Study Strengthens Case for Drug-Coated Balloons for Dysfunctional AV Fistulas

By Ruth Jessen Hickman

A recent study in the *New England Journal of Medicine* may shift the balance for clinicians who are considering the use of drug-coated balloons (DCBs) for treating dysfunctional dialysis arteriovenous (AV) fistulas (1). The improved rates of fistula patency and reassuring data on safety underscore the potential of this technology to improve patients' lives and reduce healthcare expenditures.

Percutaneous transluminal angioplasty with standard balloons is currently the recommended treatment for dysfunctional hemodialysis fistulas. A balloon is inserted into the dialysis shunt and inflated in a stenotic area to stretch the vessel and restore normal flow. Although highly effective at restoring immediate patency, this approach is prone to restenosis and recurrent dysfunction, with around 50% or more of patients needing repeat intervention within 6 months (1).

"Unfortunately, these patients on lifelong hemodialysis might at any time be told, 'Today is the day your dialysis access isn't working anymore; you have to go have another procedure on it,'" said Robert A. Lookstein, MD, professor of radiology and surgery at the Icahn School of Medicine at Mount Sinai in New York City and principal investigator on the study.

In contrast to the balloons used in standard angioplasty, DCBs are coated with a drug, typically the anti-proliferative agent paclitaxel (used in much smaller amounts compared with its applications in cancer chemotherapy). The drug elutes from the balloon into the narrowed area of the blood vessel during the procedure, helping prevent future restenosis.

Currently, such DCBs are commonly used to treat symptomatic femoropopliteal peripheral artery disease and help prevent future restenosis and reinterventions, and a large body of evidence now supports their use in that application. Yet a meta-analysis in 2018 of such devices raised concerns of higher mortality rates in patients receiving DCBs (2), resulting in the convergence of a Food and Drug Administration Safety Panel to examine the issue (3).

These safety concerns helped slow the adoption of such products for AV fistulas. Of note, a 2019 meta-analysis did not show any difference in safety between patients with AV fistula lesions treated with DCBs compared with those treated via standard balloons (4). The issue is complicated by the multiple DCBs available, which may or may not have identical effects.

Scott O. Trerotola, MD, is the Stanley Baum Professor of Radiology and professor of radiology in surgery at the University of Pennsylvania School of Medicine in Philadelphia, PA. He was the principal investigator of a 2018 study that examined a different DCB device, designed by Lutonix, in the management of dysfunctional AV fistulas (5). Although the team demonstrated equivalent safety between the DCBs and standard angioplasty (at 6 months and 2 years), the study did not meet its primary endpoint. However, it did have some positive findings, including improved patency at 9 months, significantly longer time to reintervention, and significantly fewer reinterventions at 2 years for those receiving DCBs.

"Until this new paper came out, there was this equipoise," Trerotola said. "We had some positive studies and some negative studies, coupled with that mortality question. Now you've got this compelling study with great results and really meaningful numbers. This puts the wind back in the sails of the DCBs in this application."

Medtronic study

The prospective, patient-blinded, randomized trial enrolled 330 patients, 170 of whom received treatment via the DCB. Patients had mature, upper extremity AV fistulas with either new or (nonstented) restenotic lesions that were at least 50% blocked. The global trial included data from 29 international sites (1).

The study met its primary endpoint of improved patency of the target lesion at 6 months in those who received a DCB. "When the outcomes were specifically looked at with respect to the initial stenosis, 20% more patients were patent at 6 months that were treated with the DCB as compared to those treated with standard angioplasty," Lookstein said. That amounted to 82.2% (125 of 152) of patients who were patent at 7 months on the DCB vs. 59.5% (88 of 148) of those who received standard angioplasty.

Moreover, analysis of secondary endpoints demonstrated an almost 25% benefit in patency for the entire dialysis access for those patients treated with DCBs. "If you look at the number of repeat procedures needed to maintain function of the entire dialysis access at 6 months out, this was reduced by over 55%," Lookstein said.

Among the potential reasons for different trial outcomes, Lookstein noted that the Lutonix balloon contains a paclitaxel dose of 2 μg/mm^2, whereas the Medtronic balloon carries a dose of 3.5 μg/mm^2 (5). Differences in DCB inflation duration and thus drug exposure time may have played a role. The two devices also have different excipient characteristics. Trerotola also pointed out that with one-third of participants from Japan, the Medtronic study did not have exactly the same population, including a noticeably different ratio of upper-arm fistulas to forearm fistulas.

"At this point, there might or might not be a difference between the two devices," Trerotola said. He added that he would be interested to see a randomized trial of the two devices in this context to address the question directly.

Remaining research questions

Many other research avenues remain to be explored for DCBs. Lookstein noted that Medtronic is planning to perform a postmarket registry. "It will prospectively evaluate the efficacy and safety of the technology in the use of AV grafts as well as in patients who have had previous stents placed in their dialysis fistulas." The team is also hoping to evaluate whether DCBs might play a role in addressing central venous stenoses, which are common in this population, due to previous hemodialysis catheter placement.

"I think the postmarket registry data will allow us to generate data sets that will help us determine which patients are ideally suited for this technology compared to others," Lookstein said. "We are optimistic that we are going to be able to expand the indication to a broader spectrum of the population who have end stage renal disease."

Practical barriers

Lookstein noted that practically, it should be easy for specialists to integrate DCBs into clinical use for AV stenosis if their clinical judgment supports it. Most hospitals already have similar balloons on the shelf to address arterial blockages in the leg. "It would really just be an expansion of their current inventory to allow the technology to be brought in to treat patients with dialysis dysfunction."

However promising, it is unclear whether DCBs will now be used more commonly in this application. Although standard angioplasty is still the most common method of managing AV fistula stenoses, covered stents (also known as stent grafts) are sometimes used instead (6). Data from some randomized trials in AV fistulas have shown improved patency of the lesion and access circuit with stent grafts compared with standard balloon angioplasty (7). Partly because of this, reimbursement rates are higher for such stent grafts compared with standard angioplasty.

Both Trerotola and Lookstein pointed out that although stent grafts are effective for restoring short-term patency, they can eventually become restenotic and can make future surgical revision more difficult. Stents can fracture and embolize, erode through the skin, or become infected. In effect, by utilizing a stent graft instead of angioplasty with a DCB, one may be opting for short-term patency in exchange for longer-term issues.

"The big problem for the drug-coated balloons is that there is no payment for them," Trerotola said. Yet the use of DCBs might provide a huge savings to the healthcare system in terms of long-term improved dialysis access patency and a reduction in future procedures. Trerotola exhorts, "I hope this paper will be a burning message for [the Centers for Medicare & Medicaid Services] to do something about this reimbursement issue for clinicians."

"The reason that I am so enthusiastic about this technology is that it is a procedure that all vascular specialists understand and find easy to use," concluded Lookstein. "I think that it is a very simple, inexpensive technology that does not force the patient to have a permanent implant in their body that clearly benefits our patients with end stage renal disease."

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