GLOBAL ROUNDTABLE

Real-World Experience With Drug-Coated Balloons in AV Access

Experts discuss the current use of DCBs in AV fistulas and review how upcoming trials may influence progress in this space.

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What have we learned from the drug-coated balloon (DCB) clinical experience in arteriovenous (AV) access so far?

Dr. Holden: We have known for many years that stenosis in the AV access circuit is the major cause of hemodialysis access dysfunction. We've also understood these stenoses may be resistant to angioplasty with conventional balloons, often requiring ancillary procedures such as high-pressure or cutting or scoring balloon angioplasty. With the clear antirestenotic benefit that DCB angioplasty has demonstrated in lower limb arteries, there has been considerable interest in applying this technology to dialysis access circuit stenoses. However, the pathophysiology of these fibrotic and resistant stenoses is quite different from atherosclerotic stenotic disease, so the potential benefit of drug-eluting technologies has been uncertain.

Mixed results were obtained in early small series experience, most were single center, some single arm, and some randomized between plain balloon angioplasty and DCB angioplasty. However, meta-analyses of the early experience indicated a patency trend favoring DCB angioplasty with certainly a more powerful patency benefit than other devices such as cutting balloons or covered stents.

Recently, two large, industry-sponsored, multicenter prospective, randomized controlled trials (RCTs) have been undertaken: the Lutonix AV investigational device exemption (IDE) clinical trial (Bard Peripheral Vascular; BD Interventional) and the IN.PACT AV Access IDE trial (Medtronic). The Lutonix AV IDE trial rapidly enrolled 285 patients with enrollment completed in March 2016. The 330-patient IN.PACT AV Access IDE trial has recently completed enrollment. Although there are some differences in study design between the trials, both mandate adequate vessel preparation with a high-pressure angioplasty balloon prior to randomization to either a plain balloon or DCB strategy. Both trials have a primary efficacy endpoint of target lesion primary patency at 6 months.

Interim 24-month results from the Lutonix AV IDE trial have recently been reported. Although the patency advantage for DCB angioplasty did not reach statistical significance at the primary 6-month endpoint, there is sustained separation of the patency curves out to 24 months, which favors DCB angioplasty. The primary endpoint results of the IN.PACT AV Access IDE study will be reported in 2019. Several single-arm real-world registries, such as the Lutonix AV registry, are also planned or currently recruiting.

Drs. Irani and Tan: The available data have shown that DCBs can significantly prolong the primary patency of the lesion when compared with conventional balloon angioplasty. Data from our DEBAPTA trial (NCT01544907; currently in press) suggest DCBs can prolong both the 6-month and 1-year lesion patency following treatment.

Dr. Karnabatidis: In plain words, DCBs succeeded in becoming a useful tool in everyday practice for the treatment of dysfunctional vascular access. The significance of DCBs lies in their use as drug delivery devices inhibiting venous neointimal hyperplasia.

Dr. Kitrou: The key words to consider, which we'll discuss later in detail, are *vessel preparation*, *drug delivery devices*, *geographic miss*, and *sizing*. These are the fundamental principles of approaching and treating a lesion with a DCB within a dysfunctional dialysis access circuit. It is important to differentiate and appreciate the immediate mechanical gain of an initial adequate vessel preparation of a high-pressure balloon angioplasty and the future pharmaceutical effect of paclitaxel to inhibit venous neointimal hyperplasia. Of equal importance is understanding and implementing a stepwise approach to this treatment.

Dr. Trerotola: It is very important to understand that we are still in the very early days. Only one multicenter randomized trial has been completed, which is the IDE trial of the Lutonix device. There are a number of published small single-center randomized trials; most but not all of these have shown the benefit of DCBs over plain old balloon angioplasty in AV fistulas (AVFs). There are many ongoing trials as well.

At this point, I'm extremely optimistic because most of the data that have been reported have been favorable. In particular, it is very interesting that the studies have more or less turned up the same numbers; that's very unusual in the medical literature. We have the Kitrou et al study that showed 70% primary patency at 6 months,[1] which is well above the Kidney Disease Outcomes Quality Initiative recommendation. That same number came up in the Lutonix AV IDE trial (NCT02440022) and in the ongoing Lutonix Global AV registry (NCT02746159). It is nice to see that consistency, which suggests we are onto something.

What are the strengths and limitations of the data?

