ASK THE EXPERTS

What Outcomes Will Foster or Stymie Adoption of Drug-Coated Balloon Use in AV Fistula Intervention?

Experts discuss how patency, cost-effectiveness, and reimbursement may impact if and when DCBs are used.

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Now that the benefit of paclitaxel-coated balloons over percutaneous transluminal angioplasty (PTA) in hemodialysis fistulas has been demonstrated in a large multicenter trial (Lutonix AV), and building on existing smaller studies that have demonstrated benefit in both grafts and fistulas, it is reasonable to ask what it will take for widespread adoption of the technology to occur (or not). Cost is always a consideration when discussing new technology, and because many current payment models paradoxically reward worse outcomes, demonstrating cost-effectiveness might not be sufficient to drive adoption, but it would be a good start. New payment models that reward better patency outcomes will definitely change the current perverse perspective. Under those models, if the devices were reimbursed (which would make sense because it would benefit patients), drug-coated balloons (DCBs) would likely be widely adopted. Conversely, lack of reimbursement could be a hindrance depending on the structure of the payment model. For example, if a DCB prevents having to do another procedure for free within a given period, an extra $1,000 for a DCB might still be more palatable to a provider than PTA even if reimbursement was not present.

In addition to economic considerations, if DCBs can help avoid stent grafts, particularly in "no-stent" zones such as within a fistula or a graft's cannulation zone, the cephalic arch, and the perianastomotic region, the use of DCBs in those areas should be widely adopted virtually immediately. If DCBs offer comparable patency to stent grafts when compared directly in randomized controlled trials (RCTs), it would be hard to imagine using stent grafts over DCBs given their potential long-term complications of fracture, infection, and candy-wrapper restenosis. Direct comparisons are a long way off, so for the time being, adoption primarily should be driven by

"no-stent zone" considerations. Of course, the rare situation in which elastic recoil calls for stent grafts will not be addressed by a DCB.

Obviously, should any as-yet-unforeseen late issues arise with DCBs, uptake could be stymied, but the available safety data are excellent and this seems very unlikely. Furthermore, should direct comparison to stent grafts yield poor results for DCB, this too would stymie DCB uptake, especially outside the "no-stent" zones. Although it is difficult to imagine this scenario based on available studies, only a head-to-head RCT will tell us for sure. In the interim, as more data emerge regarding DCB in hemodialysis access, their role in this challenging space will become increasingly clear.

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The relatively high rate of restenosis after PTA in arteriovenous (AV) access stenosis is well recognized and can result in multiple repeat interventions or fistula thrombosis. The pathophysiology of AV access stenosis and mechanisms of restenosis after PTA supports the use of DCBs in AV access. Neointimal hyperplasia is a recognized cause of AV access stenosis and failure. Venous smooth muscle cells have been demonstrated to be more sensitive to antiproliferative agents including paclitaxel when compared with arterial smooth muscle cells.[1] An increase in the proliferation index of the intima and media in aggressive restenotic lesions after PTA compared with primary stenotic lesions has been demonstrated.[2]

The outcomes that will foster the use of DCBs in AV access stenosis are improved patency rates with fewer repeat interventions, which leave the patient with a functional fistula and good-quality dialysis. Fewer repeat interventions and prolonging the life of a fistula should make the use of DCBs cost-effective and improve the quality of life for the patient. However, where there are multiple stenoses within a single access circuit, we do not yet know if there is a clinical benefit to using multiple DCBs and whether this approach is cost-effective.

One of the reasons why DCBs may not be more widely adopted or limited in use is we are not yet sure when and where to use them for the best outcome. The access circuit is not uniform, and there is mounting evidence that AV access stenoses are not a uniform group. Adverse adventitial remodeling is also a cause of AV access stenosis and may be seen with or without neointimal hyperplasia.[3] We do not yet know whether all lesion types respond to drug elution in the same way, and this may stymie the adoption of DCBs if not addressed in clinical trials. In the future, we should aim for a consensus statement on the use of DCBs in AV access based on the best evidence available.

