

Maintenance of Hemodialysis Access With Covered Stents

The salvage of hemodialysis access advances beyond angioplasty.

BY BART DOLMATCH, MD

The most recent national data show that at the end of 2006, nearly a third of a million Americans with end-stage renal disease were receiving renal replacement through chronic hemodialysis.¹ In order to receive hemodialysis, a person must have some type of vascular access that permits a large volume of blood to be cycled from the patient through the dialyzer and back into the patient. For most Americans on hemodialysis, vascular access is achieved through a vascular circuit with either a direct arteriovenous anastomosis (arteriovenous fistula [AVF]) or an interposed conduit between the artery and vein (arteriovenous graft [AVG]).

Both AVFs and AVGs are considered permanent hemodialysis access, although it is widely recognized that both of these types of access circuits are prone to failure on the basis of stenosis and thrombosis, as well as aneurysmal and pseudoaneurysmal degeneration. In Huber's meta-analysis of AVFs and AVGs, the primary patency of more than 1,800 AVFs was 51% at 18 months, but that does not include AVFs that never matured for use, often due to stenosis or thrombosis. In fact, in a recent multicenter prospective study of 877 AVFs,² 60% of all AVFs did not mature for use within 4 months, and more than half were abandoned without expectation of future use. When one looks at primary patency of an AVF based on the intention to use it for hemodialysis, the combined effect of failed maturation and attrition due to late stenosis and thrombosis would probably result in fewer than half of the AVFs remaining primarily patent and functional at 1 year.

For AVGs, early failure and maturity problems are not that common. Nevertheless, primary patency of a useable AVG is inferior to that of a useable AVF. In their meta-analysis, Huber et al found that primary patency for more than 1,200 AVGs was only 33% at 18 months.³ Miller et al⁴

reported 12-month AVG patency that was only 23% in their study of 256 AVGs. Most often, AVGs fail due to the development of stenosis at the venous anastomosis as well as in the venous outflow central to the graft.

AV ACCESS ANGIOPLASTY

The point is that there is a high failure rate for both AVFs and AVGs at 1 year, and both surgical and percutaneous options are available for maintaining hemodialysis access. Percutaneous transluminal angioplasty (PTA) has been widely adopted as a first line of therapy for AV access stenosis largely because it can be readily scheduled and performed (compared to surgical revision) due to the proliferation of outpatient treatment facilities where it is available.

AV access PTA has an extremely high technical success rate. In the early 1990s, Beathard⁵ reported that PTA was 94% anatomically successful (536 procedures in 285 patients) with a complication rate of 3%. In a more updated review, Beathard et al⁶ reported a 97% anatomic success rate in 1,561 AVF PTA procedures and a 98% success rate in 3,560 AVG procedures. The major complication rates were only 0.19% and 0.11%, respectively, for AVF and AVG angioplasties. Today, using the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) definition of post-PTA, anatomic success in which a treated lesion should have less than 30% residual stenosis,⁷ AV access PTA is widely seen as a terrific technique that effectively treats stenosis, maintains access function, and has few associated major complications.

Yet despite achieving an acceptable anatomic result in nearly all patients, the problem with AV access PTA is that it is not very durable. Recoil and neointimal proliferation at the PTA site frequently lead to recurrent stenosis within several months after PTA. Based on many reports, the

2000 KDOQI Vascular Access Clinical Practice Guideline 19 recommended a target goal of “50% unassisted patency at 6 months” after successful PTA of an AVG stenosis.⁶ Clearly, the expectation for PTA durability in AV access is much lower than that of PTA used almost anywhere else in the body, whereas failure of PTA in half the patients at 6 months would not be acceptable.

AV ACCESS STENTS AND PERCUTANEOUS CUTTING BALLOON ANGIOPLASTY

Once believed to hold promise in prolonging PTA patency, it is now accepted that stents offer no advantage over successful AV access angioplasty.⁸⁻¹¹ This is largely due to neointimal proliferation leading to in-stent stenosis (Figure 1). Contemporary use of stents in AV access intervention is

best summarized in the 2000 KDOQI Vascular Access Clinical Practice Guideline 19,⁶ which states that, “stents are useful in selected instances (eg, limited residual access sites, surgically inaccessible lesions, contraindication to surgery) when PTA fails.” Simply stated, stents are used as a PTA bailout. Although stents play a small role in AV access intervention, this role is nevertheless important. It is therefore surprising that during the past decade, the only stent that has actually received FDA approval for use in AV access is the Wallstent (Boston Scientific Corporation, Natick, MA), and it has been approved for use in central veins only.

Hopes that the Peripheral Cutting Balloon (Boston Scientific Corporation) would improve conventional angioplasty patency were dashed by the Cutting Edge trial, one of the few prospective, randomized, multicenter clinical trials

PIVOTAL INSIGHTS: STENT GRAFTS VERSUS PTA

An interview with Ziv J. Haskal, MD, lead investigator of the FLAIR trial, which compared endovascular stent grafts versus balloon angioplasty for the treatment of dialysis access graft failure.

