Drug-Coated Balloon Evaluation in Dialysis Access Intervention

An interview with Scott O. Trerotola, MD, regarding the study of DCBs in arteriovenous fistulas.

How would you briefly summarize the existing data landscape for drug-coated balloons (DCBs) in dialysis access intervention?

Dr. Trerotola: This is a very exciting time in the study of dialysis access intervention. Until very recently, the dialysis literature has largely been composed of level 2, 3, or 4 evidence. Even 5 years ago, if you were looking for prospective studies evaluating a specific device or technique, you would just not find them, or perhaps you might find a registry, or at best, one randomized trial. But in the brief, recent history of DCB research, we have seen as many randomized studies published as nonrandomized studies. Although it's unlikely to last, the evidence pyramid has been turned on its head in this space. And, despite its limitations, the available evidence is very positive, which is what convinced me that this might work. A series of randomized trials, several from the Greek group of Kitrou and Katsanos et al[1-3] and another trial from Lai et al[4] effectively all show more than doubling of patency, and in some cases, even tripling of patency with the DCB compared to plain old balloon angioplasty.

What are the key studies and trials currently underway?

Dr. Trerotola: Today, you will find the Lutonix (Bard Peripheral Vascular, Inc.) AV trial, now closed[5]; the PAVE trial, a randomized trial in the United Kingdom[6]; a randomized trial evaluating cephalic arch stenosis in Israel; the APERTO randomized trial being undertaken in the Netherlands[7]; the FISBAL randomized trial recruiting participants in Spain[8]; as well as the completed DEBAPTA trial from Singapore,[9] which has not been published yet.

What are some key design elements for the Lutonix AV trial, for which you serve as principal investigator?

Dr. Trerotola: The Lutonix AV trial is a fistula-only trial, which randomized patients to DCB or balloon angioplasty. Both arms received a predilation with a high-pressure balloon, followed by a sham treatment in the control arm with a comparable balloon to the DCB (a lower-pressure balloon), or treatment with a DCB in the treatment arm. Just under 300 patients were enrolled, and enrollment finished earlier this year, so we should have 6-month follow-up toward the end of the year. The study evaluated all lesions within the circuit (anywhere from the anastomosis to the end of the terminal arch but not the central veins or arterial lesions). Most other studies evaluated or are evaluating fistulas across the board; as far as I know, none are currently evaluating grafts. Some experts have been vocal about the need for a randomized trial evaluating stent grafts, and obviously stent grafts are only approved in limited areas, which may make these trials more challenging to conduct.

What are the key endpoints in the DCB arteriovenous (AV) fistula trials, and in what way might expectations for performance and outcome measures differ from superficial femoral artery (SFA) and limb salvage studies?

Dr. Trerotola: The Lutonix AV trial is a 2-year study, and we will also look at 6-month primary patency, specifically access circuit primary patency and target lesion primary patency, as well as number of interventions to maintain patency and the usual safety measures. In angioplasty for dialysis access, patency is measured in months as compared with years for arterial angioplasty—for example, 5 years for the iliac and several years for the SFA. In dialysis access, at best, there is

somewhere between 30% and 50% primary patency at 1 year for a fistula. Primary patency rates are variable; for instance, in the FLAIR trial[10] where there was a mandatory fistulogram at 3 months, primary patency was 25% for angioplasty at 6 months, far from the expected 50% according to the KDOQI guidelines. The bottom line is that everybody talks about 50% primary patency per year for a fistula—and it's probably lower than that. Most likely, rates will be measured in months versus years. I don't think we'll soon be talking about 5-year primary patency rates for fistula therapies.

With cost being an increasingly important factor in end-stage renal disease patient care, how much more successful must a DCB be versus percutaneous transluminal angioplasty (PTA) alone in order to show a cost benefit?

Dr. Trerotola: This is a very difficult question. In our study, we included some endpoints to allow for a cost analysis, such as loss of permanent access and number of interventions. When you look at the overall cost of the intervention and the collateral costs of lost dialysis days or hospitalization, the cost of the PTA balloon may not be a good index to use, and the benefit would almost certainly be seen if two or three additional interventions can be avoided. That would be particularly important in any valid economic model that provides a lump sum payment for a patient's care over the course of a set period regardless of how many interventions are required.

