Supplement to

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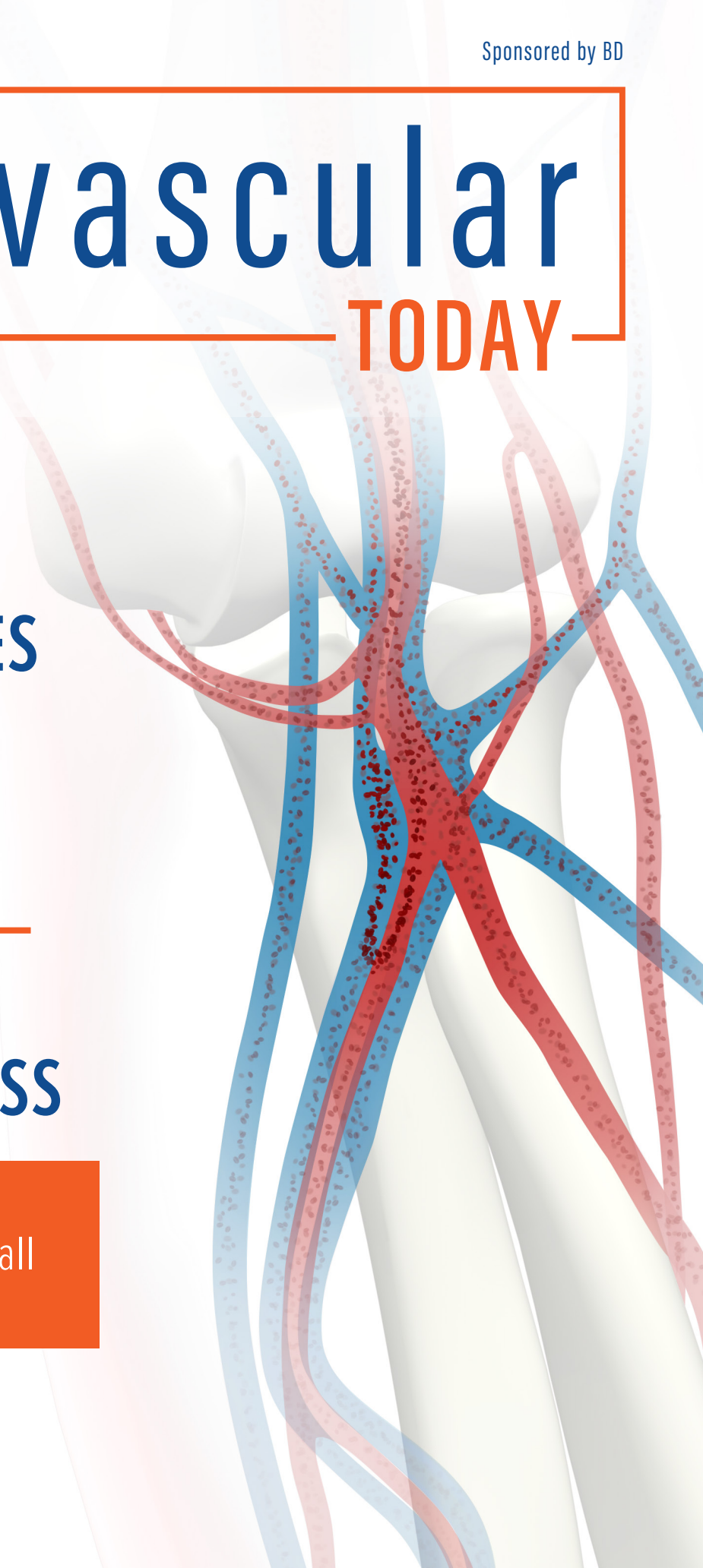
Endovascular TODAY

Fall 2019

NEW TECHNOLOGIES PUT THE THRILL BACK IN DIALYSIS ACCESS

Fistula Creation, Maintenance, and Overall Patient Management



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NEW TECHNOLOGIES PUT THE THRILL BACK IN DIALYSIS ACCESS

At BD, our commitment to patients extends beyond selling innovative product solutions—we are also passionate about expanding the breadth and depth of the physician's practices to support the delivery of patient care through our comprehensive and wide-ranging approaches. Our portfolio includes more than 100 different training events this year that are focused on end-stage kidney disease (ESKD) education for the multidisciplinary treatment team (nephrology, interventionalists, surgeons, ultrasound technicians, and dialysis nurses and technicians).

Our ADVANCE Professional Development and Clinical Education programs in the area of ESKD and the important element of vascular access support physicians' professional growth by providing shoulder-to-shoulder training with globally recognized experts and collaborators using innovative interventional tools, such as Fluency® Plus Endovascular Stent Graft, Covera™ Vascular Covered Stent, and Lutonix® 035 Drug Coated Balloon PTA Catheter, which are designed to address the frequent and challenging lesions in the arteriovenous (AV) circuit.

We also offer training on how to create an endovascular AV fistula (endoAVF) using a catheter-based system as an additional option to surgical creation. Our WavelinQ™ 4F EndoAVF System training, partnering with world-class Centers of Excellence around the country, utilizes innovative procedural simulations and learning programs to provide exceptional peer-to-peer clinical discussions and practical hands-on experience. The WavelinQ™ 4F EndoAVF System consists of using two thin, flexible magnetic catheters inserted in adjacent blood vessels in the arm, and after a small burst of radiofrequency energy, an endovascular fistula is created. This training program extends beyond the procedural aspects of fistula creation, including education on patient selection for ultrasound technicians during vascular mapping and supporting dialysis centers on cannulation of this new endovascular fistula.

Our dedication to restoration and maintenance of the AV access circuit is demonstrated through our comprehensive educational programs that are designed to help you as clinicians deliver exceptional patient care across the entire disease state, which in turn, helps your patients.

—JD Meler, MD
VP, Medical & Clinical Affairs
BD Peripheral Intervention

BD-10848

In August 2019, the U.S. Food and Drug Administration (FDA) issued an updated letter to health care providers noting an increased risk in late mortality (2-3 years post-treatment) with paclitaxel-coated devices when used to treat peripheral arterial disease in the femoropopliteal artery as compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel-coated device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients. BD will continue to work collaboratively with FDA and industry for additional safety data collection and inform labeling as appropriate. These communications as well as information about the FDA Panel meeting can be found at: https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel.

All authors of this supplement were compensated by BD.

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In the Spirit of Medical Innovation

BY DHEERAJ RAJAN, MD, FRCPC, FSIR, FACR

It has always been the dream of any physician who performs dialysis interventions to create a dialysis access percutaneously. When I was asked in 2011 to join TVA Medical (now part of Becton, Dickinson and Company), to be a part of the early stage development team of the WAVELINQ™ EndoAVF System, I thought, "Okay, the concept may work theoretically, but it won't work in practicality." As the device and technique took shape, it was very exhilarating to witness our ability to perform procedures that resulted in patent dialysis fistulas. After our initial success, the thought was, "Let's keep going, let's do better, let's create more opportunities." That spirit of innovation, translated over the last 8 years, has led us to where we are now (Figure 1). I believe that the WAVELINQ™ 4F EndoAVF System gives physicians the ability to shorten the time between the original need for a fistula and actually getting it done because a surgical consult or procedure is no longer needed. Instead, if a patient comes in for a dialysis catheter, an endovascular arteriovenous fistula (endoAVF) can be created at that same visit. I would assume that many of you have dreamt of creating a functional percutaneous dialysis access as I did in the past, and you now have the opportunity to do it. I think that this will be pivotal in your practice. It's an innovative, minimally invasive approach that I think patients will seek out and will stimulate further innovations. ■

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DEVELOPMENT OF THE ENDOAVF

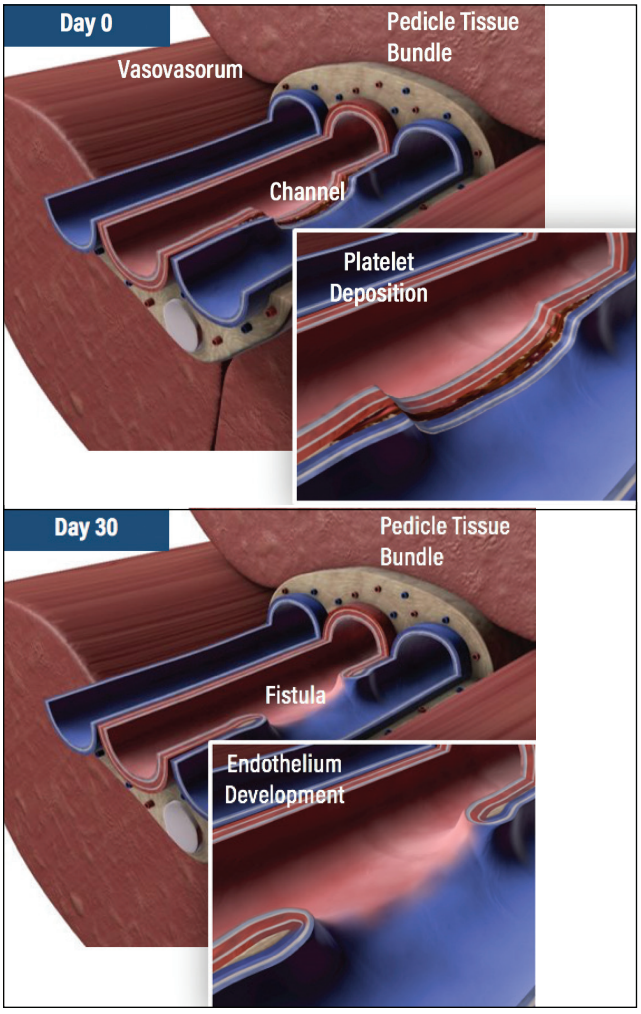

Figure 1. The endoAVF develops from a channel cut through tissue. Then, the blood follows the path of least resistance from artery to vein. Initial platelet deposition leads to endothelium development over time (within 30 days).

