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

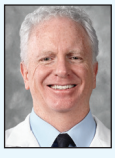
A multidisciplinary panel of PAD experts discuss the impact on patient care and the health care system and how these results may shift current treatment algorithms.

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

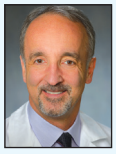
MODERATOR

Michael R. Jaff, DO
President
Newton-Wellesley Hospital
Professor of Medicine
Harvard Medical School
Newton, Massachusetts
mjaff@partners.org
Disclosures: Noncompensated advisor to Abbott Vascular and Boston Scientific Corporation; compensated advisor to Biotronik, Medtronic, Philips, and Vactronix.

PARTICIPANTS



Gary M. Ansel, MD, FACC
System Medical Chief, Vascular Services
OhioHealth
Associate Medical Director
OhioHealth Research Institute
Columbus, Ohio
Assistant Clinical Professor of Medicine
Department of Medicine
University of Toledo Medical Center
Toledo, Ohio
gary.ansel@aol.com
Disclosures: Consulting or on advisory board for Boston Scientific Corporation, Medtronic, Abbott Vascular, Cook Medical, Surmodics, Philips, BD Interventional, Gore & Associates, Veryan Medical, Reflow Medical, and VIVA Physicians.



William A. Gray, MD
System Chief of Cardiovascular Services
Main Line Health
President, Lankenau Heart Institute
Wynnewood, Pennsylvania
grayw@mlhs.org
Disclosures: Consultant to Medtronic, Boston Scientific Corporation, Gore & Associates, Abbott Vascular, Intact Vascular, Inc., Shockwave Medical, Inc., Philips, and Surmodics, Inc; IMPERIAL Principal Investigator.

Steve Henao, MD, FACC, FACS
Medical Director for Cardiovascular Research
New Mexico Heart Institute
Heart Hospital of New Mexico at Lovelace Medical Center
Albuquerque, New Mexico
steveh@nmhi.com
Disclosures: Consultant for Boston Scientific Corporation, Abbott, and Endologix.

Robert A. Lookstein, MD
Professor of Radiology and Surgery
Vice Chair, Interventional Services
Mount Sinai Health System
New York, New York
robert.lookstein@mountsinai.org
Disclosures: Consultant for Boston Scientific Corporation and Medtronic.

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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. ■

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