The Unanswered Questions of Venous Stenting

Michael R. Jaff, DO, discusses the differences between the arterial and venous stent landscapes and what the future might hold.

Why does progress in the venous stenting arena remain so disparate from that of arterial environments?

The progression of venous stenting is far behind that of arterial interventions from a clinical trial and approval standpoint because, up until recently, industry was not really interested in venous intervention. For a long time, I don't think industry appreciated the number of patients who suffer due to central venous obstruction. Second, there was no predicate device for comparison. There was no clear pathway to device approval, so it was a little daunting to figure out how to get something approved on-label. It's a different vascular bed, so understanding the disease requires new focus that most companies did not have the expertise and resources to tackle.

I think the arterial side was addressed first because patients complained of symptoms related to leg artery blockage, and they ended up seeing vascular doctors. With venous disease, patients didn't routinely see vascular doctors most of the time unless they had very severe symptoms. They went to their primary care doctor, their internist, their OB/GYN, and those are not the physicians who would consider doing procedures to treat venous obstruction.

Lately, I think venous disease has caught on due to a few big, high-profile trials that highlighted the opportunities available to patients and industry: the ATTRACT trial from the National Institutes of Health, which is almost finished, and a couple of trials in Europe, such as CAVENT, which was published in *The Lancet*.

What factors outside of the anatomy/disease state have factored into this disparity (eg, regulatory challenges, industry attentions)?

The regulatory challenges are huge because the US Food and Drug Administration is determining clinical trial designs with individual sponsors. Comparisons of clinical trial designs have not yet occurred. In an arterial stent study in a leg, for example, we can follow patency of a stent with duplex ultrasonography and determine if restenosis occurs within a stent and the severity of the restenosis. In the venous circulation, determining thrombosis is one thing, but in-stent restenosis? There are no validated methods of determining this, either with ultrasound, CT venography, or even contrast venography. Therefore, there has been extensive debate over what the regulatory pathway for approval would be. In addition, from a design standpoint, the devices are different. They act in an environment in which the vessel wall is very thin, as opposed to in the artery, where it's muscular and strong. The flow in an artery obviously is very fast, whereas in the venous side, the flow is very slow, approximately 40 mm Hg. There are valves inside veins that aren't present in arteries. The complexities to develop a device to work in a vein compared are significant.

What are the main questions that need to be answered by current and future trials?

The ATTRACT trial has probably got it right in asking, does getting rid of a blood clot in a deep vein in a leg make the patient clinically better? We still don't know the answer to that question after all these years. Right now, most patients are treated

with blood thinners alone. Now that blood thinners are available in pill form, it makes it even easier—you don't have to give yourself a shot to treat a blood clot in a vein in a leg (or the lungs, for that matter). It's incredibly easy to do, and compared to bringing somebody into the hospital and performing a procedure, the initial costs of outpatient treatment will be significantly less. You must clearly show that doing a procedure to open up a clogged vein not only makes the patient better, but makes the patient better for a long enough period of time to prevent chronic complications from that blood clot, ultimately resulting in lower total medical expense.

Not only is there an issue with a clot that forms in a vein, but there is the additional concept of a vein being extrinsically compressed. Because veins have very thin walls, if an artery lies on top of the vein, this causes compression and makes the venous flow slow. This may result in long-standing leg swelling and make patients more prone to blood clots and even leg ulcers. The question there is, once you get rid of the blood clot, should you put a stent inside that narrowed/compressed vein? And if you do, does it stay open? How long does it stay open? Does it break like stents occasionally do in the arteries? We don't know any of the answers to those questions.

We also don't know what medical therapy the patients should receive once a stent is placed in a vein. Should patients receive blood thinners? Should they get warfarin and aspirin, aspirin and clopidogrel? We have no idea of the right answer.

What are the trials currently underway?

Cook Medical has a venous stent trial that began in January and is currently enrolling. Veniti, Inc. is also enrolling patients in their venous stent trial.

What is unique about venous stenting trial designs?

There are different types of patients who become eligible for these trials: the acute patients, with deep vein thrombosis of ≤ 14 days, and the subacute to chronic patients, which are those who have experienced symptoms > 14 days out to 30 days. Some say > 30 days is the chronic group. The way you manage those groups is going to be entirely different, so the indications for the devices will be different based on the patients that the companies select to study. Companies may have to do separate trials for each patient demographic or have different endpoints in one trial.

I think most companies interested in venous stenting will aim for the chronic indication, because if the patients have acute thrombus, the management would include percutaneous mechanical thrombectomy, thrombolytic therapy, and restore blood flow to the vein. But when the clot has been there for more than a couple of weeks, it damages the valves permanently, and the vein starts to scar, become atretic, and get smaller. You have to restore flow by opening it and deploy a stent to keep it open. It's potentially more difficult to perform.

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What are the key trial endpoints? How do these differ from arterial endpoints?

ATTRACT's endpoints include patency—can you keep a vein open after you remove the blood clot? Do you preserve the valve function in the veins so that blood flow is actually maintained in the appropriate direction? How does the patient feel, both acutely, following the procedure, and months down the road? We are doing quality-of-life surveys over time, and studying cost-effectiveness, which is, as I mentioned earlier, incredibly important. Of course, complications associated with the procedure—bleeding, recurrent blood clots, etc—will be closely studied.

I think other devices like stents and thrombectomy devices will use some type of anatomic outcome (is it still patent on an ultrasound or venogram?), as well as quality-of-life surveys. The survey that everybody seems to be gravitating to is the Villalta scale, which is well established and accepted as a reliable score. Physicians also use the Venous Disease Severity Score. ■

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