BD-10643

ROUNDTABLE DISCUSSION

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From a Patient's Perspective: Multiple Views Focused on the Best Patient Care

Experts discuss challenges and concerns that dialysis patients face, decisions surrounding the type of vascular access, how to improve the dialysis patient's experience, and the role of endoAVFs in patient satisfaction.

WITH ALEJANDRO ALVAREZ, MD, AND CHARMAINE LOK, MD

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Why is vascular access so crucial for dialysis patients, and what are the biggest challenges or concerns that dialysis patients face with vascular access?

Dr. Alvarez: Vascular access is crucial for dialysis patients because it is their lifeline. Dialysis patients need an access that can handle high blood flow volume for delivering dialysis. One of the main challenges dialysis patients face is failure of their vascular access modality. A major barrier to increasing the usage of arteriovenous fistulas (AVFs) is the high failure rate, including their failure to mature to be used for dialysis. They are left with an alternative option of arteriovenous grafts (AVGs), which mature faster but require more frequent interventions. A central venous catheter (CVC) allows for immediate use but has an increased risk of infection that can lead to metastatic infections, such as osteomyelitis or endocarditis, which eventually increase morbidity and mortality.

Dr. Lok: A hemodialysis patient cannot undergo life-sustaining dialysis without a reliable connection between the dialysis machine and his or her body's circulation: the vascular access. Interestingly, the biggest challenges patients face with their vascular access may not necessarily be the same as their biggest concerns. For example, a patient's comorbidities and vessels may result in a fistula that is challenged to ever mature, yet the patient's main concern may be their fear of cannulation pain or fistula disfigurement. The challenges with vascular access depend on many variables, including the type of vascular access a patient is considering or already has. For simplicity, AVFs and AVGs will be referred to as arteriovenous (AV) access, and CVCs will refer to tunneled hemodialysis catheters. Both vascular access challenges and patient concerns can then be broadly considered through the patient's "vascular access journey" as before access creation, during creation, and after creation. A subset of key challenges according to vascular access type by phase of journey are listed in Table 1.

In your experience, how do you see your choice of vascular access benefiting patient experience?

Dr. Alvarez: Ideally, these patients should be referred when they have stage 4 chronic kidney disease. Then, the patients can plan the modality of dialysis and the kind of access. If the choice is hemodialysis, an access can be planned such that a hemodialysis catheter may be avoided in a majority of patients. If an AVF is created at this stage, it will allow ample time for the AVF to mature, as well as for assisting maturation percutaneously (if needed) and exploring the possibility of surgical revision or conversion to an AVG. Ideally, the access can be tailored to the specific needs of the individual patient. Some patients may be candidates for a fistula as primary access and others for an AVG or catheter.

TABLE 1. KEY CONSIDERATIONS AND CHALLENGES TO VASCULAR ACCESS BY TYPE AND PHASE

Type of Vascular Access	Focus	Precreation (Planning)	Creation	Postcreation (Maintenance)
AV access	Patient	▪ Comorbidities: cardiac condition, diabetes status, peripheral vascular disease ▪ Functional status, support system (may limit ability of patient to attend necessary preoperative investigations or follow necessary preparatory instructions) ▪ Previous and future access and its impact on currently planned access ▪ Patient's concern about cannulation pain, disfiguration	▪ Ability to administer desired anesthesia for optimal outcomes (eg, need ultrasound to guide regional axillary block) ▪ Limitations based on comorbidities	▪ Timely and appropriate postcreation procedure follow-up ▪ Ongoing monitoring for complications (eg, high-flow heart failure)
	Vessel	▪ Size, distensibility, location, and depth to allow for future cannulation ▪ Impact of previous medical procedures (venipunctures, peripherally inserted central catheters, cardiac interventions) on ability to create AV access	▪ Ability to create desired anastomosis to allow for proper AV access maturation and cannulation—sometimes, what is planned preprocedure may not be feasible at the time of creation	▪ Ongoing monitoring for cannulation "readiness" ▪ Ability to cannulate and accept required flows for adequate dialysis ▪ Monitoring for complications (patency, infection, steal syndrome, aneurysms)
CVC	Patient	▪ Patient's concern about insertion pain, cosmetic appearance, ability to swim/shower	▪ Ability to position properly for insertion (eg, the patient may not be able to lie flat if volume overloaded)	▪ Concerns about accidental dislodgement, cosmetic appearance, ability to swim/shower
	Vessel	▪ Previous procedures/vessel manipulations and stenosis may impact insertion ability and location	▪ Ability to insert in cases of severe central occlusion/ stenosis	▪ Concerns of malfunction and infection

Abbreviations: AV, arteriovenous; CVC, central venous catheter.

Dr. Lok: My choice of vascular access would take into consideration the current feasibility and future access needs. This considers patient and vessel characteristics, the patient's history and end-stage kidney disease life plan,[1] and local resources. Importantly, my choice aims to align with the patient's own wishes and dialysis goals. Doing so will hopefully improve patient experience, which directly impacts patient satisfaction.

Why are patient approval measures one of the most important factors to consider when treating dialysis patients?

Dr. Alvarez: Hemodialysis patients go to dialysis three times a week. If you can provide them with an access that minimizes the times they have to come for an intervention, then this will contribute to their satisfaction. It is important to remember that their life does not revolve around dialysis. They also see their primary doctor and other subspecialists regularly, and they still need personal time for their family and work. It is our responsibility as caregivers to guide them to choose a dialysis modality and access that will best accommodate their daily routine with minimal disruption.

Dr. Lok: When treating dialysis patients, we need to remember that dialysis is not just a one-time treatment; it's part of their life and daily routine. It becomes a key part of their lifestyle. Because vascular access is so critical for dialysis, their satisfaction with their vascular access becomes an important measure of the quality of that part of their lifestyle (dialysis). But what matters most to patients when it comes to their vascular access?

According to the SONG-HD Vascular Access project, what matters most for vascular access is vascular access function, which is measured by the rate of interventions.[2] Interventions are often associated with negative patient experience due to the inconvenience (time required, extra facility visit), cost, and discomfort. By extension, the patient can become dissatisfied. Although vascular access and hemodialysis care may not fully improve patient satisfaction, it can add to it—or at least not detract from it! Reliable vascular access with few complications/procedures and low maintenance is the goal to help increase patient satisfaction with vascular access care.

Why is extending the time between reinterventions important to a dialysis patient?

Dr. Alvarez: Of all stakeholders, the patient is most important. If we decrease the number of interventions, it will mean more time for family or work and translates to better patient satisfaction.

Dr. Lok: As mentioned previously, the rate of interventions is a measure of vascular access function and a primary concern for patients. Any time free from interventions means more time not in traffic, not in a waiting room, not sedated, and not in pain. It's similar to the longer the time away from the dentist, the better! It means more time to do what the patient really wants.

What role do you think endovascular AVF (endoAVF) creation could play in reducing catheter incidence?

Dr. Alvarez: I think endoAVFs could reduce the incidence of catheters. The technique itself broadens the number of potential providers who can create fistulas. Currently, mainly surgeons create surgical AVFs. In theory, if the number of physicians capable of creating AVFs increases, the time from consult and screening to creation and maturation should decrease.

The endoAVF technique lends itself to potential same-day creation. With adequate expertise, this technique allows for same-day creation just like with any other endovascular intervention for AV access. The patient could potentially arrive in the morning for initial consult, be screened with ultrasound, and if the patient is a candidate, the endoAVF could be created that same day under conscious sedation. EndoAVFs can make things more efficient for patients without compromising quality.

Dr. Lok: I do think an endoAVF can reduce catheter incidence, especially in incident dialysis patients. There are many benefits to this, including not exposing patients to the associated risks of catheter-related complications, inconvenience, and costs. Furthermore, data suggest that patients who have a fistula without previous ipsilateral catheters have superior fistula survival. Overall, I think this adds positively to overall patient experience.

