAL, conclusions from the IMPERIAL study are

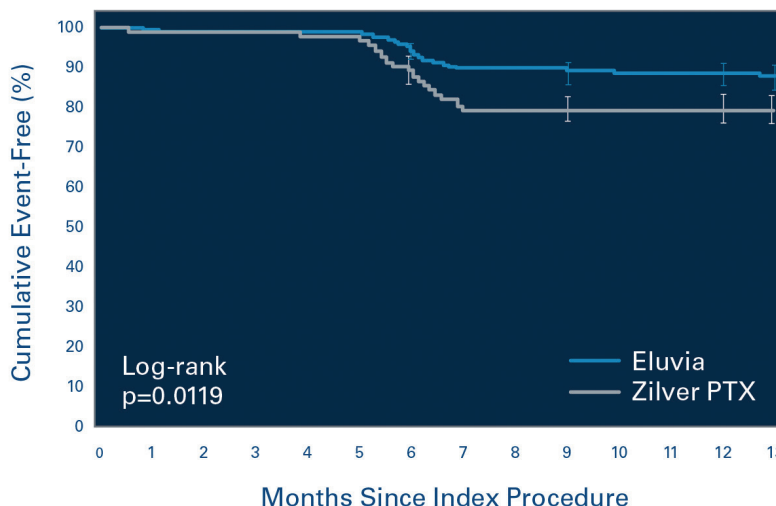
driven TLR was 6.5%. Considering these data, indications for Eluvia could be extended to more complex lesions.

Dr. Holden: Although both DES platforms performed very well in this trial, a post hoc analysis of the 12-month primary patency in the full patient cohort revealed a significant patency advantage for Eluvia over Zilver PTX. There was also a lower clinically driven TLR rate at 12 months for Eluvia, although this did not reach statistical significance. Although there will be other variables influencing physicians' decisions regarding choice of DES, these patency results should certainly be a major point for consideration.

valuable in patients with Rutherford category 2, 3, and 4 superficial femoral and proximal popliteal artery lesions that range in length from 30 to 140 mm. Outside these criteria, high-level evidence between both devices still needs further study, despite some promising initial data from the IMPERIAL long lesion sub-study.²

This single arm included 50 patients with lesions from 140 to 190 mm. At 1 year, the primary patency rate was 87.9% and the rate of clinically

IMPERIAL RCT FULL COHORT KAPLAN-MEIER PRIMARY PATENCY



Eluvia (n=309)

88.5%

Zilver PTX (n=156)

79.5%

Figure 2. The superiority analysis for primary patency was determined with a prespecified post-hoc analysis (12-month primary patency rate of 86.8% in the Eluvia arm and 77.5% in the Zilver PTX arm [$P = .0144$]).

What are your thoughts on Eluvia's performance in IMPERIAL (88.5% primary patency), based on the very challenging lesion characteristics studied (40% severe calcium in the Eluvia arm and nearly a third chronic total occlusions)?

Dr. Holden: These results are outstanding, particularly given the complexity of lesions treated. In particular, the performance of Eluvia in the presence of severe calcification is particularly impressive and suggests drug elution may be more effective in calcified arteries than previously thought. The Innova stent (Boston Scientific Corporation), which is the BMS platform for Eluvia, has also provided an excellent platform in these challenging lesions.

"Leave nothing behind" has become a popular saying in the endovascular space. However, Eluvia demonstrated a TLR rate of just 4.5% in IMPERIAL. Do you believe that outcome could cause some physicians to rethink a leave-nothing-behind strategy, when a DES provides such excellent TLR rates?

Prof. Gouëffic: "Leaving nothing behind" should not be an objective for the treatment of femoropopliteal disease. For each interventionalist, the question should be, "What is the best treatment for this lesion?" In the absence of comparison between Eluvia and DCB, we should be careful to extrapolate conclusions from non-head-to-head comparison. Moreover, due to the performance of drug-eluting devices, differences in patency or reintervention are becoming so narrow that it could become increasingly difficult to design a trial to show the superiority of one device over another one. For this reason, cost effectiveness and procedure times could assist with decision-making.

Dr. Holden: The leave-nothing-behind concept was popularized in treating femoropopliteal disease when early-generation nitinol self-expanding stents revealed unacceptably high rates of restenosis and stent fracture. However, it is well established that scaffolds are required as lesions increase in length and complexity to manage significant residual stenosis and dissection. The combination of new stent platforms and drug-elution for restenosis has promised to significantly challenge

the leave-nothing-behind approach, and the IMPERIAL trial results have certainly done that. When applying this information to lesions that respond poorly to predilatation with plain balloon angioplasty, we can expect excellent results with DES treatment, at least to 12 months, and probably longer.

How might the IMPERIAL data affect your SFA treatment algorithm moving forward?