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Restenosis after AV fistula angioplasty is a common and aggressive problem, which means many hemodialysis patients face multiple interventions during the life of their AV access site. Techniques to improve the durability of patency after intervention have been extensively evaluated. Although devices such as high-pressure, cutting, and scoring balloons have provided a significant advance in adequately dilating AV fistula stenoses, they have been less effective at preventing restenosis. In this setting, there has been considerable interest in the use of DCBs, particularly given their impressive impact on patency in other vascular beds.

The early investigation of DCBs in AV fistula angioplasty was limited to single-center, site-reported studies with relatively small patient numbers. Results were mixed, with some studies showing no patency advantage for DCB over PTA. However, three physician-initiated, randomized trials all showed a patency advantage for DCB over PTA at 6 months postprocedure. These positive results encouraged the planning of large, industry-

sponsored, multicenter, core laboratory–adjudicated RCTs. The Lutonix AV clinical trial enrolled 285 patients with 1:1 randomization. Although the primary effectiveness endpoint of patency at 6 months did not show a statistically significant advantage for DCBs over PTA, there was statistically significant superiority of the DCB at many other time points. The 330-patient IN.PACT AV Access study has a similar trial design and recently began enrolling patients.

A key learning point from early work with DCBs in AV fistulas is that lesions must be dilated to near-nominal diameter prior to the deployment of the DCB. Adequate vessel preparation is often not achieved with PTA balloons given the fibrotic nature of fistula stenoses. High-pressure, cutting, or scoring balloons are often necessary. High-pressure balloon angioplasty with a residual stenosis of ≤ 30% diameter loss is required in both the Lutonix AV clinical trial and IN.PACT AV Access study. The combination of adequate vessel preparation followed by DCB use promises to significantly extend the patency of angioplasty for AV fistula stenoses. If proven, this will make a big impact on our management of this common and important problem.

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I believe we could be on the cusp of a new era for AV access intervention with the advent of DCBs. The combination of a "nothing left behind" approach and a focus on added value could result in more widespread adoption of this technology, depending on the following factors.

- **Efficacy data**—At the end of the day, whether or not the treatment works still remains the single most important determinant of success. Early data from small studies on AV access have been positive, as were the 8-month data from the Lutonix AV clinical trial that were recently announced at the Leipzig Interventional Course. As opposed to stent-based interventions, there could be significant benefits from a pathophysiology standpoint that result from the "nothing left behind" strategy that characterizes DCB technology.
- **Added value**—The concept of added value is going to be key to the adoption of the DCB technology, with *value* being defined as outcomes over cost. This means that the cost of interventions to maintain patency will be an important determinant in adopting this technology. Thus, if an increase in cumulative patency is also accompanied by a decrease in the number of interventions, then the product becomes extremely attractive as opposed to an increase in patency that needs to be maintained through an increase in the number of interventions.
- **Global payment systems**—Another important factor that could influence the adoption of the use of DCB technology in this setting relates to global payment systems such as the ESRD Seamless Care Organizations (ESCOs). In particular, the ESCOs could incentivize innovation. If the use of a DCB reduces downstream endovascular and surgical interventions and also reduces the duration of tunneled dialysis catheter use and subsequent catheter-related bacteremia and intensive care unit admissions, then this would greatly enhance the adoption of the DCB in a global payment system where the cost of the device is coming from the same source as all of the previously described costs.
- **Patient preference**—The patients' perspective on whether or not a new intervention is targeting the things that are truly important to them will be an important factor that influences the potential adoption of DCBs. An intervention that reduces future additional procedures and allows for complication-free dialysis could be an extremely patient-friendly option. Of note, the US Food and Drug Administration has been at the forefront of trying to incorporate patient insights and preferences into the regulatory pathway.
- **Synchronizing with the process of care**—A smooth integration of the DCB technology into the existing process of care—be it in the interventional suite, access center, or operating room—will be a key determinant in the adoption of this technology.

I believe that we are at the threshold of significant change in the way we care for patients with AV access dysfunction. Incorporating the previously mentioned issues into the adoption (or lack thereof) of DCB technology will ensure that we do the right thing for our patients. ■