Do you think that an endoAVF procedure affects the appearance of a patient's vascular access, and could this affect overall patient satisfaction?

Dr. Alvarez: Appearance is just as important to patients with renal disease as it is for anyone else. With my patients, it appears that disfigurement due to aneurysmal degeneration is less with endoAVF. One of the most appealing aspects of the procedure is the absence of a surgical scar. As an example, one of our young patients had a family history of kidney disease; his father received dialysis toward the end of his life. The patient refused a surgical AVF because his dad had large disfiguring "bumps." When endoAVF was offered as an option, he moved forward with the procedure. He loves it and is currently catheter free. This technology has been a game changer for our patients. In fact, word of mouth has led to some patients asking their primary nephrologist for referral to be evaluated and screened for endoAVF.

Dr. Lok: Early experience with the endoAVF appears promising with regard to its appearance—but longer time will tell. Given the distribution of flow, the procedure may contribute to the cosmetic appearance. Therefore, if patients are happy with the appearance of their endoAVF, it would contribute to their satisfaction. ■

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BD-10694

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Clinical Utility of the WavelinQ™ EndoAVF System

Considering future options and analyzing current application in predialysis patients, basilic and brachial vein fistulas, and conditioning poor veins.

BY NICHOLAS G. INSTON, PhD

Definitive vascular access is a key element in the pathway of care for patients requiring hemodialysis. The arteriovenous fistula (AVF) was first described in 1966,[1] and although new anatomic sites and configurations have been described, few improvements in outcomes have been made.

Well-functioning autologous AVFs have demonstrated superiority over prosthetic grafts and central venous catheters (CVCs), but they are not without problems.[2-4] The failure rate of surgical AVFs is dismally high, with 28% to 53% never becoming functional for dialysis.[5]

AVFs that are never adequate for dialysis are defined as failure to mature (FTM), occurring in around 25% to 40% of cases.[6-8] Maturation is dependent on vessel remodeling and the endothelial response to dramatic changes in venous blood flow. Poor vessel selection, vessel trauma from surgical manipulation, and abnormal patterns of blood flow are all implicated as causes of FTM. Modifications to surgical techniques and devices developed to reduce FTM have been described but have not been widely adopted.[9,10]

Even when successful, AVFs have a high incidence of dysfunction and late failure from nonthrombotic causes such as aneurysm and steal syndrome or, more commonly, from stenosis and thrombosis.[11]

THE ENDOVASCULAR AVF

A recent technical advance in vascular access creation is the WavelinQ™ 4F EndoAVF System (BD; formerly everlinQ, TVA Medical). This is the next-generation device, innovating the design from its predecessor, the WavelinQ™ 6F EndoAVF System. This endovascular AVF (endoAVF) device consists of a dual magnetic catheter system with a venous and arterial catheter, which creates a fistula in the proximal forearm via a percutaneous route, without the need for surgical incision or suturing (Figure 1). The catheters can be introduced from the upper arm or wrist* in a parallel or antiparallel fashion and are guided to the creation site with fluoroscopic imaging (Figures 2 and 3). A radiofrequency energy burst creates a channel between the radial or ulnar artery and one of the adjacent paired deep veins, a previously underused creation site. Blood flows from this anastomosis through a venous perforator into the superficial veins (either the cephalic vein, the basilic vein, or both). To direct blood flow superficially, coiling the deep vein is recommended. Suitable anatomy to create this type of fistula is estimated to be present in up to 90% of the population.[12]

A GROWING CLINICAL EVIDENCE BASE

Both the 6- and 4-F systems have been investigated in several clinical studies and are commercially available in Europe, Canada, and the United States. The FLEX study was a safety and feasibility study of the WavelinQ™ 6F EndoAVF System. Results were favorable, and an endoAVF was successfully created in 32 of 33 patients. Cumulative patency at 6 months was 96.2%, and the mean time to maturation was 58 days.[13]

The FLEX study was followed by the international, multicenter NEAT study, which demonstrated a procedural technical success rate of 98% (59 of 60 patients) and a 12-month primary patency rate of 73% (88 of 91 patients) (Kaplan-Meier estimate).[14] Device- and/or procedure-related serious adverse events were reported in 8% of patients (5 of 60 patients). Eliminating the use of closure devices has been recommended, along with using a stabilization arm board. The requirement for further interventions was low at 0.46 interventions per patient-year.

Although the WavelinQ™ 6F EndoAVF System requires contrast imaging, the doses can be low and no adverse impact on kidney function in predialysis patients has been demonstrated; in fact, 76% of predialysis patients in the NEAT study did not initiate dialysis during the 12-month

*In the United States, the safety and performance of the device via arterial wrist access have not been fully established. The incidence of vessel stenosis or occlusion that occurs in the radial and ulnar arteries after arterial wrist access has not been evaluated. The endoAVF should only be created using brachial artery access. Please consult the instructions for use for indications, contraindications, hazards, warnings, and precautions.

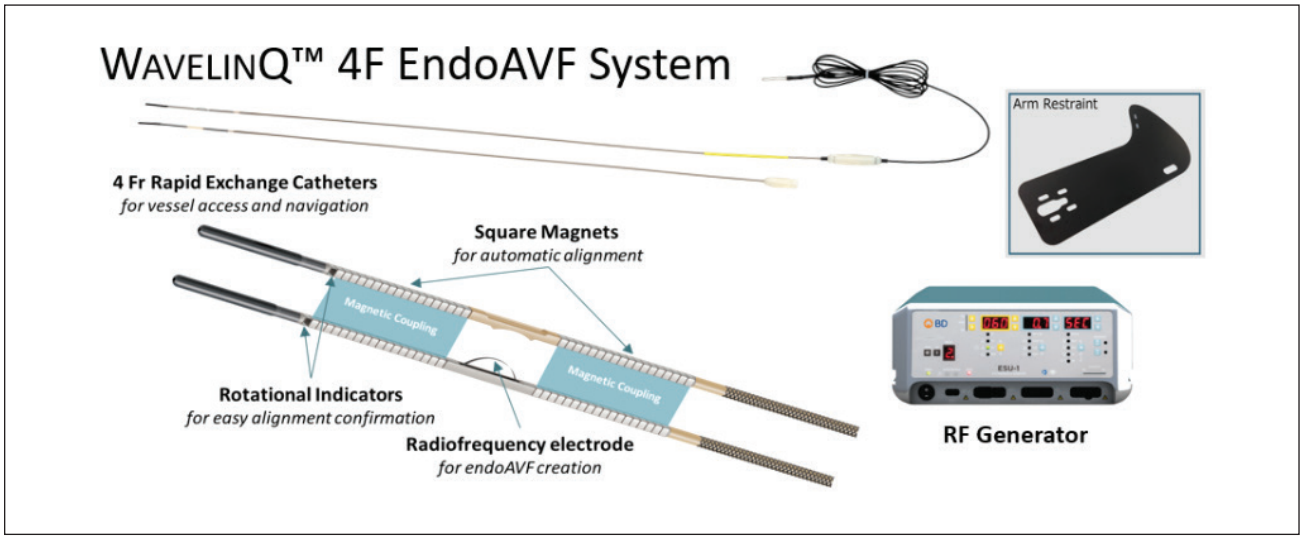

Figure 1. WavelinQ™ 4F dual catheter system for creation of endoAVFs. The device consists of an arterial and venous catheter, which are inserted via an upper arm, wrist, or antiparallel approach into the forearm vessels. They oppose magnetically, allowing a radiofrequency burst, which creates a fistula.

study follow-up, despite undergoing the fluoroscopy-based endoAVF procedure.

CONSIDERATIONS FOR USE OF THE WAVELINQ™ ENDOAVF SYSTEM

Current guidelines precede the introduction of endoAVFs and, therefore, do not include specific recommendations for when it is appropriate to choose one.[15,16] When compared with a surgical AVF cohort using matched propensity scoring, the WavelinQ™ 6F EndoAVF System demonstrated lower average first-year costs per patient-year associated with postcreation procedures.[17]

Because the WavelinQ™ EndoAVF System creates a native autologous AVF, it logically fits into the standard algorithm for AVF creation locations. The WavelinQ™ EndoAVF site is in the proximal forearm; a distal-first approach would imply use of the endoAVF when a radiocephalic AVF is not an option but prior to an upper arm fistula. However, considering the patency and low intervention rate of the WavelinQ™ EndoAVF System and the high failure rates of radiocephalic AVFs,[16] some physicians may consider creating an endoAVF with the WavelinQ™ EndoAVF System as a first option for certain patients.

Use in Predialysis Patients

Guidelines support the creation and establishment of a working AVF at the initiation of dialysis.[15,16] Despite these recommendations, the number of patients starting dialysis with a CVC is high.[18]

The WavelinQ™ 6F EndoAVF System may offer advantages for predialysis patients. The approach is minimally invasive and does not require surgery. The created fistula results in a shared flow between the cephalic, basilic, and brachial veins. This may account for the low incidence of subsequent complications. In the WavelinQ™ 6F EndoAVF System studies to date, no aneurysms and only one incidence of steal syndrome have been described, and the need for secondary interventions to maintain patency was much lower than with surgical AVFs.[13,14,17] This would be especially advantageous for predialysis patients in terms of decreasing the likelihood for multiple procedures, along with the associated contrast that may be needed to support the use of their fistula.