Dr. Karnabatidis: Although there is mounting evidence regarding DCB use in vascular access, data from major RCTs are still only available from congress announcements. The problem with evidence so far, based on smaller proof-of-concept RCTs or cohort studies, is the wide heterogeneity of methodology. This is normal to a certain extent, as DCBs were a new tool that had to find the right use.

Dr. Kitrou: Published and announced data provide information on DCB use in about 1,000 patients. However, there are additional company- and investigator-initiated studies on the horizon in the next couple of years. Data suggest a strong, significant overall positive result on DCB use in the treatment of dysfunctional dialysis access. Still, despite the mounting evidence, there are still not enough data to perform adequate subgroup analyses to focus on different subsets of lesion sites, types, and so on, because of the current extensive heterogeneity between RCTs. There are different devices involved, and more importantly, different procedures. Therefore, I believe that trying to couple certain types of stenoses to DCBs at such an early stage could be rather misleading and we may end up getting lost in translation. At the moment, a more solid and specific treatment approach is what we should be aiming for.

Dr. Trerotola: The strengths are that we have randomized data. We have more randomized data for DCBs in AVFs than any other technology, including stent grafts. Stent grafts have more multicenter trials, but if you look at the total number of trials, there already are a lot for DCBs. That puts them in very good stead.

In the 52 years since the description of the AVF, this is the first technology to be shown in a large multicenter randomized fashion to be better than angioplasty. However, it's not a panacea that will eliminate angioplasty forever.

Also, we have only tested DCBs in broad brush strokes. We haven't tested them in central vein stenosis, except for one small trial out of Greece.[2] Immature fistulas, clotted fistulas, in-stent restenosis, and candy-wrapper stenosis are also areas that we have yet to study.

Drs. Irani and Tan: At present, there are limited published data on the use of DCBs in AVF/AV graft stenosis. Available data are mainly from single-center, retrospective cohort studies with a small number of patients enrolled, and there are very few prospective randomized trials. However, more data will be available from the larger multicenter trials in the near future.

Dr. Holden: The early studies were not adequately powered, and most did not clearly define the concept of vessel preparation prior to DCB angioplasty. Despite these limitations, many of these trials demonstrated an encouraging patency trend favoring DCB angioplasty. Adequate vessel preparation was mandated in all of the femoropopliteal DCB randomized trials, and it is also likely to be a key requirement in the AV access circuit. The two large, prospective RCTs have similar trial design but are potentially evaluating different patient cohorts. The IN.PACT AV Access IDE study is a multinational trial, that includes a large patient cohort from Japan who tend to have a higher percentage of radiocephalic access circuits than their United States contemporaries.

At which locations in an AVF you would prefer to use a DCB to treat stenosis and why? Which would you avoid?

Drs. Irani and Tan: Unlike stents, DCBs can be used at any location within the access circuit because they leave nothing behind. Stenosis at the AV anastomosis, juxtaanastomotic segment, outflow vein, and cephalic arch are all amenable to treatment with a DCB. The availability of larger-diameter DCBs will allow for the treatment of central vein stenosis.

Dr. Kitrou: I use DCBs everywhere I perform an angioplasty, provided that I perform the angioplasty well! Vessel preparation, a successful immediate mechanical result after angioplasty, is the route to success. I never use DCBs in a suboptimal initial angiographic result. In my opinion, more important than "where" is "when" to use a DCB. I also don't use DCBs where there is no size available yet and within expanded polytetrafluoroethylene, within the synthetic part of an AV graft, and within a covered stent. That certainly does not include the sites where the fabric meets the tissue on the side.

Dr. Trerotola: The only device approved in the United States is the Lutonix 035 DCB, and it is approved for mature AVF from the anastomosis up to and including the terminal arch of the cephalic vein. Any use in immature fistulas, grafts, central vein stenosis, or thrombosed fistulas would be considered off-label use.

That said, there is no location where I wouldn't use the device, with the acknowledgment that some of those areas are off-label use. The beauty of it is, unlike stents and stent grafts, with which there are serious limitations, especially in what I call "no-stent zones" such as cannulation areas, the terminal arch of the cephalic vein, and the perianastomotic area, you can use the DCB anywhere.