What was the study design of the clinical trial to evaluate the Flair stent graft (Bard Peripheral Vascular, Inc., Tempe, AZ) in dialysis patients with stenosed accesses?

It was a prospective multicenter controlled trial, conducted at 13 sites. Ninety-seven patients were randomized to the Flair arm and 93 to the PTA control arm. The groups proved well-matched by more than 20 demographic, graft-type, medication, graft dysfunction, and other criteria.

How was follow-up conducted, and for how long? What are the efficacy milestones in this patient population, and how might they differ from those with other vascular indications?

To my knowledge, this study was the first controlled study to compare a treatment intended to improve access function and the patency of interventions at the venous anastomosis of failing AV access grafts with the current standard of care, angioplasty. It was notable in its definitions of patency by treatment area, as well as access circuit, which were novel at the time. The definitions dovetailed well with the then-published National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative guidelines and Society of Interventional Radiology Reporting Standards for Dialysis Access Interventions.

Some notable features included assessment of outcomes by clinical, hemodynamic, and anatomic results. We also performed mandatory 2- and 6-month catheter-based, magnified multiview venography in all patients independent of graft function, with external core lab analysis. This provided verifiable analysis of restenosis by anatomic criteria. The latter element aside, the study was driven by clinical criteria—the ultimate relevant end-

points. Graft function was the paramount issue, not simply percent restenosis.

One of the benefits of a prospective clinical study with uniform patency and outcomes definitions is removal of the reporting bias that accompanies the many retrospective feasibility papers looking at other dialysis therapies; that bias and lack of patient accountability typically results in inflated patencies for other therapies. As with other randomized trials, the sobering efficacy of the standard therapy—angioplasty—is revealed only then. Balloon angioplasty, performed by the experienced operators within the study, showed durabilities worse than the rosier ones reported by consensus of experts and retrospective series. We should settle for little less than controlled trials whenever possible in the area of dialysis access.

What else have the data shown?

The data have shown a clear and highly statistically significant improvement in graft patency, function, treatment area patency, freedom from interventions, and binary restenosis—all favoring the stent graft patients. This benefit persisted to the limits of the study analysis, at 210 days. This is a game-changer.

Based on your experiences in the trial, which patients responded most favorably to treatment using a stent graft?

We studied patients with patent but clinically failing prosthetic AV access grafts with venous anastomotic stenoses. These patients responded well, in very potent fashions. In simplest terms, I conceived the study, controversial at its outset, to validate the idea of an endovascular revision of an AV access graft, allowing immediate return to dialysis. Further, it converted an end-to-side surgical

regarding maintenance of AV access circuits. This study demonstrated that there was no patency advantage of the Peripheral Cutting Balloon over standard balloon angioplasty for treating venous anastomotic stenosis in AVGs.¹² The Cutting Edge trial not only found that the initial results and 6-month patency were similar for the Peripheral Cutting Balloon and conventional angioplasty groups but that there were more procedure-related complications in the Peripheral Cutting Balloon group.

COVERED STENTS FOR AVG STENOSIS

In 2004, a multicenter, randomized clinical trial of the Flair covered stent (Bard Peripheral Vascular, Inc., Tempe, AZ) was completed and reported in 2005.¹³ The Flair is a self-expanding nitinol stent embedded within expanded polyte-

trafluoroethylene (ePTFE) graft material. The Flair trial compared conventional PTA to PTA with immediate covered stent placement for treatment of stenosis at the venous anastomosis of AVGs (where most AVG stenoses develop). Unlike nearly all other AV access studies, the Flair trial required that both angiographic and clinical criteria be achieved in order for the AVG to be declared patent. In other words, if the access was functional without any clinical problem but a 50% stenosis was seen at the treatment site, patency was lost. Or if there was any report of AV access dysfunction (based upon KDOQI parameters and defined in the clinical protocol) but no stenosis was found anywhere in the AVG, then access circuit patency was lost. Finally, if the interventionist decided to treat a 30% stenosis in a fully functional access even though there were neither

anastomosis into an end-to-end anastomosis, hopefully reducing or slowing the development of the next edge stenosis. The logic of both of these points was proven. Interestingly, a recent independent flow analysis appears to further validate the design concept of the flared end of the Flair by showing reduced turbulence (and perhaps less shear stress) than with a purely tubular device.

Were any types of patients shown to be better candidates for angioplasty without stent graft placement?