Because the upper arm vessels all receive blood flow from the anastomosis in the forearm, they all become potential fistula conduits and facilitate combinations of cephalic and/or basilic vein cannulation zones.

Further studies are required to assess the impact of the WavelinQ™ EndoAVF System on patients who started dialysis with a CVC, but this approach appears attractive, particularly when the consequences of a failed surgical AVF and the use of CVCs are poor, both clinically and economically.[19,20]

The Conditioning Fistula

In my experience, creation of an endoAVF with a WavelinQ™ EndoAVF System may be an option for patients with marginal superficial veins deemed not suitable for a surgical AVF. The creation of an endoAVF in the proximal midforearm vessels may be a viable option. With brachial vein coiling, blood flow can be directed into the superficial system via the perforator, which may result in superficial

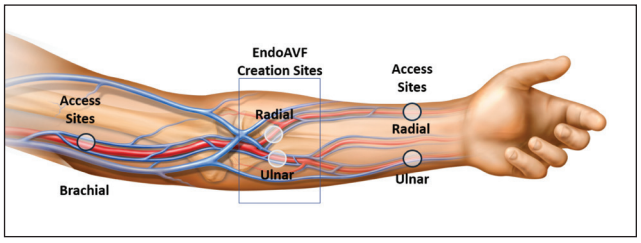

Figure 2. The catheters can be introduced from the upper arm or wrist in a parallel or antiparallel fashion and are guided to the creation site with fluoroscopic imaging. Note: In the United States, only the brachial artery should be used for arterial access. Illustration by Mike Austin. All rights reserved.

vein remodeling. This may result in superficial veins that mature sufficiently for cannulation or simply enhance the vessels such that a surgical or radiologic procedure can be subsequently employed to create a suitable autologous surgical AVF and avoid prosthetic grafts and CVCs (Figures 2 and 3).

BASILIC AND BRACHIAL VEIN FISTULAS

In my practice, the basilic vein is a useful second- or third-line access option. With good anatomy, a basilic vein fistula can be created in a single-stage procedure. However, in many cases, it is divided into two stages; the first stage is creating the anastomosis at the elbow, and then a superficialization and transposition of the basilic vein is subsequently performed at 4 to 6 weeks when the vessel has dilated and matured.

The WAVELINQ™ EndoAVF System can be used as a minimally invasive approach to the first stage of this process. The advantages over a surgical approach are that more length is available for the second-stage procedure because the anastomosis is in the forearm and there is no scar tissue at the site of mobilization (Figure 4). This may help reduce the incidence of basilic angle of transition lesions because angulation of the swing segment may be optimized.[21]

In many patients, the basilic vein communicates with the brachial veins, and a basilic vein fistula is not an option.[22,23] The WAVELINQ™ EndoAVF System may provide a suitable option for these patients because the blood flow will pass through the path of least resistance, creating a suitable conduit for superficialization and transposition. The resultant fistula may be a brachial–basilic or a transposed brachial vein alone.

LONGER-TERM OPTIONS

Data have demonstrated fewer complications and reinterventions with the WAVELINQ™ EndoAVF System compared with surgical AVFs, although long-term data are awaited.[17] A possible benefit of the split-flow WAVELINQ™ EndoAVF System is the flexibility it creates for future options. Unlike single-draining conduits, if an endoAVF has issues with the cannulation vein, the blood flow will subsequently be redirected. An example would be a postcannulation hematoma compressing the fistula vein. In this setting, the fistula will be kept open by collateral drainage and allow resolution of the issue without occlusion of the anastomosis or loss of the fistula. In the event the cephalic vein requires a tie off, the basilic and brachial veins will already have matured, allowing for an immediate solution rather than having to create a new fistula and await maturation.

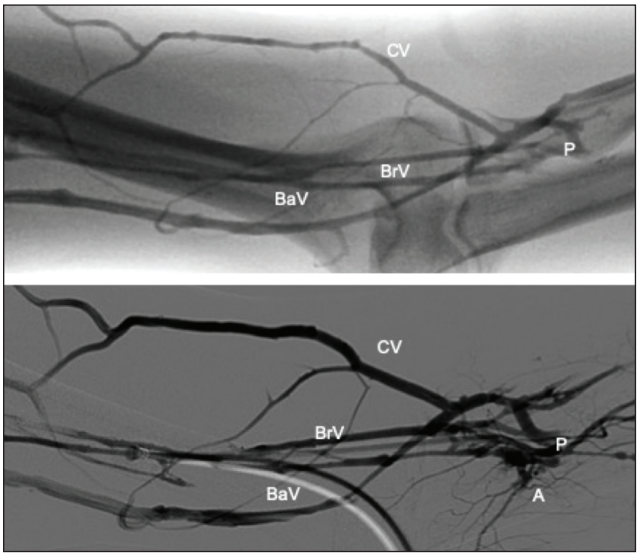

Figure 3. The upper fluoroscopy picture (top image) is a preprocedure venogram showing marginal vessels in the upper arm. The site of the perforator (P) can be seen in the proximal forearm. The bottom image was taken immediately after the creation of a WAVELINQ™ EndoAVF (A) in the same patient. The cephalic vein (CV), the basilic vein (BaV), and brachial vein (BrV) all have increased flow and the potential to mature into suitable fistula conduits, although the CV appears to be the dominant vessel in this patient.

THE FUTURE OF ENDOAVF

The introduction of the WAVELINQ™ EndoAVF System into clinical practice is welcomed. Surgical fistulas, the mainstay and gold standard of dialysis vascular access for so long, are far from a perfect option. The evidence to date supports endoAVFs created using the WAVELINQ™ EndoAVF System in terms of technical success, patency, and reduced interventions. Further benefits may be realized from this approach across various aspects of the patient pathway, from predialysis use to tertiary access options.

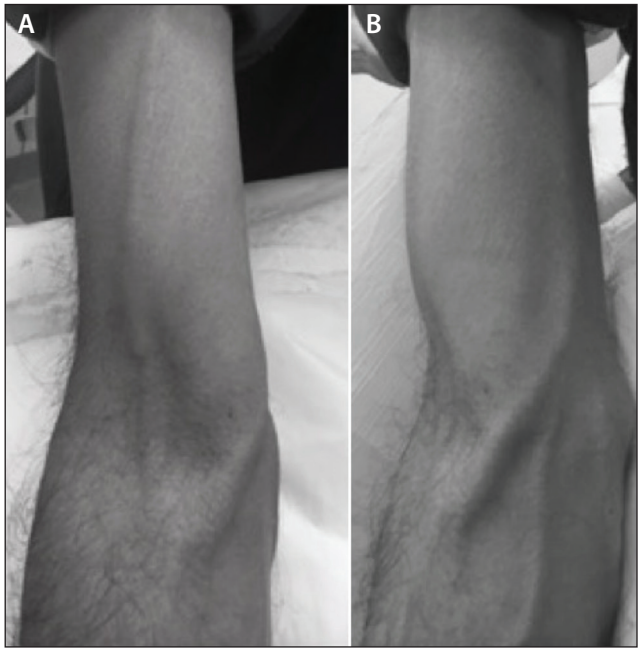

Figure 4. Clinical photographs of WAVELINQ™ EndoAVFs. Note that there is no antecubital scar and the fistula arises in the midforearm. Label A demonstrates that the cephalic and basilic vein have become suitable cannulation candidates. Label B demonstrates excellent development of the basilic vein suitable for a surgical transposition. (Picture reproduced with patients' permission.)

The endoAVF appears to offer increased opportunities in vascular access. The potential for extending options in the vascular access pathway requires further exploration to maximize their use for patient benefit. ■

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BD-10758

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PANEL DISCUSSION

How Do You Utilize Your Network Partners Cohesively to Successfully Create an EndoAVF Program?

Experience-based insights of initiation and adoption of endoAVF creation using the WavelinQ™ EndoAVF System.

WITH ALEJANDRO ALVAREZ, MD; AURANG Z. KHAWAJA, MD; AND GEORGE L. MUELLER, MD

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We run an outpatient vascular access center under the umbrella of ambulatory services of our hospital. We provide customized care to each patient. This allows the entire team to provide an experience for the patient that feels as though the process is an extension of the referring physician's practice. We keep the referring physician updated regarding the treatment and plan for his/her patient; every study—from screening, creation, and follow-up to cannulation—is made available. This allows us to set up expectations for both the patient and the referring nephrologist to maximize success.

