PANEL DISCUSSION

What Is the Future of Paclitaxel-Coated Balloons in AV Access?

Key investigators discuss the impact of the *JAHA* mortality and safety meta-analysis and what it means for ongoing studies, follow-up protocols, informed consent, and more.

WITH PANAGIOTIS M. KITROU, MD, MSc, PhD, EBIR; ROBERT LOOKSTEIN, MD, MHCDL, FSIR, FAHA, FSVM; AND SCOTT O. TREROTOLA, MD

Panagiotis M. Kitrou, MD, MSc, PhD, EBIR
Assistant Professor in Interventional Radiology
Interventional Radiology Department
Patras University Hospital
Rio, Greece
panoskitrou@gmail.com
Disclosures: Lecture and travel honoraria from BD; investigator in Lutonix Global AV registry.

Robert Lookstein, MD, MHCDL, FSIR, FAHA, FSVM
Professor of Radiology and Surgery
Executive Vice Chairman
Department of Diagnostic, Molecular, and Interventional Radiology
Icahn School of Medicine at Mount Sinai
New York, New York
robert.lookstein@mountsinai.org
Disclosures: Consultant and scientific advisory board member for Medtronic; national PI for the IN.PACT AV Access trial.

Scott O. Trerotola, MD
Stanley Baum Professor of Radiology
Professor of Radiology in Surgery
Vice Chair for Quality
Associate Chair and Chief, Interventional Radiology
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
streroto@pennmedicine.upenn.edu
Disclosures: Consultant to BD Bard; Lutonix national PI; Lutonix AV trial US PI; Lutonix AV postmarket study.

Dr. Kitrou, given your extensive experience with drug-coated balloons (DCBs) in the arteriovenous (AV) access circuit, were you surprised at your group's findings in the superficial femoral artery (SFA)?[1]

Dr. Kitrou: One needs to understand the unique environment under which the findings from our meta-analysis in *Journal of the American Heart Association (JAHA)* came to light. Patients in the included studies were mostly claudicants (89%) and had fewer comorbidities compared with patients undergoing dialysis or patients with critical limb ischemia (CLI). The patient sample was such that these rare events could become apparent because the meta-analysis included > 4,400

patients. It is obvious that these findings could not become significant or reproducible in a single center's everyday practice. In AV access patients, who have a mortality rate of 33% at 2 years,[2] it would be highly unlikely for DCBs to have the same effect in terms of risk.

Since the publication of the *JAHA* meta-analysis, how have the Lutonix AV and IN.PACT AV investigators further reviewed the trial data for mortality/safety concerns, and what has been determined?

Dr. Trerotola: We don't know what the theoretical cause of the supposed increased mortality in the *JAHA* meta-analysis might be, but the bottom line is that there is no signal in terms of different types of mortality. In the Lutonix AV trial (NCT02440022), the safety endpoint was met at 30 days and there were no differences in safety or mortality. The safety and mortality analysis was carried out to 2 years. The 2-year data are currently under review for publication. Although I can't go into detail because of that, there are no surprises forthcoming.

Additionally, if you look at the Medicare analysis, it shows no difference in mortality.[3] Because the FDA has decided to up the ante, there has been more focus paid on this one *JAHA* paper than I've ever seen before. Normally, when something is this substantial in the medical literature, we look for validation. Then, when you have discordant data, you look for more papers to settle the odds. We're not doing that here, and, unfortunately, it may be hurting people who are not getting something that would probably benefit them.

Dr. Lookstein: In the IN.PACT AV Access study, we decided to continue our mortality and safety analysis for the entirety of the study period. We are committed to specifically identifying whether any long-term safety concerns exist for the use of this product. During enrollment, we had no safety concerns regarding the device and its use in patients undergoing hemodialysis. The primary clinical and safety endpoint analysis will be presented this fall.

Dr. Kitrou, have you further reviewed the data from your studies regarding DCBs in AV access for mortality/safety concerns? If so, what has been determined?

Dr. Kitrou: You cannot retrospectively review your data and come to conclusions regarding deaths owed or not owed to paclitaxel. There is no comparator in this way—no control group. The comparator is the risk profile of the population, and this is the key. Different populations will have different health profiles and, hence, different death rates irrespective of paclitaxel use. Additionally, keep in mind that in a high-volume center like ours that treats claudicants and patients with CLI and AV access, the majority of patients have already undergone some type of paclitaxel-related therapy. So, what conclusions can you make?

Have your long-term follow-up protocols been modified in any way?

Dr. Kitrou: For AV access, the majority of our patients will visit our department at some point for a redo procedure. In that sense, the follow-up is ongoing anyway. However, we do lose patients to follow-up.

