Drug-Coated Balloons: The Road Ahead

Experts weigh in on the current data supporting the use of drug-coated balloons.

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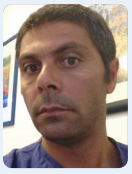

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Do the drug-coated balloon (DCB) clinical data to date lead you to believe that there are differences between DCB technologies, or do DCBs perform consistently as a class?

Dr. Tepe: I think there is a difference between DCBs; there is no class effect, and there are balloons that are going to perform better than others. There are also some balloons that don't seem to work at all. I think this is very important to note; it might be that some of the DCBs have good results at 6 months, or at least some effect, but in the long term, say 1 to 3 years, they are not doing any better than any control group. So, there is a difference.

Dr. Rocha-Singh: Given the available peer-reviewed data, and understanding that the inclusion and exclusion criteria in the two largest RCTs (LEVANT 2 and IN.PACT ADMIRAL) were fairly similar, I believe that there is no class effect, and additional data with longer-term follow-up on the durability of the DCB effect will bear this out. We need only look at the emerging additional data from the IN.PACT DEEP Amphirion CLI trial as an example. In the end, this trial failed due to the fundamental failure of the DCB used in the trial. The Amphirion balloon (Medtronic plc), when compared to the same manufacturer's SFA platform, showed that differences in the coating methodology (ie, applying the paclitaxel to the balloon in its deflated configuration), although resulting in the same amount of total drug on the balloon, had a drug distribution that was nonuniform and dissimilar from the In.Pact Admiral coating process. Perhaps more importantly, the different balloon materials had very different balloon "surface energy," meaning the Amphirion balloon material retained paclitaxel with substantially more affinity than the In.Pact Admiral balloon material. These two differences resulted in the discrepant findings published from the two trials and underscore how a class effect cannot be assumed.

Additionally, I believe that when the two FDA-approved DCBs get into more general use, we will observe several things that will cause all of us to pause. First, the crossover rate to stenting is not going to be less than 5%. Physicians will use these products outside the inclusion criteria, may not predilate the lesion, and will use them in longer chronic total occlusions and de novo lesions; this will drive provisional stenting in these patients and affect the cost equation of device use.

Second, with regard to severe circumferential vascular

calcification, while such lesions were to be excluded in the two regulatory trials, I believe they were enrolled by investigators and, when analyzed further, their clinically driven target lesion revascularization (TLR) rates through 12 months will be higher than the clinically driven TLR rates in noncalcified lesions.

Dr. Micari: Oh, yes, definitely. I strongly agree that there is no class effect in the DCB technology because, while I think that the effects of paclitaxel are quite the same for all the balloons within the market, there is a great difference in the technology.

What lessons have been learned from the studies of first-generation DCBs?

Dr. Micari: All we have learned from first-generation DCBs should be reappraised in the light of second-generation DCB technologies and clinical data. It is quite a similar story for drug-eluting stents in the coronary arena; if you consider the first-generation drug-eluting stents, of course, they are not comparable with the newer generation in that second-generation stents normally showed important improvement over their predecessors. Ultimately, all lessons build upon (originate from) robust clinical programs, which is what second-generation DCB manufacturers should continue to commit to.

I think this field of drug-combination devices progresses in step-by-step increments and, as much as first-generation DCBs showed very encouraging data (some backed by robust randomized trials), I expect new-generation DCBs to deliver the same or better clinical results while relying on refined coating technologies with lower drug load, higher coating stability, and improved drug transfer efficiency.

Dr. Tepe: DCBs are safe. I have not heard, at least in the SFA, of any side effects attributed to a DCB that caused major problems. Also, most of the studies have shown that DCBs are effective. It is also very important to note that if you compare studies, the patient cohorts are different; sometimes, there are longer lesions, sometimes shorter lesions, and sometimes more calcified lesions, so it's very difficult to compare. But, such a comparison does reveal that there are differences.

Dr. Rocha-Singh: I think there may have been a rush to market whereby specific clinical issues have not been adequately addressed in the preclinical animal models, and I am again referring to calcium. The FDA only requires you to look at safety and effectiveness and understand the preclinical science as it relates to safety. However, industry has not invested in the development of a preclinical in vivo model of vascular calcification, and relies on cadaver models.

There is an evolving concern that higher grades of vascular calcium may impact the paclitaxel elution into the vessel wall and affect the clinical durability of DCBs. We have already seen preliminary, hypothesis-generating data from the DEFINITIVE AR trial, which in post hoc assessments presented by Prof. Thomas Zeller,[1] would lead one to consider the use of atherectomy prior to DCB use as a potential method to address this perplexing issue. Of course, we do not have clear signals that this is a validated method. Unfortunately, I suspect clinicians and industry marketing folks may not wait for such data before advocating its use.