With this kind of open communication, we are able to work as a team when the arteriovenous fistula (AVF) is ready for cannulation. We perform follow-up blood flow volume studies using ultrasound to confirm that the AVF has met blood flow volume and anatomic criteria for cannulation, per our facility's protocol (Qb > 500 mL/min and a venous outflow diameter of > 5 mm). The AVF is mapped on the surface of the skin prior to first cannulation, and a representative from our center (typically our nurse practitioner) and a clinical specialist from BD are usually present at first cannulation. At this time, the process comes full circle. The onus of this communication primarily falls on the physicians. As leaders of this multidisciplinary team, we make sure that expectations at each step of the process are clear for everyone (physicians, nurses, technicians, and most importantly, the patient), and we make ourselves available as a resource to maximize success—ultimately, cannulation and delivery of hemodialysis through a working fistula. To achieve this goal, we work closely with vascular surgeons who provide the necessary support to ensure success. This includes all of the surgical interventions when necessary, from transposition of deep fistulas to surgical revision of AV anastomosis when patients cannot be treated endovascularly.

When a patient is referred for endovascular AVF (endoAVF) evaluation, we screen the patient to determine if they are a candidate for the AVF procedure, and if candidacy is determined, they are usually scheduled for creation within a week. This decreases the time from first visit to creation, which should translate into faster cannulation of the fistula and decrease the risk of starting dialysis with a tunneled catheter.

In a situation where a patient is not a candidate for endoAVF, we proceed with full vascular mapping and the patient leaves the center with alternative options for vascular access creation. We then set up an appointment for the patient with a vascular surgeon, and all of the screening studies are communicated to the referring physician and the AV access surgeon. The idea is to make the process easy for the patient, the vascular surgeon, and the referring nephrologist.

Ultimately, this program should provide a quicker turnaround time for creating a successful AV access, whether it is an endoAVF or a surgical AVF.

BD-10756

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Planning, initiating, and establishing an endoAVF program requires a collaborative multidisciplinary approach between clinical and nonclinical stakeholders, and at our tertiary referral center, this has followed a long, cultivated, and deeply embedded culture of cross-specialty collaborative working. The first step is an up-to-date, in-depth knowledge and analysis of the local dialysis landscape, including operational characteristics and potential effects that an endoAVF program may have.[1] This allows development of a robust business case outlining potential collaborative benefits. Introducing a program can be approached in a three-step process[2]:

1. Feasibility analysis of current collaborative infrastructure and developing a strategic framework with appropriate knowledge acquisition, exchange, and expansion
2. Preparation of a formal proposal based on the aforementioned structure
3. Execution of the proposal, implementation of the program, and continued development and expansion under standards of care across all stakeholder domains

From our center's experience, adoption of a patient-centered approach that considers the benefits versus risks for all stakeholders can aid in developing a suitable, sizable, and sustainable program. Evidence reported in the literature has highlighted clinical efficacy and safety of an endoAVF program across various geographic populations, and the clinical efficacy and safety has been reproduced between study sites.[3-9] The higher costs of the endoAVF device as compared with a surgical AVF may be justified by the potential for reduced risk of maturation failure, reduced number of interventions for maintenance in the first year after creation, and potential for dialysis catheter avoidance.[4,10-13]

Deriving from our experience and based on existing literature, a framework may be proposed for initiation and development of a collaborative endoAVF program:

- **Recruitment.** What is the target renal patient population and what are the conceptualized benefits? How will patients be approached?
  - Predialysis and on dialysis
  - In center versus home versus satellite unit dialysis
  - Certain or targeted centers to build up experience
  - Failing transplant patients and peritoneal dialysis converters
- **Training the trainers.** Is there good stakeholder support and multidisciplinary collaboration to build on existing knowledge and promote knowledge exchange?
  - Dialysis nursing staff and technicians
  - Surgeon with an interest in dialysis access
  - Interventional radiologist with an interest in dialysis access or interventional nephrologist
  - Nephrologist with an interest in dialysis access or access outcomes
  - Management and/or administrative staff heavily invested in the targeted population
  - Local, regional, or national authorities' support for cultivating culture of native dialysis access
- **Infrastructure sustainability.** What is the capacity of the facility's dialysis program and ability to accommodate an endoAVF program?
  - Is access creation capacity being/been reviewed, whether it is a surgical, radiologic, or interventional nephrology lead, including educational needs?
  - Is access maintenance capacity being/been reviewed?
  - Has sufficient capacity in the targeted recruitment patient population and suitable educational potential for sustainability been determined? Positive patient feedback may drive demand and has been a trend observed in our experience after initiation of endoAVF creations.
  - Will the targeted population have access to respite/fallback care (eg, tunneled dialysis catheter care, alternative or other potential access, in-center support)?
  - What are the targeted costs compared with long-term cost savings related to admissions, interventions, and medications (ie, expect initial costs to be disproportionate with subsequent balance achieved as the program expands)?

Stakeholder involvement is critical, as is patient voice.[14-16] Performing structured or semistructured interviews and dialysis unit educational seminars via a variety of media can simultaneously promote awareness and demand for the endoAVF program.[17,18]

In conclusion, our experience based on the previously mentioned methodology has allowed for successful adoption of endoAVF creation. By following a collaborative framework, knowledge can continue to be disseminated across peers locoregionally and beyond to allow continued viability and sustainability.

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BD-10691

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Early on, my facility recognized that a team effort is required to ensure successful management of dialysis access and, specifically, the initiation of an endoAVF program.

Our outpatient department team has been specifically trained in the nuances of the dialysis access patient. We have a dedicated WavelinQ™ EndoAVF System (BD) team, all of whom have been trained on the specifics of creating an endoAVF. The entire team contributes to the successes we have with our patients.

An important aspect of developing an endoAVF program is building relationships with the AV access community. Our core philosophy is that all who interface with the dialysis patient need to be informed and involved. To facilitate communication, we implemented a dedicated hotline that connects dialysis centers to an access coordinator (problem solver). That coordinator is armed with protocols and authority to manage acute crises as well as support an efficient workup of a candidate for the WavelinQ™ EndoAVF System. The nurses and technicians at our dialysis centers are an essential part of the team, as they are the end users cannulating the WavelinQ™ EndoAVF System creation. Another way we interface with the AV access community is through a program run by our midlevel providers called "Lunch and Bond," which has allowed us to share information and educate others about the WavelinQ™ EndoAVF System.

Both pre- and postoperative ultrasound protocols are essential to the success our team has achieved with the WavelinQ™ EndoAVF System thus far. We have developed an A, B, and C grading system for the preoperative assessment of the potential WavelinQ™ EndoAVF System candidate. An "A" patient has excellent arterial inflow, an ulnar vein in proximity to the ulnar artery, a generous perforator, and patent superficial outflow. The "C" patient is a "no-go," and the "B" patient is a plus/minus. This grading system has kept us away from patients who should have an alternative form of dialysis access other than a WavelinQ™ EndoAVF. Additionally, it has provided confidence during the procedure that patients who are candidates for endoAVF have a pathway to fistula creation. Postoperatively, the ultrasound team is oriented to diameter, depth, and flow at the proposed cannulation site. Their mission is early identification of patients with patent fistulas who need secondary procedures to achieve an optimal cannulation site, so that the nurses and technicians at the dialysis center can cannulate the WavelinQ™ EndoAVF with confidence.

One of the most positive aspects of initiating the WavelinQ™ EndoAVF System program for me personally has been watching the team come together with a common goal and observing each individual's enthusiasm for serving the needs of this very important and oftentimes ill patient population. ■

BD-10692

PANEL DISCUSSION

The Growing Role of Endovascular Therapy in AV Access

Multidisciplinary experts weigh in on the effect of endovascular therapy in Europe.

WITH JM ABADAL, MD, PhD, EBIR; LAMPRINI G. BALTA, MD; RAPHAËL COSCAS, MD, PhD; AND GEERT MALEUX, MD, PhD

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Endovascular arteriovenous fistula (endoAVF) treatment is our daily work, and the demand for it is continuously increasing. Since balloon angioplasty was first reported in 1981 by Dr. Andreas Grüntzig,[1,2] there has been a revolution in both technology and technique.

Nowadays, endovascular procedures in AVF have become the first-choice treatment modality, relegating surgery to a few unsuitable lesions or when percutaneous transluminal angioplasty or stents have failed. The treatment is safe, effective, and technically simple, and it has been stated in the latest guidelines.[3]

AVF surveillance and noninvasive imaging have increased the detection of significant stenosis and diminished the rate of AVF thrombosis. Classic diameter stenosis quantification with angiography is not enough to indicate treatment of the AVF. Clinical and physiologic characteristics and Doppler ultrasound (US) must now be included. Doppler US improves the sensitivity of detecting AVF lesions, adds an important hemodynamic parameter, and confirms treatable lesions before performing angiography. In our experience, US is the main type of imaging guidance used in endoAVF procedures, using fluoroscopy only for central lesions. Technical success relies now on morphologic vessel diameter, intrastenosis velocity peak drop, and AVF flow. These data strongly correlate with the clinical dialysis parameter. Our US guidance also avoids radiation to the patient and staff and the use of iodinated contrast.