Dr. Trerotola: In the context of a clinical trial—our postmarket analysis study, for example—follow-up is mandatory. Unless we lose someone to follow-up, which is uncommon, we have very good follow-up—keeping in mind that this is a population with an extensive mortality rate of approximately 30% at 2 years. The difference in a dialysis population as opposed to a peripheral artery disease (PAD) population is that they are a captive audience that visits the same dialysis unit repeatedly, which makes it easier to locate patients for follow-up. Also, the FDA clearly stated that AV access was not part of the advisory. It's a completely different patient population with a different mortality rate. Additionally, PAD involves long lesions with multiple long balloons, but AV access involves single short balloons. Therefore, there could be very substantial differences in the total dose.

Dr. Kitrou, as previously mentioned, your meta-analysis was based on lower extremity PAD data, including 89% claudicants, rather than AV access patients. To what degree do you view the signal as potentially representing a class effect among all applications versus SFA revascularization alone?

Dr. Kitrou: There is a major difference in the patient health status between populations like claudicants, patients with CLI, and patients undergoing dialysis. A high-risk patient population profile would "dilute" the signal in its high death rate. The comparator group is significant because it reflects the population profile. This is why randomized controlled trials are so important. There are many studies nowadays that prove the benefit of using DCBs in patients undergoing dialysis, and there are more studies with results pending. We need longer follow-up in these studies, however, to verify whether the benefit outweighs the risk.

How do you each weigh the difference in risk versus benefit from a patient population of predominantly claudicants to those with end-stage renal disease (ESRD)?

Dr. Lookstein: The natural history of patients with ESRD is unfortunately much worse than a typical claudicant population. The incidence of major adverse events, including all-cause cardiovascular death, is anticipated to be higher compared with a mildly symptomatic PAD cohort based on previous epidemiologic studies of these populations. The major cardiovascular risk factor that we routinely see in patients with ESRD is right-sided heart failure, which is rarely (if ever) seen in claudication trials.

Dr. Trerotola: You have to think about what you are trying to gain from using a DCB. For most devices in the SFA, the benefit is generally strong. You are telling these patients that there's a < 10% chance they will come back in a year. When you think about what is involved in those reinterventions (eg, hospitalization, thrombolysis, amputation), that is significant. In our experience, most patients in our PAD population are fine with accepting a possible increased risk of death in exchange for that clear benefit.

When I asked people about this at the recent Society of Interventional Radiology meeting in Austin, Texas, about half said that they still use DCBs in AV access, and the other half said they were thinking about it. In the dialysis population, the benefit of DCBs is a bit more modest; however, I also think that the risk is probably less because there is, theoretically, a lower dose. The baseline mortality rate is higher, so the chance that there will be an issue with these patients, particularly over 5 years, is much lower. On the other hand, some may say that there are better, viable alternatives, such as stent grafts. I feel strongly that stent grafts have a late disadvantage; you buy short-term patency at the expense of late patency. We have to weigh the relative benefits in each area.

Dr. Kitrou: In the case of paclitaxel use in AV access, the risk/benefit ratio is the ratio between the systemic and the local effect of the drug. In patients with ESRD, who have a high death ratio and a high number of comorbidities, the benefit they get by extending the intervention-free period, improving quality of life due to fewer hospital visits, and extending vascular access survival is clear.

Dr. Lookstein, before the recent focus on mortality data, what questions were you asked most by your colleagues regarding the application of DCBs in the AV access setting? How did you respond?

Dr. Lookstein: As the national Principal Investigator for the IN.PACT AV Access investigational device exemption trial, I believe the most common questions and my answers were:

1. **Where will this technology be the most impactful (eg, native AV fistulas, prosthetic AV grafts, central vein stenosis, anastomotic lesions)?**
   The IN.PACT AV Access trial solely studied patients with native AV fistulas and only treated lesions within the fistula segment (anastomosis to axillary vein). Future studies will be needed to identify what role DCBs play in regard to AV grafts and central veins.

2. **How will this technology be used in different clinical settings (eg, hospitals, ambulatory surgical centers, office-based labs)?**
   I would hope that if the trial shows a clear benefit to patients, the technology would be widely adopted in all clinical settings. This will undoubtedly be affected by the level of reimbursement that is seen for the use of this technology in the different locales.

3. **Will there be a difference in the effectiveness of different devices, or will we see a class effect for all DCBs in AV access?**
   We are very early on in the clinical study of this technology for hemodialysis access patients. The Lutonix AV study results were certainly encouraging, but more research is necessary to determine if other devices may prove to be more effective or uniquely beneficial for specific anatomic or clinical subtypes.

Dr. Trerotola, what's your current algorithm for treating a stenosed AV access?