Not specifically. We found that long stenoses performed better with stent grafts, as well as short ones, and that anticoagulation or antiplatelet therapy was irrelevant to the stent graft patients. We specifically excluded elbow joint lesions from the study. Thus, the role of the device across joints was not tested. I expect that well-performed angioplasty in one area is certainly appropriate. We also focused on treating patent but stenotic grafts, but not thrombosed grafts. Having said that, in my experience, there is a similar upside in stent graft revision of stenoses in occluded grafts as well.

In what ways is this procedure unique from placing a stent graft in a native vessel such as the superficial femoral artery (SFA)?

It is certainly unique—different disease, different anatomy, different endpoints. From a technical perspective, the access is relatively easy, because the access is local to the treatment area and easily seen under road mapping. SFA skills should place an operator in good stead for using this device, although a specific understanding of hemodialysis accesses and their unique needs is naturally essential.

Over the course of the trial, did you learn any technical do's and don'ts that might be helpful to interventionists interested in stent graft placement in stenosed accesses?

As with any new device, there are technical points that are essential to learn in order to maximize graft patency. Like other ePTFE stent grafts, graft expansion during release is slightly slower than a bare stent, owing to the amount of stent metal and graft material packed tightly into the deployment capsule. Thus, I release the devices more slowly, allowing them to partly self-expand, making small positioning adjustments before full release. Sizing is important, as with any stent graft. Oversizing this device, like ePTFE stent grafts, can possibly lead to incomplete graft expansion and the potential for greater luminal late loss. I use a marker catheter or generally size the device no more than 1 mm larger than the known caliber of the graft. Also, I choose device lengths that allow the downstream "landing zone" of the Flair to be entirely within the normal-appearing outflow vein. The ability to control long stenoses equal to short ones means that we can aim to control the entirety of the affected outflow vein during revision, not just the most critically stenotic segment. This prevents or delays restenosis. ■

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clinical nor angiographic criteria for failure, primary patency was lost.

Given the very high standard that each AVG had to pass and also noting that in both groups there were bona fide stenoses in dysfunctional AVGs, the patency rates for the entire study were much lower than studies in which only clinical outcomes are measured.

Requiring both angiographic and clinical patency success at 6 months, primary patency for AVGs in patients who received the covered stent was nearly twice as good as for patients who were treated with PTA alone (38% vs 19.8%; $P=.008$), and patency at the treatment site was more than doubled (50.6% vs 23.3%; $P<.001$). Not only did the Flair group have much better treatment site and access circuit patency, but some of the 6-month angiographic follow-up studies of the Flair demonstrated that a covered stent could remain free from hemodynamically significant stenosis. In some cases, there was negligible tissue anywhere within the covered stent or at either end (Figure 2), which was very different from the experience with bare-metal stents.

Now, largely based on these clinical data, the Flair has received FDA approval for primary use when performing PTA of AVG venous anastomotic stenosis, even when PTA is technically successful. With release of the Flair in the US, a larger randomized clinical study (the Post Approval Study of the Flair Endovascular Stent Graft [RENOVA] trial) has been initiated to collect data in 270 patients with venous anastomotic stenosis. The RENOVA study is an FDA-required postapproval trial. Although there are many similarities to the pivotal Flair study completed in 2004, the RENOVA trial will go further, following patients to 12 months after treatment. It is a prospective, multicenter, randomized trial of PTA versus Flair that will characterize outcome not only on the basis of AVG patency following PTA or Flair, but also freedom from intervention and time between interventions for both groups. Concurrently, there is a 280-patient prospective, multicenter, randomized clinical trial of the Viabahn Endoprosthesis (W. L. Gore & Associates, Flagstaff, AZ) for treating AVG venous anastomotic stenosis. This trial, the Vascular Access Revision with Viabahn Endoprosthesis vs Percutaneous Transluminal Angioplasty (REVISE) study, announced enrollment of its first patient in September

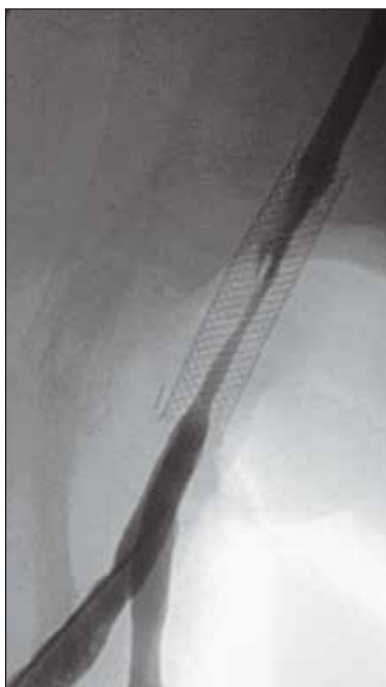


Figure 1. In-stent restenosis within a Wallstent after 5 months. This stent was placed at the site of venous anastomotic PTA to maintain patency; however, the patient returned with AVG dysfunction after 5 months due to ingrowth of neointimal tissue through the stent causing recurrent anastomotic stenosis.