But I can tell you that the problems of severe calcification, given the epidemic of diabetes, are not going away, and we need to start designing relevant trials to address this hypothesis.

There has been an evolution of clinical endpoints associated with DCBs. Early studies focused on late lumen loss, and newer studies are focused on primary patency or TLR. What clinical outcomes do you look at to make informed treatment decisions?

Dr. Tepe: The first studies were done with a late lumen loss only to see if there was a treatment effect. The endpoints are restenosis, which is patency and TLR, and for claudicants, it's walking distance and TLR—especially because what we prevent with DCBs is restenosis, and restenosis then transforms into the TLR rate.

Nevertheless, it has to be stated that unlike late lumen loss, TLR is not such an independent point that it cannot be influenced based on patients' symptoms because (1) we do not perform PTA on a patient with no symptoms, and (2) some patients are fine with a walking distance of 150 meters, whereas others are not.

Dr. Micari: Endpoints in clinical trials should focus on the true clinical impact of any specific therapy on that specific disease. Particularly for claudication, metrics such as walking distance and quality of life, besides target lesion and target vessel revascularization, indeed describe what matters the most for patients. Critical limb ischemia is a totally different disease in which functional limb preservation is the most important goal. That said, vessel patency remains a similarly important revascularization metric that needs to be rigorously measured and reported in device trials of both claudication and critical limb ischemia. The correlation between patency and patient-relevant endpoints, in fact, can only be assessed when both variables are taken into account and rigor-

ously measured. Moreover, other "extravascular" variables, such as medical therapy or wound healing, should also be taken into account, controlled for, and carefully measured because they affect the final clinical outcome. If they are not properly assessed, they end up being confounding factors.

Dr. Rocha-Singh: I think these issues of surrogates of late lumen loss relate more to getting at an assessment of the adequacy of the therapy. I'm more interested in patient-centric endpoints. I think we have to start putting these claudicants on a 6-minute walk test, minimally. I believe we must also call into question binary restenosis and its correlation to clinically driven TLR. I would suspect that the peak systolic velocity may be a superior surrogate than simple binary restenosis. Finally, we MUST follow and publish longer-term clinical data in claudicants. The 1-year time frame is an established and accepted regulatory endpoint; if 2- and 3-year adjudicated data reflect a substantial loss of durability, that will be difficult to defend.

Which data had the most impact on your use of DCBs?

Dr. Rocha-Singh: Understanding the established differences between the currently available drug-eluting platforms, I believe that there may be reasons to interpret the effectiveness of one balloon to be potentially superior to the other, appreciating the differences in trial inclusion/exclusion criteria. There are multiple variables that should be noted that may account for the prevailing opinion that no "class effect" was evident between platforms; these include the balloon-coating technologies and excipients and our understanding of the potential differences in balloon surface energy that allows the elution of the drug off of the balloon surface and into the arterial wall, etc.

In reviewing data presented at Bard's FDA panel, which is available to the public, I am concerned by the drop-off in vessel primary patency when the 30-day window past the prespecified 365-day endpoint (ie, 13 months) is analyzed. When intervals are compared, the drop-off in patients extended out to 13 months comes close to that of angioplasty.

As such, we are left to question the durability of this therapy as we await the 2-year data, which will better assess the durability of this technology. Importantly, a similar decline, although not to the same extent, was observed in the ADMIRAL data. Documentation of the clinical durability of this new technology beyond 1 year will be very important in order to substantiate the added financial expenditures.

Dr. Tepe: I had the honor of using the first DCBs ever used in clinical practice. The first result of this balloon was very important to me because the follow-up angiograms at 6 months or 1 year looked even better compared to the postintervention results. There's a kind of imprint of the DCB where the balloon was inflated. This was most impressive to me, and it translates into the current studies. What I'm currently looking at first is, of course, clinical results: the TLR rate and patency rate. I also look at how a study is done. But I also can look at the images, and if I see a 6-month angiogram with a positive remodeling effect compared to the postintervention imaging, I know that the DCB is going to work.

Dr. Micari: After the initial promising signals from proof-of-concept trials (THUNDER and FEMPAC), I led one of the very first large DCB multicenter registries on patients with claudication and rest pain due to SFA disease, characterized by a systematic and rigorous assessment of functional endpoints.[2,3] We demonstrated that the use of DCBs not only can translate into excellent patency rates at 1 and 2 years, but also showed that patency preservation was associated with a significant clinical benefit that was well-perceived by the patient, as measured by quality of life and absolute claudication distance improvements. These are the important lesion-based, and more importantly, patient-functional endpoints that matter to me.