Dr. Trerotola: I'm a huge fan of high-pressure balloon angioplasty. One of the interesting things to come out of the Lutonix AV trial is that the control group has much higher patency than in many other studies. You have to ask yourself why it's higher than the Kidney Disease Outcomes Quality Initiative expectation, by a large margin. We believe it's because we held our investigators to a high standard and asked them to (1) only treat lesions that matched the clinical indicator, and (2) perform an essentially perfect angioplasty, with < 30% residual stenosis, prolonged angioplasty, and progressive balloon oversizing, as needed. A really good angioplasty is still my go-to. When that fails, you look at the failure mode. If the failure mode is elastic recoil, which is very rare, and it's a stentable area (eg, not a cannulation zone or anastomotic), then I will put a

stent graft in. If the failure mode is early restenosis, then I will use a DCB.

And, what are some other key lessons learned from control arms in studies of DCBs for AV access?

Dr. Trerotola: There is only one control arm that's been completed so far, other than the small studies. I reiterate that if you do a good angioplasty, the relative benefit of DCBs will be reduced. There are some studies that have the same device, inclusion criteria, and exclusion criteria but have completely different results. Some of the differences could be due to how the control arm angioplasty is performed and how diligent people are. I've been refining my angioplasty for 30 years, and the addition of high-pressure angioplasty was a massive game changer. If you really pay attention, then you'll have a great outcome.

For those of us who worked in the pre-stent era, all we had was an angioplasty balloon. We did progressive oversizing and prolonged inflation, and we tacked down any dissections. It took a long time. It's too easy for the new generation and noninterventional radiologists to just drop stents in. Until the Zilver PTX device (Cook Medical), stents had horrible restenosis. You were buying short-term patency at the expense of long-term patency. That's why people are looking at this like everything that's old is new again.

If you were treating a stenosed AV access today and elected to use a DCB, what specifically would you include in your informed consent?

Dr. Lookstein: I believe the entire vascular specialist community has taken the recent FDA communication very seriously. We have modified our workflow with regard to how we consent and treat all patients. For hemodialysis access, we would review the FDA correspondence with a patient who was determined to be at high risk for restenosis, and we would ask the patient to specifically consent to the use of paclitaxel-coated balloons.

Dr. Kitrou: In our center, patients are informed about our study and the effect the specific drug has on claudicants, and we explain that this is a different patient group.

Dr. Trerotola: We have reviewed this with the risk management and legal consultants at our institution. For my own practice and for both SFA and dialysis, they believe that we should specifically seek consent from patients and inform them of the safety signal indicated by the *JAHA* meta-analysis. Our approach will be to have an opt-out consent as opposed to an opt-in consent. In terms of our postmarket study, the consent for the clinical trial is being modified to reflect the FDA's advisory.

Given the considerable cost of care for patients with ESRD, where do you think DCBs fall into the cost-effectiveness spectrum? What are the challenges and confounders to studying cost-effectiveness in this challenging patient population, and what are your thoughts on the degree to which findings in other studies may differ?

Dr. Kitrou: We are in the process of creating a model that will give us an answer regarding DCB cost-effectiveness in AV access management. It's not an easy project!

In terms of studying cost-effectiveness, to borrow a quote from Dr. O. Jaffer, it is the difference between treating "lifestyle" (claudicants) and "lifeline" (dialysis) patients. There is no comparison between these populations in any aspect, including risk, benefit, and cost. To that extent, it is not possible to transfer cost-effectiveness models from one population to the other.

Dr. Lookstein: I believe that the use of DCBs in AV access can lead to (1) significantly fewer interventions for a patient undergoing hemodialysis each year and (2) a greater number of successful dialysis sessions. This should lead to greater cost-effectiveness for patients' overall hemodialysis care and improvements in their overall quality of life by avoiding unpredictable episodes of incomplete or unsuccessful hemodialysis and reintervention.

Dr. Trerotola: There are two published cost analyses that more or less use the same approach, which is to compare stent graft results to using bare-metal stents.[4,5] If someone takes the same approach with a DCB and compares it with the results of using bare-metal stents, they will likely show that it's cost beneficial. ■

1. Katsanos K, Spiliopoulos S, Kitrou P, et al. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2018;7:e011245.
2. United States Renal Data System. 2018 USRDS annual data report: volume 2: ESRD in the United States. https://www.usrds.org/2018/download/v2_c05_Mortality_18_usrds.pdf. Accessed June 3, 2019.
3. Secemsky EA, Kundi H, Weinberg I, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. JAMA Cardiol. 2019;4:332-340.
4. Mohr BA, Sheen AL, Roy-Chaudhury P, et al. Clinical and economic benefits of stent grafts in dysfunctional and thrombosed hemodialysis access graft circuits in the REVISE randomized trial. J Vasc Interv Radiol. 2019;30:203-211.e4.
5. Dolmatch B, Hogan A, Ferko N. An economic analysis of stent grafts for treatment of vascular access stenosis: point-of-care and Medicare perspectives in the United States. J Vasc Interv Radiol. 2018;29:765-773.e2