Has there been much discussion on the potential for downstream effects of the drug?

Dr. Trerotola: There are data on the use of DCBs in other areas, and of course, when designing a trial, patient safety is considered first and foremost. One of our medical advisory board members—Dr. Roy-Chaudhury—worked with the study sponsor to develop a very specific model in swine that evaluated downstream effects, and this was submitted to the US Food and Drug Administration before human studies were undertaken. We also know from the arterial side that the coating was specifically designed to maximize efficacy without sacrificing safety, and this is not just Bard but the other DCB manufacturers as well—no one would ever want to compromise patient safety in the interest of restenosis treatment. In my personal opinion, the manufacturers have erred on the side of safety, and I think the chance of downstream effects is extremely low.

In terms of any salutory effects, the Lai et al trial[4] analyzed 20 lesions in 10 patients with tandem stenoses, in which the lesions were randomly assigned to treatment with a DCB or control—half of the DCB-treated lesions were upstream and the other half were downstream lesions. There was no difference in patency between the upstream and downstream DCB-treated arms, so in essence, there was no downstream effect.

Are you able to describe any memorable lessons learned during the design of the investigational device exemption trial you are heading up?

Dr. Trerotola: We found that it's very difficult to measure fistulas, although we knew this before initiating the study. With a graft, there are internal references, but with a fistula, what is considered normal? There are areas of aneurysmal dilatation and spaces in between that are relatively narrow, so we are beginning to recognize that the whole concept of percent stenosis may not apply very well to fistulas. Our core lab has been using some proprietary software and comparing measurements from the software to manual measurements, and the measurements have been accurate. Future trials evaluating fistulas should have a standardized way of assessing stenosis, and I am hoping to write a paper on what we have learned in this regard.

In addition, there is tremendous practice variation in this area and no real evidence regarding the optimal diameter or percent stenosis goal or how to size the angioplasty balloon, especially in a fistula. Also, fistulas are heterogeneous. A forearm fistula is different from a transposition fistula and from an upper arm fistula, and trying to create a specific protocol is very challenging. I think we'll make a nice contribution to that understanding regardless of the outcome of this trial.

If the initial trials continue to be successful, do you foresee modifications to the platforms to better suit the specific needs encountered in dialysis access, or do you believe the current technologies will be suitable for both lower extremity peripheral artery disease and dialysis access settings?

Dr. Trerotola: I've been a proponent of ultra–high-pressure angioplasty for a long time, but some emerging evidence about recoil may make us rethink that whole concept. One of the things that I've learned is that nothing is static, and you have to keep an eye on the literature. I still believe ultra–high-pressure angioplasty is the way to go, and I would not be surprised if someone figures out a way to put this coating on high-pressure balloons. On the other hand, we may find out that we do not need to fully efface the waist, or that we might get better drug delivery with a compliant balloon because there is better contact. Although I have

been against compliant balloons for over 20 years, we have to pay attention to the emerging literature.

Vessel preparation, such as predilation or the use of atherectomy, are frequently discussed in terms of their effect on DCB use in peripheral artery disease. Leaving atherectomy aside, as it's not part of the study, what can you tell us about predilation in the trial?

Dr. Trerotola: Predilation was done in both arms. Our goal is to get less than 30% residual stenosis. This goal was set was before Dr. Dheeraj Rajan's recent article was published,[11] which may change future planning. In order to be enrolled in the study, patients had to have < 30% residual stenosis. The core lab has been verifying this and also making sure that successful angioplasty has been done before the patient is enrolled.

On a side note, an interesting element, especially for those of us who do not do much peripheral work, is the new terminology emerging with the use of DCBs, such as transit time (how quickly you get the DCB to the lesion and inflate it, which is relevant because the drug has the potential to wash off before the balloon is inflated), geographic miss (making sure you're getting the drug to the right place), and, surprisingly, compliance related to angioplasty balloons. Each trial informs the next one.

If all goes well in the investigational device exemption trial, what is a ballpark time frame on when a DCB might have an AV indication in the United States?

Dr. Trerotola: We completed enrollment earlier this year, and we are now in the 6-month follow-up window. Although these things are difficult to predict precisely, we believe that we will have results sometime in the fourth quarter and anticipate premarket approval submission in the first quarter of 2017, with the goal of launching in the United States in the second half of 2017. ■

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