Have any predictors for restenosis been identified either in your experience or in clinical studies, and how do you treat patients with these predictors?

Dr. Micari: In our registry, predictors of restenosis were searched for but not identified, which is not surprising because this was still a relatively small population for that scope. In general, DCB-specific predictors have not been rigorously studied or found so far. However, we may expect diabetes, long lesions, and calcium to reduce the therapeutic effect of DCBs even though this technology may continue to be superior to plain balloons or bare-metal stents in these settings.

Dr. Tepe: There are some predictors of restenosis after DCB treatment that can be changed and others that cannot. In the retrospective study that I have done, I have seen that diabetes affects restenosis rates. Also, as compared to use in de novo stenoses, DCB use in restenosis has not met the same level of results.

In general, DCBs perform better than uncoated balloons, even in this difficult patient cohort. Nevertheless, these risk factors for restenosis cannot

be modified. In contrast, there are other circumstances that might be modified before DCB therapy, such as calcium, which is also a predictor of less favorable outcome. An artery that is heavily calcified is also something that cannot be easily treated with a DCB compared to other lesions. However, unlike other outcome predictors, calcium can be modified. You can use either atherectomy or a cutting balloon to prepare the vessel for drug uptake.

Dr. Rocha-Singh: My primary concern relates to the issue of vascular calcification and its severity and location (intimal, medial, or both). This was and continues to be a prespecified exclusion criterion in United States regulatory DCB trials. The CTA-based evaluation by Fanelli et al[4] of the clinical impact of various degrees of circumferential SFA calcification on de novo lesions of various lengths was small (n = 60) and unadjudicated, but it certainly defines a concern for a potential mode of failure of this new technology.

These findings will also, intentionally or unintentionally, drive the unproven hypothesis that "vessel preparation" with atherectomy prior to DCB use will favorably affect the clinical results in severely calcified SFAs. Unfortunately, as we proceed down this path of "vessel preparation," I am uncertain as to whether there are sufficient data to guide physicians as to which of the five commercially available atherectomy devices is the most efficient and safe at debulking calcified atheroma. In this regard, I believe there is fertile ground for clinical research.

Do known failure modes exist for DCBs? If so, what are those failure modes?

Dr. Tepe: The one major failure mode is when a DCB does not transfer enough drug into the vessel wall, resulting in an effect similar to an uncoated balloon. What is important is not how much drug is on the surface of the balloon, but rather how much drug really gets into the vessel wall and stays there for some time. The use of a so-called spacer that makes the drug adherent to the balloon and then also allows for good delivery to the vessel wall is also very important. This differs from DCB to DCB. The major failure mode of a DCB is that, even if there is enough dose on the surface of a balloon, there is an underdosing in the vessel wall. This underdosing does not give a result that is any different from plain-old balloon angioplasty.

Dr. Rocha-Singh: Unfortunately, we are challenged by the simple fact that we do not have a unified, validated definition of calcium severity in the peripheral vasculature. However, work to establish such a calcium grading scale is actively ongoing.

Given this, we do know that patients with "severe" calcium have been enrolled in DCB trials; however, these numbers were small, and we have not been provided with any angiographic follow-up of this cohort to see if there are any adverse clinical trends associated with the presence of severe calcium.

Dr. Micari: Severe calcium probably represents a barrier to optimal drug elution into the media. Particularly in the presence of full circumferential calcium (360°), the expected biological effects of the drug may be reduced, as demonstrated by the small study by Fanelli et al.[4] ■

1. Zeller T. DEFINITIVE AR 12-month results. Presented at the VIVA 2014; November 4, 2014, Las Vegas, Nevada.
2. Micari A, Cioppa A, Vadala G, et al. Clinical evaluation of a paclitaxel-eluting balloon for treatment of femoropoplliteal arterial disease: 12-month results from a multicenter Italian registry. JACC Cardiovasc Interv. 2012;5:331-338.
3. Micari A, Cioppa A, Vadala G, et al. 2-year results of paclitaxel-eluting balloons for femoropopliteal artery disease: evidence from a multicenter registry. JACC Cardiovasc Interv. 2013;6:282–289.
4. Fanelli F, Cannavale A, Gazzetti M, et al. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. Cardiovasc Intervent Radiol. 2014;37:898–907.