With the new declotting devices, effective and fast pharmacochemical treatment of thrombosed AVF can be performed. The underlying stenosis can be treated in the same procedure, and the patient can be sent immediately to hemodialysis, avoiding the placement of a catheter. This all-in-one procedure has gained wide acceptance from our nephrologists and has positively impacted patient quality of life.

Even so, restenosis remains an unresolved issue and is the continued burden of interventional radiology. Patency rates at 6 months and 1 year are not comparable with other vascular territories. Predictors of patency and treatment algorithms should be designed. To solve this problem, high-pressure, cutting, scoring, and drug-coated balloons (DCBs) are emerging as new tools to treat complex stenosis and increase primary patency of AVFs. New stent grafts are used for recurring lesions at frequent intervals with solid data.[4,5]

Lastly, endoAVF creation is now a reality, with preliminary reports in selected patients demonstrating equivalent, if not superior, outcomes and lower complication rates compared with an open surgical technique.[6]

Endovascular treatment must be seen as an effective procedure to treat dysfunctional AVF, and the key is the patient with an AVF. Maintenance of the AVF requires a dedicated multidisciplinary team combining the roles of nephrologist, surgeon, and interventional radiologist to obtain good outcomes.

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Despite all the progress achieved in dialysis technology in the past years, vascular access is both the lifeline and the Achilles' heel for patients undergoing hemodialysis.

Without a well-functioning vascular access, hemodialysis adequacy is reduced, and the relative morbidity and mortality of patients increases.[1] Autologous AVF is recommended as a first option for vascular access, especially due to infections and thrombotic complications that are most commonly associated with AV grafts (AVGs) and central venous catheters[2]; unfortunately, a large proportion of dialysis patients are not suitable for autologous AVF.

Stenosis, thrombosis, and maturation failure are the main problems accounting for a large proportion of failed or abandoned accesses.[3]

NEW AVF OPTIONS WITH WAVELINQ™

The WAVELINQ™ EndoAVF System (BD) offers two additional AVF creation site options compared with surgically created fistula. Creating an AVF through an endovascular procedure preserves vasa vasora and the surrounding feeding tissues, diminishing fibrotic changes at the anastomotic site, which is a main characteristic and drawback of surgical AVF creation. In addition, patients with end-stage renal disease—who are usually old with multiple comorbidities and limited vein accesses—may benefit from an endoAVF creation procedure such as that offered by the WAVELINQ™ EndoAVF System, thus avoiding a surgical procedure along with its risks. The WAVELINQ™ EndoAVF procedure creates an AVF in the deep vasculature (eg, an ulnar–ulnar or a radial–radial AVF). EndoAVF creation improves the field of vascular access by providing patients with more options for AVF, both for predialysis and dialysis patients who had previous failed access attempts.

Additionally, the endovascular technique is a minimally invasive procedure that can facilitate AVF creation in an outpatient setting and will increase the spectrum of specialties and physicians who can perform it. This will hopefully reduce long waiting times by eliminating the time needed for surgical consultation and pre- or postoperative follow-up. Hemodialysis patients with preexisting malfunctioning AVFs are usually well informed and seek alternatives to classic surgical AVF, thus making it our obligation to keep up with the latest techniques in vascular access.

In conclusion, from a nephrologist's point of view, the key will be to continue screening patients, gather clinical evidence, refine patient eligibility, and ensure the physicians are properly trained and equipped to perform endoAVF. A well-founded cooperation between medical specialties and a well-trained nursing staff are considered of utmost importance for the evolution and wider application of this method.

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For years, in France and especially in the Paris area, AV access care was performed either by vascular surgeons or interventional radiologists. However, these two specialties have different missions and areas of expertise with little overlap. Vascular surgeons were in charge of AVF and AVG creations as well as open revisions of failed AV accesses. Interventional radiologists performed thromboaspiration of occluded AVFs and AVGs in addition to angioplasties of AV accesses and central veins. In the end, the nephrologist in charge of the patient was making the decision to send the patient to the radiologist if he/she wanted endovascular management and to the vascular surgeon for open surgery. This was not always based on a clear paradigm, and it led to exclusivity of endovascular procedures or open surgical managements. This is the past, and it must change.

Fortunately, the rigid referral patterns of the past are changing to better serve the unique situation of each patient. The emergence of new techniques, such as endoAVF creation, DCBs for failed AV accesses, and thrombectomy devices, gives physicians better tools

to develop an optimized treatment plan. At the same time, it's important we stay balanced in our use of new technologies. We must keep in mind that a native AVF at the wrist still might be the best AV access option. Each patient's treatment plan should be individually evaluated for the optimal access creation procedure.

With so many options, it is paramount to build a multidisciplinary (or multitechnique) team that performs high-quality open surgeries and endovascular management of AV accesses. For example, consider the patient with recurrent cephalic arch stenosis who has undergone 9 or 10 angioplasties. With a comprehensive plan for access creation, that patient might be referred to the vascular surgeon for open cephalic-axillary reimplantation. Similarly, open surgeons now have additional options distal to the elbow when the possibility of a wrist fistula has been ruled out. We can now create percutaneous proximal forearm AVFs with endovascular systems such as the WavelinQ™ 4F EndoAVF System. This technology is a game changer for AV management and, when appropriate, must be incorporated into the AVF creation algorithm while still considering the indications and contraindications.

I do not believe in using only open surgery or endovascular management for AV access. I believe in being able to choose the best technique for each situation. It is already clear that endovascular techniques have a growing role in our field. To give our patients the best care possible, physicians taking care of dialysis patients need to master all available techniques by continually training and learning the newest procedures available. It is also important that all specialties involved in the care of the patient (nephrologists, radiologists, vascular medicine) acquire the knowledge for the different options available. Until an established algorithm for AVF creation and management is available, a multidisciplinary approach of AV creation and maintenance will allow us to offer the best care for our dialysis patients.

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Hemodialysis remains the backbone treatment for the majority of patients with end-stage renal disease. Different access methods for hemodialysis exist; however, autologous AVF is the most durable access for these patients. If an autologous fistula is not an option, other accesses such as an AVG or a tunneled dialysis catheter are still an option.

The main drawback of an autologous fistula, however, is the high incidence of venous stenosis, which may lead to a dialysis dysfunction. For more than two decades, balloon angioplasty of these venous stenoses has been the gold standard according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines,[1] despite the high incidence of recurrent stenosis. Today, the introduction of DCBs may result in prolonged patency of veins[2] and fewer angioplasty sessions over time.[3] This may impact patient quality of life and reduce the total cost of medical treatment in patients undergoing dialysis. Future research is still needed to better understand the working mechanism of DCBs, including which drug is the most efficient (mainly paclitaxel is used today), and better define the technical aspects of this new technology, including inflation time and combination with regular angioplasty balloons.

Another step forward in the treatment of patients with dysfunctional dialysis fistulas is the introduction of expanded polytetrafluoroethylene–covered stent grafts. For many years, it has been demonstrated that expanded polytetrafluoroethylene–covered stent grafts are superior to conventional balloon angioplasty in patients with venous outflow stenosis associated with an AVG.[4-6] However, there is more evidence that these covered stents are also of major importance in treating efferent venous stenosis in autologous fistulas, especially for treating cephalic arch stenosis.[7] Further research on covered stents versus DCBs, downsizing stent graft delivery systems, and optimizing covered stents for venous applications are interesting challenges for the future.

These new technologies and future innovations may result in better treatment of dialysis patients and, finally, a better quality of life. ■

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Endovascular Treatment of Dysfunctional Vascular Access: From Fundamentals to an Algorithmic Approach

Choosing the ideal device for the right location in dialysis access management.

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The main reason for vascular access dysfunction is stenosis. Reasons for stenosis are mainly the open surgical vascular access creation, which involves cutdowns, incisions, sutures, and ultimately fibrosis; the inherent problems of end-stage renal disease, primarily oxidative stress and hypoxia; and the actual cannulation of vascular access with two cannulae, three times a week for 4 hours.[1] These factors produce inflammation and endothelial dysfunction, which in turn causes venous neointimal hyperplasia (Figure 1). Neointimal hyperplasia is characterized by the presence of myofibroblasts and differentiated contractile smooth muscle cells that produce an extensive extracellular matrix and together create a robust, aggressive fibromuscular thickening.[2]

Percutaneous transluminal balloon angioplasty (PTA) is the trademark procedure of endovascular treatment for vascular access stenosis. Although successful, PTA patency rates can be as low as 23% at 6 months in case of arteriovenous grafts (AVGs).[3] This is mainly attributed to the fact that barotrauma due to PTA triggers a cascade of events that inevitably cause vessel restenosis. Improving the vicious cycle of stenosis-treatment-restenosis should therefore be the aim of every treatment strategy. Patients with a stenosed, dysfunctional vascular access circuit will need to immediately return to dialysis. Thus, the mechanical part of the procedure, establishing a lumen with a < 30% residual stenosis, is the cornerstone first step and also a prerequisite (known as vessel preparation) for the second step, which is an attempt to decelerate the restenotic process.