Dr. Holden: Both of the large RCTs defined the access circuit as extending from the AV anastomosis to the cephalosubclavian junction, and these are the lesion locations in which I would use DCB angioplasty. The most important cases to avoid are those that cannot be adequately predilated; a residual stenosis of < 30% diameter loss without flow-limiting dissection is a minimum requirement to treat with DCB angioplasty. Stenoses associated with false or true aneurysm formation should also be avoided. There is minimal evidence supporting the use of DCBs in central venous stenoses, and vessel diameters are often larger than

currently available balloon diameters, so I would not currently advocate their use in this location.

Dr. Karnabatidis: Wherever there is a place for angioplasty, there is a place for DCBs—from central veins, to outflow veins, to the treatment of immature fistulas. This is because the paclitaxel mounted on DCBs is used to inhibit the cascade of downstream events following angioplasty to inhibit the formation of venous neointimal hyperplasia. I do not use DCBs in cases where covered stents have proven their superiority.

From a practical standpoint, how does performing angioplasty with a DCB differ from other balloons used in AVFs? What are some key lessons you have learned in your time using DCBs in this setting?

Dr. Trerotola: This is really important, especially if you're not already doing superficial femoral artery (SFA) work. If you're doing SFA work, you're familiar with terms such as *vessel preparation*, *transit time*, and *geographic miss*. If you are new to DCBs and if you haven't been in the angioplasty game for 30 years, you may not know about techniques used to establish a good angioplasty, such as prolonged inflation. Because the DCB won't do anything about elastic recoil, you have to maximize your acute gain by getting a very good angioplasty. What a DCB does is minimize late loss by preventing intimal hyperplasia; the better the acute gain, the less late loss. We did high-pressure angioplasty in the Lutonix AV trial in order to get an optimal starting result so that the clock starts ticking, in a sense, on restenosis at a big diameter. In the parlance of DCBs, this is called *vessel preparation*.

Then there's transit time, defined as the time from when you insert the balloon into the sheath to the time you inflate it. It is recommended that transit time is < 30 seconds because the drug is washing off until you inflate the balloon. Furthermore, you need to ensure accurate placement to avoid geographic miss, or geomiss. There are some things you can do to accomplish this. You can use the GeoAlign markers (BD Interventional) on the catheter, or you can use an external marker. We used Glow 'N Tell Tape (LeMaitre Vascular, Inc.) in the study. In any case, physicians should be ready and know where they want to place the balloon. Additionally, make sure when you choose your DCB that it is at least 5 mm longer on either end than the predilation balloon. That means if you do your predilation with a 4-cm balloon, you're going to use a 6-cm or longer DCB. All of these measures help ensure you do not get a geographic miss, meaning that the drug is not placed where the angioplasty occurred.

The last thing is that at least a 2-minute inflation is recommended for DCB inflation; it's suggested that a 3-minute inflation may be even better. I do prolonged inflation (5 minutes) all the time in AV access percutaneous transluminal angioplasty (PTA), yet as I've traveled around the world talking about this, I've observed that some physicians are hesitant to do prolonged inflation because they're afraid the access will thrombose, but that just doesn't happen. Prolonged inflation is the way we manage elastic recoil and rupture, so it is a good step.

Dr. Holden: There are no major differences when using a DCB in the AV access setting compared with lower limb arterial indications. However, adequate vessel preparation routinely requires a different strategy than plain balloon angioplasty. Both RCTs have used high-pressure balloon angioplasty. The relative benefit of high-pressure balloons compared with scoring or cutting balloons remains to be shown. The DCB must be inflated for at least 2 minutes to allow optimum drug delivery and angiographic result and must extend to vessel segments either side of the target lesion not treated in the predilatation stage. Sometimes accurate balloon sizing may be challenging when the AV access vein varies considerably in diameter; it is important to size angioplasty balloons to the nearest normal vessel diameter and not areas of poststenotic dilatation.

Dr. Karnabatidis: DCBs are compliant drug delivery devices. Therefore, the core immediate outcome, or vessel preparation, will be achieved with high-pressure noncompliant balloons. This is important as we've come across studies directly comparing high-pressure balloons with DCBs without performing adequate vessel preparation. Of equal importance is drugging the whole area previously angioplastied with high-pressure balloons avoiding geographic miss, which is avoiding a mismatch between vessel preparation and drug apposition to the vascular wall.