2008. With both the RENOVA and REVISE clinical trials underway, it is hoped that we will get a comprehensive understanding of the role of ePTFE-covered stents in AVGs.

COVERED STENTS FOR AVF STENOSIS

Although clinical trials are being done to explore the role of covered stents in AVGs, today, there are fewer AVGs than AVFs largely due to the success of the Fistula First program.¹⁴ How do covered stents fare when used to treat stenoses in AVFs? There are very little clinical data. A recent retrospective, single-center report describes use of the Fluency ePTFE-covered stent (Bard Peripheral Vascular) to treat five stenotic AVFs with 80% 9-month patency.¹⁵ Shemesh et al described a series of AVF cephalic arch stenoses randomized to treatment with either angioplasty and bare stent (Luminexx, Bard Peripheral Vascular) versus angioplasty and covered stent (Fluency).¹⁶ The Fluency covered stent afforded superior primary patency, less angiographic restenosis, and fewer reinterventions compared to the bare stent, with a mean clinical follow-up of 13.7 months. Although covered stents may

be useful adjuncts to angioplasty in AVFs, larger studies are needed before covered stents can be broadly advocated for maintenance of AVF patency.

OTHER APPLICATIONS OF COVERED STENTS IN AV ACCESS

A few other potential applications of covered-stent technology in hemodialysis access should be mentioned, such as treatment of PTA-induced rupture, pseudoaneurysm repair, and as an adjunct to PTA during treatment of central vein stenosis and occlusion.

At the 2008 Society of Interventional Radiology meeting, we reported use of the Fluency covered stent to treat immediate PTA-induced rupture in both AVGs and AVFs¹⁷ with excellent technical success, although 6-month patency of the AV access was similar to reports in which bare stents were used to treat rupture. It is not clear why patency was not improved, although these access circuits may fail for many reasons, often related to the development of new stenoses elsewhere in the circuit.

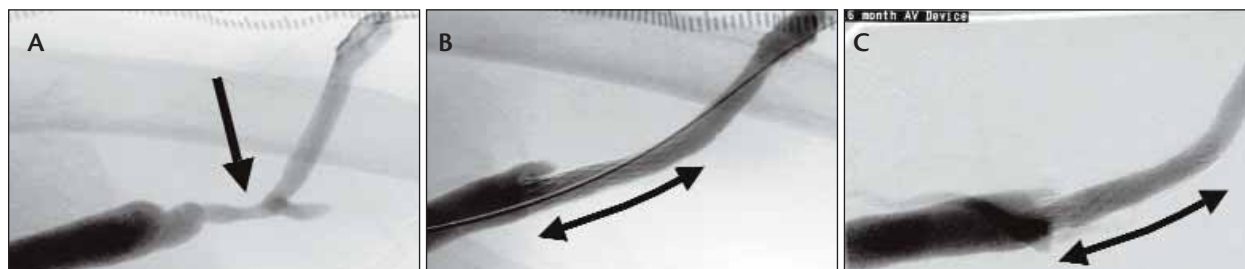


Figure 2. Stenosis at the venous anastomosis of a left upper arm AVG (arrow) (A). Post-PTA and Flair placement (double-headed arrow) (B). Sixteen-month angiogram demonstrating a widely patent Flair at the AVG venous anastomosis (double-headed arrow) (C).

There may be a role for covered stents in the treatment of AV access aneurysms and pseudoaneurysms as well. The Viabahn covered stent has been successfully used to treat AVG pseudoaneurysms, as reported by Vesely.¹⁸ These pseudoaneurysms form at the cannulation sites of the AVG due to repeated puncture of the graft material with dialysis needles. Treatment of these pseudoaneurysms with the Viabahn necessitated its placement at a cannulation site where it would be repeatedly punctured, so it was not a great surprise that Viabahn stent fractures were seen over time.

Finally, both Fluency and Viabahn covered stents have been used to treat central venous stenosis in hemodialysis circuits with anecdotal success, but so far, the data are insufficient to support this practice. Neither the Fluency nor the Viabahn were specifically designed for use in central veins, where covered stent length, diameter, design, and delivery system requirements are very different from what is needed in the AV access circuit, tracheobronchial, or peripheral arterial systems. While these devices may work better than PTA in central veins (although we do not know that for sure), they have not been optimized for this application.

CONCLUSION

The Flair covered stent is the first FDA-approved, stent-based device for use in peripheral AV access, where it is indicated as a primary treatment, rather than a bailout. Its approval was based on better patency than PTA when treating AVG venous anastomotic stenoses. Both the REN-OVA and REVISE clinical trials will likely add a great deal to our understanding of covered stent use in AVGs. Meanwhile, the challenges and opportunities that lie ahead include evaluation of covered stent usefulness in AVFs, AV access pseudoaneurysms, and central vein obstructions. ■

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