FUNDAMENTALS

Balloon Size and Type

PTA balloon size and balloon type are the initial decisions one needs to make. The first step is to determine reference vessel diameter. This can be challenging in cases where only digital subtraction angiography is used.

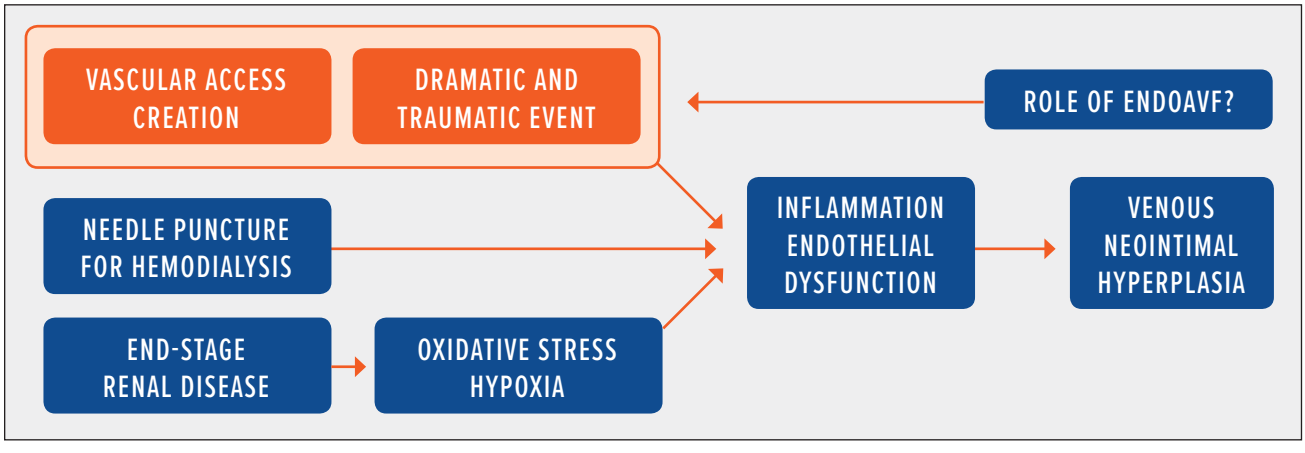

Figure 1. Characteristics of AV stenosis. endoAVF, endovascular arteriovenous fistula.

However, although B-mode ultrasound measurements can give a more accurate measurement of vessel diameter, this is restricted to outflow veins. Intravascular ultrasound can be a useful tool for central vein measurements, but its price remains prohibitive in many countries. Regardless of measurement accuracy, reference diameter will always remain subjective, and thus, percentages of stenosis and residual stenosis are also subjective, which is why in real-world practice, a visual estimation of vessel diameter is used. The difficulty of sizing a vessel is further compounded by the patient's breathing, which induces changes in thoracic pressure and causes variability in vessel and reference diameter. The importance of extending the diameter of the angioplasty balloon to an additional millimeter is of great importance and is based on the mathematical equation $A = \pi R^2$, where A is the lumen area and R is the radius of the vessel lumen. Shifting from "undersizing" to "normal sizing" of balloon diameter will greatly influence immediate luminal gain.

The type of the balloon used for angioplasty is also important. As mentioned previously, vascular access stenosis is characterized by a strong fibromuscular venous thickening, unlike the calcified vascular wall of arteries in peripheral artery disease. To manage this stenosis, a noncompliant, high-pressure balloon will be needed in the majority of cases. These high-pressure balloons, also known as "fiber" balloons or "fistula" balloons due to their extensive use for the treatment of vascular access stenosis, not only provide high-pressure inflation but also a constant pressure and predictable diameter throughout their length.[4]

Elastic Recoil and Parietal Thrombus

Elastic recoil is the vessel response to the barotrauma of a PTA balloon, and resolution may require a mechanical scaffold (bare or covered) for its treatment. An observational study by Rajan et al proved that elastic recoil is common in vascular access (16% [24/154] of patients had elastic recoil, defined as > 50% vessel narrowing, within 15 minutes after angioplasty); however, its presence did not affect target lesion primary patency (TLPP).[5] Additionally, Swinnen confirmed the increased presence of early elastic recoil after angioplasty.[6] Indirect signs of a successful technical result could therefore be used. Waist effacement during balloon angioplasty is a sign that the fibrotic part of the stenosis was treated. The decrease or absence of collaterals and a direct antegrade flow are also signs of successful angioplasty. Finally, the "blood-diluted contrast phenomenon" could also be of assistance. During the initial angiogram, stenosis will create slow blood flow within the vascular circuit, making contrast flush through the system more slowly and appear dense. When the stenosis is successfully treated, contrast appears more diluted and flushes through the system more quickly.

One should also keep in mind that vascular access circuits are characterized by the presence of parietal thrombus. The latter could easily turn to free-floating thrombus after angioplasty. Migrating to the lungs is highly unlikely to cause any clinically significant pulmonary embolism; however, its presence within the circuit creates a thrombogenic area that could lead to vascular access thrombosis.

Deceleration of Restenosis: The Role of Drug-Coated Balloons

The second step of the procedure is an attempt to slow down the process of restenosis. It is of utmost importance to remember that restenosis is a healing process and a response of the vascular wall to the barotrauma caused by balloon angioplasty. It involves a cellular process with cells migrating from the vascular wall layers' outer tissues, while circulating cells also take part in the process. Hence, the action of the chemotherapeutic factor (which currently is paclitaxel carried by drug-coated balloons [DCBs]) is exerted on the cells accumulating after angioplasty, not on cells/matrix present prior to angioplasty. Paclitaxel is a chemotherapeutic drug that acts on a cellular/nuclear level by inhibiting the disassembly of microtubules during the mitotic phase of the cell cycle, leading cells to apoptosis. Because they are semicompliant balloons, DCBs without vessel preparation would most likely fail to accomplish the initial mechanical part of treatment and rather function solely as drug delivery devices. This was observed in a subgroup analysis of the results of the Lutonix AV Global Registry presented earlier this year at Charing Cross (London, United Kingdom; 2019) by Kitrou et al, in which patients who did not undergo vessel preparation with a high-pressure balloon had significantly inferior patency rates compared with those in which initial balloon angioplasty was performed.[7]

There are three important points that should be taken under consideration when using a DCB: avoidance of "geographic miss," inflation time, and pressure. As mentioned previously, a DCB is used to diminish the destructive effect of balloon angioplasty due to barotrauma. The length of the DCB should be longer than the predilatation injury, extending 5 mm proximally and distally, to ensure full coverage of the area. An inflation time of > 2 minutes is also advised. Subgroup analysis of the Lutonix Global AV registry presented during Charing Cross suggested a significantly better patency rate when DCB was inflated more than 2 minutes.[7] In the author's experience, for better drug apposition to the vascular wall, a pressure of 2 atm higher than the nominal should be applied (Figure 2).

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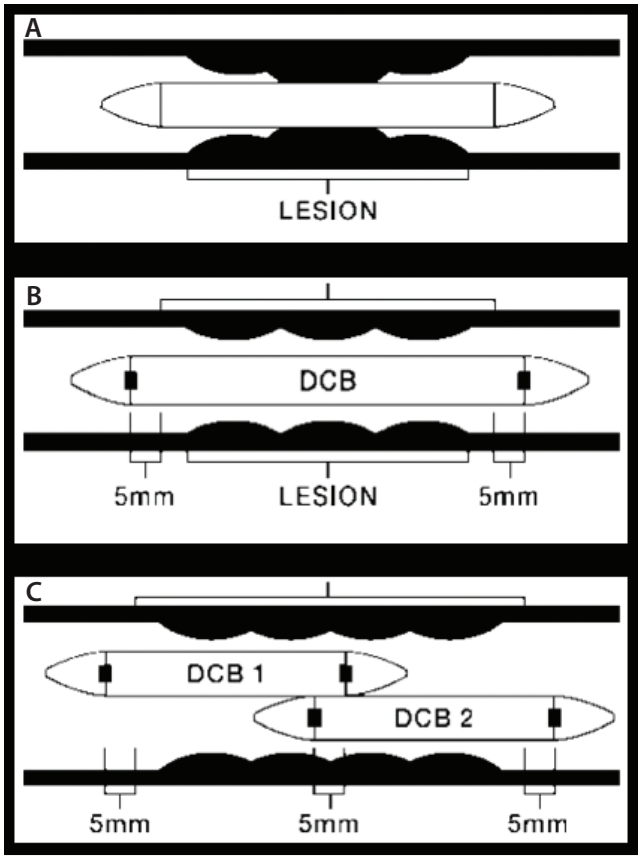

Figure 2. A technique of using DCBs to secure adequate treatment of postangioplasty area. Predilation with high-pressure balloon (A); DCB treatment for vessel preparation injury (B); and dual DCB treatment for predilation/injury segment (C).