Dr. Kitrou: DCBs are drug delivery devices. Paclitaxel is used for the inhibition of restenosis, not the treatment of the current stenosis. The immediate mechanical result of angioplasty in vascular access is still performed by high-pressure or ultra-high-pressure balloons. DCB angioplasty is amplifying the result in the long term. Thus, implementation of DCB technology for the treatment of dysfunctional dialysis access modified the treatment algorithm, making the process a two-step procedure. Additionally, there are two important things that need to be stressed. First, as previously mentioned, the part of the vessel that is angioplastied in the initial mechanical dilation should be fully covered by paclitaxel, which is why DCBs should be about 5-mm longer from each side of the lesion. Second,

the sizing of DCBs should be at minimum the same diameter with the initial angioplasty balloon used. In my practice, I also tend to overinflate a couple of atmospheres above the nominal pressure.

Drs. Irani and Tan: Lesion preparation before DCB use is crucial. The stenosis must first be ameliorated using a conventional, high-pressure, or cutting balloon. In DCBs, the balloon acts as a mere vehicle to apply the drug to the vessel wall and is not an angioplasty in the conventional sense. Use of a DCB one size larger in diameter as compared with the actual angioplasty balloon allows for better wall apposition and elution of the drug into the intima. Keeping the balloon inflated for the recommended time (1 minute) is necessary because it allows complete elution of the drug into the vessel wall.

Stent grafts are proven to be superior to PTA for treating in-stent stenosis. What is the role for DCBs?

Dr. Holden: The role of DCB angioplasty in patients with in-stent restenosis in the AV access circuit remains unclear. Although there are significant geographic variations in practice, we rarely place stents in the AV access circuit, and it is even less common to use stent grafts (apart from patients with significant aneurysmal disease).

Dr. Karnabatidis: It is rather early to conclude on specific and definite indications for DCBs, because the cases for their use in in-stent restenosis are quite minimal. From a theoretical point of view, however, wherever there is place for angioplasty, there is place for DCBs, keeping in mind that covered stents already have superior results.

Drs. Irani and Tan: In the arterial system, the use of DCBs for treatment of in-stent restenosis is well established. There are not much DCB data available for dialysis access. Swinnen et al showed that DCBs significantly reduce reintervention on recurrent in-stent AVF stenosis.[3]

Dr. Kitrou: There is still little evidence regarding a proper subgroup analysis, but from a theoretical point of view and based on the experience of arteries, DCBs could have a role in in-stent restenosis.

Dr. Trerotola: I have no idea, as this hasn't been tested on a large scale. In-stent restenosis is included in the global registry that is underway, and there's a handful of people who have been enrolled with that indication, but I think it's going to be a while before we see outcomes. I hope that we can at least buy some time before we need to place a stent graft, because once you put a stent graft in, you start the clock ticking to a time when you are going to have to give up on that access. Stent grafts probably prolong that time, but as soon as you put metal in it's the beginning of the end for that access. I'm hoping that we can stave that off with a DCB. The nice thing about not putting metal in is that you can always go back. However, it's off-label use right now and largely unstudied.

Many central vein stenoses are due to extrinsic compression, such as thoracic outlet-related subclavian vein stenosis, and left brachiocephalic vein stenosis due to aortic compression. What do you think is the role for DCBs in treating central vein stenosis?

Dr. Karnabatidis: Our published experience in DCB use in symptomatic central venous stenosis suggests that DCBs do have a role in that field. If angioplasty does not have a role as in cases of extrinsic pressure or when vessel diameter exceeds the available DCB sizes, their use should be avoided.

Drs. Irani and Tan: At present, there is little evidence for the use of DCBs in the central vein. Massmann et al[4] evaluated custom-made balloons and showed that the restenosis interval after angioplasty with a DCB was longer compared with conventional balloon angioplasty (median, 9 months vs 4 months; $P = .023$). The availability of large-size balloons to treat central lesions would make it easier to generate data to better elucidate DCB use in central veins. Stenosis due to external compression needs a scaffold, but stents in the central veins do not have a good track record. The role of DCBs in the central veins would be to prevent neointimal hyperplasia as a result of shear injury or endothelial injury from the constant pulsation injury.

Dr. Kitrou: We have performed a RCT on the use of DCBs in symptomatic central venous stenosis, and a significant difference in favor of DCB was observed when compared with high-pressure balloons.[2] However, as previously mentioned, the mechanical effect of beating the stenosis is produced by angioplasty; DCBs will be used to inhibit restenosis. An important limiting factor is the size; in most cases, a 12-mm balloon is inadequate to treat a stenosed superior vena cava.