Prof. Gouëffic: Just as for other vascular interventionalists, IMPERIAL provides me with evidence that a sustained-release polymer-based DES is superior to a polymer-free DES, but it does not constitute an algorithm by itself. I believe that scaffolding is still required for femoropopliteal treatment, and that a stent does not compromise further future options, such as open surgery. A stent, which is a foreign body, is a source of inflammation and chronic arterial damage, but these side effects seem to be counterbalanced by a controlled and sustained drug release. Soon, other robust trials will release data comparing DES, DCB, or BMS to help physicians treating femoropopliteal lesions. We should keep in mind that, so far, the simplest lesions (< 14 cm) have been studied, but for the longer lesion, high-level evidence is still lacking despite the promising outcomes that have been observed for the treatment of longer femoropopliteal lesions.^{2,3}

Dr. Holden: The IMPERIAL trial data have supported my current treatment algorithm to SFA disease. I use plain balloon angioplasty to nominal diameter to assist in the choice of subsequent drug-eluting technology. For lesions that respond well to plain balloon angioplasty, I use a DCB. For lesions that respond suboptimally to predilatation, I use a DES with the confidence of replicating the excellent results of the IMPERIAL trial. I believe this approach will result in better short- and midterm patency and freedom from TLR rates than a primary DCB approach with provisional BMS, although this remains to be conclusively proven. ■

1. Gray AW, Keirse K, Soga Y, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet*. 2018 Sept 24. pii: S0140-6736(18)32262-1. doi: 10.1016/S0140-6736(18)32262-1. [Epub ahead of print]
2. Gray AW. 1-year outcomes for Eluvia in long lesions: IMPERIAL long lesion substudy. Presented at: Vascular Interventional Advances (VIVA); November 5–8, 2018; Las Vegas, Nevada.
3. Bisdas T, Beropoulos E, Argyriou A, et al. 1-year all-comers analysis of the Eluvia drug-eluting stent for long femoropopliteal lesions after suboptimal angioplasty. *JACC Cardiovasc Interv*. 2018;11:957-966.

ELUVIA Drug-Eluting Vascular Stent System

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete "Directions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator's Instructions.

INTENDED USE/INDICATIONS FOR USE

The ELUVIA Drug-Eluting Vascular Stent System is intended to improve luminal diameter in the treatment of symptomatic de-novo or restenotic lesions in the native superficial femoral artery (SFA) and/or proximal popliteal artery with reference vessel diameters (RVD) ranging from 4.0-6.0 mm and total lesion lengths up to 190 mm.

CONTRAINDICATIONS

- Women who are pregnant, breastfeeding, or plan to become pregnant in the next 5 years should not receive an ELUVIA Drug-Eluting 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

- The delivery system is not designed for use with power injection systems.
- Only advance the stent delivery system over a guidewire.
- The stent delivery system is not intended for arterial blood monitoring.
- In the event of complications such as infection, pseudoaneurysm or fistula formation, surgical removal of the stent may be required.
- Do not remove the thumbwheel lock prior to deployment. Premature removal of the thumbwheel lock may result in an unintended deployment of the stent.
- It is strongly advised that the treating physician follow the Inter-Society Consensus (TASC II) Guidelines recommendations (or other applicable country guidelines) for antiplatelet therapy pre-procedure to reduce the risk of thrombosis. Post-procedure dual antiplatelet therapy is required for a minimum of 60 days.

PRECAUTIONS

- Stenting across a bifurcation or side branch could compromise future diagnostic or therapeutic procedures.
- The stent is not designed for repositioning.
- Once the stent is partially deployed, it cannot be "recaptured" or "reconstrained" using the stent delivery system.
- The stent may cause embolization from the site of the implant down the arterial lumen.
- This product should not be used in patients with uncorrected bleeding disorders or patients who cannot receive anticoagulation or antiplatelet aggregation therapy.
- Persons with a known hypersensitivity to paclitaxel (or structurally-related compounds), to the polymer or its individual components (see details in Primer Polymer and Drug Matrix

Copolymer Carrier section), nickel, or titanium may suffer an allergic response to this implant.

- Persons with poor kidney function may not be good candidates for stenting procedures.

PROBABLE ADVERSE EVENTS

Probable adverse events which may be associated with the use of a peripheral stent include but are not limited to:

- Allergic reaction (to drug/polymer, contrast, device or other)
- Amputation
- Arterial aneurysm
- Arteriovenous fistula
- Death
- Embolization (air, plaque, thrombus, device, tissue, or other)
- Hematoma
- Hemorrhage (bleeding)
- Infection/Sepsis
- Ischemia
- Need for urgent intervention or surgery
- Pseudoaneurysm formation
- Renal insufficiency or failure
- Restenosis of stented artery
- Thrombosis/thrombus
- Transient hemodynamic instability (hypotensive/hypertensive episodes)
- Vasospasm
- Vessel injury, including perforation, trauma, rupture and dissection
- Vessel occlusion

Probable adverse events not captured above that may be unique to the paclitaxel drug coating:

- Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds) or the polymer stent coating (or its individual components)
- Alopecia
- Anemia
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- Myalgia/Arthralgia
- Peripheral neuropathy

There may be other potential adverse events that are unforeseen at this time.

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THANK YOU

for your work on the IMPERIAL DES SFA Trial!

Your efforts are helping to improve
the lives of PAD patients worldwide.

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Sincerely,
Your partners at Boston Scientific