Dr. Trerotola: Symptomatic brachiocephalic extrinsic compression is very rare. Extrinsic compression of the subclavian is increasingly being recognized and talked about, but nobody really has any idea what percentage of people who have subclavian stenosis have extrinsic compression versus true intrinsic stenosis due to intimal hyperplasia; they could also coexist.

That said, a DCB won't do anything for extrinsic compression. Now, if you want to ask the question, will DCBs work in central venous stenosis, the answer is yes. As previously mentioned, there is a randomized trial from Greece that showed an improved outcome with DCB use,[2] and they used time to reintervention as the measure, which was a slightly different measure than their previous studies. But again, there was an improved outcome over plain old balloon angioplasty in central veins. Thus, for intimal hyperplasia of the central veins, I believe DCBs would be better than plain angioplasty.

Dr. Holden: It is true that parts of the central venous anatomy can be hostile, particularly the subclavian vein passing over the first rib and behind the clavicle. In this location, it is well known that stents can be extrinsically crushed and fractured. In addition, the etiology of central venous stenoses may be multifactorial, including hemodialysis access–related barotrauma, previous central venous catheters, and extrinsic compression seen in the Paget-Schroetter syndrome. In hemodialysis access patients with central venous stenoses, restenosis is a common problem, and an antirestenotic strategy would appear sensible. However, the role of DCB angioplasty remains unclear as their use has only been observed in sporadic reports, and ideal balloon sizes are not currently available. Likewise, as yet there is no clear role for DCBs in Paget-Schroetter syndrome.

What is the financial viability of DCBs? Does the additional cost of a DCB make fiscal sense given the potential for decreased reintervention?

Dr. Kitrou: A cost-effectiveness analysis was performed in our department regarding the use of DCBs in vascular access and was published in our initial study.[5] Their use was cost-effective back then, when the price DCBs was higher than today. Larger, upcoming multicenter RCTs will hopefully yield a definitive answer.

Dr. Trerotola: I'm not an expert in medical finance, but one of the things that really strikes me as odd is that the very same people who won't think twice about putting a bare-metal stent into a dialysis access say they won't spend the same amount of money to use a DCB. The problem right now is that we have a reimbursement system that favors poor outcomes and actually incentivizes bad results. As soon as that patient comes back, doctors get paid for another angioplasty, stent, or stent graft.

But that's changing; for instance, we have ESCOs (ESRD Seamless Care Organizations) now. In Japan, doctors will be paid for only one angioplasty in a 3-month period, and I'm told Poland has just done the same. These are models that make more sense because they incentivize doctors to do a good job. If we can get 4 months more out of a DCB treatment than we can from a plain old balloon angioplasty as we showed in the trial, then maybe we'll only have to do one intervention in that 3-month period and, therefore, save the ESCO some money. That's the way we have to look at it.

However, before that stuff comes about, I believe in doing the right thing for the patient. If we can prolong postangioplasty patency, keep the patient out of the hospital, and avoid catheters or missed dialysis, then we're doing the right thing and it's worth the additional money.

Dr. Holden: We know that hemodialysis is an expensive therapy for health providers to offer, and a significant component of this cost is maintenance of dialysis access. There is potential for DCB angioplasty to be highly cost-effective in the AV access setting if this strategy can prolong freedom from clinically driven access reintervention and, therefore, reintervention-free days. The interim 24-month Lutonix AV IDE trial results reported that the DCB cohort had, on average, 120 more reintervention-free days than the plain balloon group. In New Zealand, DCB angioplasty is reimbursed for AV access stenosis, although the technique tends to be reserved for patients with restenotic rather than de novo stenoses. This may change as evidence continues to evolve.

Dr. Karnabatidis: In our initial first-in-human proof-of-concept RCT testing DCBs in vascular access, a cost benefit was observed. I am expecting much more solid data from multicenter studies coming up.

Drs. Irani and Tan: DCBs are expensive and can significantly increase the cost of a procedure. However, because DCBs have been shown to prolong patency and reduce reintervention rates, they may prove to be a long-term, cost-effective solution. Kitrou et al conducted a cost-effective analysis of DCBs and found a satisfactory incremental cost-effectiveness ratio of €2,198 per primary patency year of dialysis access gained.[5] We are in the process of evaluating our data for establishing the cost-effectiveness of DCBs within our local Asian health care market. Within our health care system, the patient copays the cost of the device. ■

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