THE PATRAS UNIVERSITY ALGORITHM

There are two main vascular access circuits, AV fistulas (AVFs) and AVGs. Both end up in central veins (subclavian, brachiocephalic, and superior vena cava), have outflow veins (venous part of the circuit between cannulation zone and central veins), and an inflow artery. The difference lies in the cannulation zone, which in AVFs is a vein, whereas in AVGs is the synthetic fabric. Accordingly, AVFs have one anastomosis (between the artery and the vein), and AVGs have two (venous-graft and arterial-graft anastomosis) (Figure 3). Figure 4 is an algorithm that reflects the general treatment approach of the authors and under no circumstances holds the place of guidelines.

Central Veins

Symptomatology is the only criterion for the treatment of central venous stenosis. Most common symptoms are either a dysfunctional circuit or edema, swelling, or presence of collaterals. There is also a correlation between the level of stenosis and symptom manifestation. If a symptomatic central venous stenosis occurs, vessel preparation is performed with high-pressure balloons. The CONQUEST® 40 PTA Dilatation Catheter (BD) is available in up to a 12-mm vessel diameter, but for larger diameters, the ATLAS® GOLD PTA Dilatation Catheter (BD) is the balloon of choice. If successful, a LUTONIX® 035 DCB Catheter (BD) can be used for lesions up to 12 mm in diameter (which is the largest available diameter of DCB for dysfunctional AVFs in the United States). Kitrou et al showed a significant benefit of using a LUTONIX® 035 DCB Catheter in central veins compared to high-pressure balloon angioplasty alone.[8] If vessel preparation is not successful, a metallic scaffold may be used—covered stents

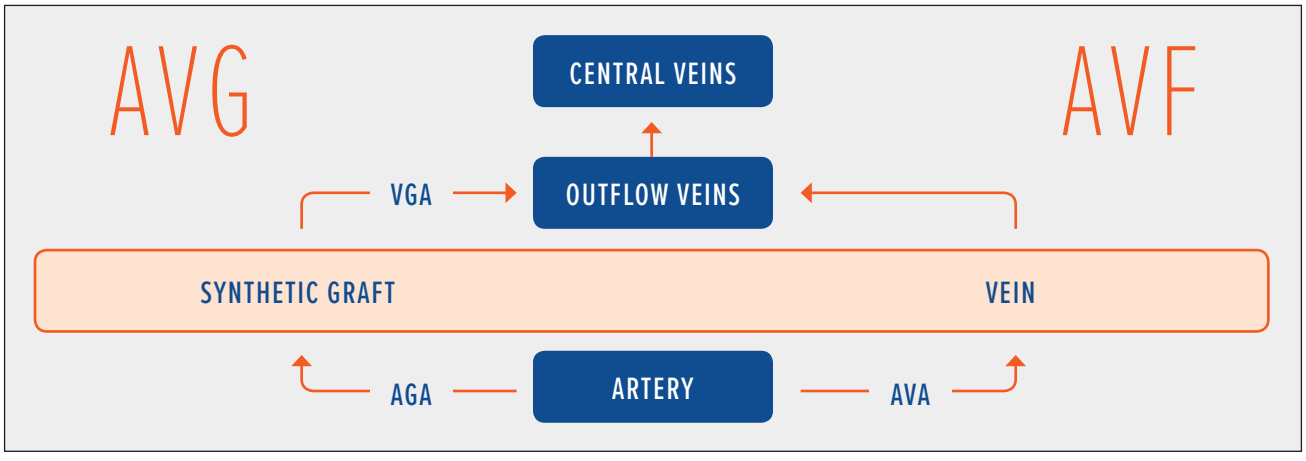

Figure 3. Different segments of AV circuits. The difference between AVGs and AVFs lies in the cannulation zone and the different anastomoses. AGA, arterial-graft anastomosis; AVA, arteriovenous anastomosis; VGA, venous-graft anastomosis.

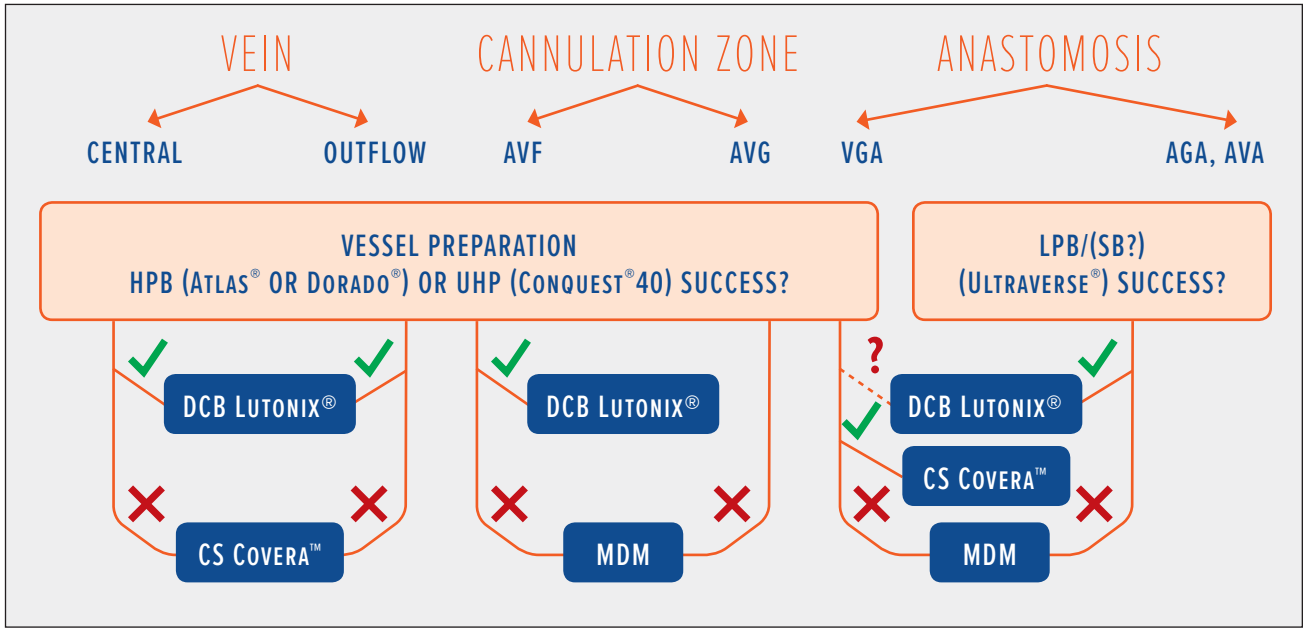

Figure 4. Algorithm of the authors' general treatment approach to AV access stenosis. AGA, arterial-graft anastomosis; AVA, arteriovenous anastomosis; CS, covered stent; HPB, high-pressure balloon; MDM, multidisciplinary meeting; LPB, low-pressure balloon; SB, scoring balloon; UHB, ultra-high-pressure balloon; VGA, venous-graft anastomosis.

are preferred, as they have been shown to have better patency rates compared to bare-metal stents.[9]

Outflow Veins

Our treatment algorithm for outflow vein stenosis is to incorporate ultra high pressure with a CONQUEST® 40 Catheter. Successful angioplasty is then followed by a LUTONIX® 035 DCB Catheter. This is the treatment site where the majority of data regarding DCB use are available. Trerotola et al showed a TLPP of 71.4% at 6 months.[10] Kitrou et al reported a TLPP of 72.2% at 6 months in their retrospective analyses,[11] and a 73.5% TLPP at 6 months was shown in the Lutonix Global AV registry at the specific site, as presented earlier this year at SIR.[12] If vessel preparation fails, use of the COVERA™ Vascular Covered Stent (BD) has proven to be effective in the AVeNEW trial, with a TLPP of 78.7% at 6 months compared with a rate of 47.9% for PTA for the treatment of outflow veins in patients with AVFs.[13]

Cannulation Zone and AVGs

Unlike in AVFs, the cannulation zone of an AVG is a synthetic material. A stenosis at this site is mechanical, mainly due to repeated cannulation because no endothelium exists and venous neointimal hyperplasia does not take place. Therefore, DCB use is not supported. Additionally, no evidence exists on the use of the COVERA™ Vascular Covered Stent at the cannulation zone. In my experience, an ultra-high-pressure balloon angioplasty reaching 40 atm, as in the case of the CONQUEST® 40 Catheter, will typically eliminate the stenosis. However, in the event of suboptimal angioplasty, a multidisciplinary approach should be chosen for further action to be taken.

Venous-Graft Anastomosis

Level 1 evidence exists for the primary use of covered stents for the treatment of stenosis at the graft-vein anastomosis. Three randomized trials (FLAIR, RENOVA, REVISE) have consistently proven superiority of the use of covered stents compared with PTA for treatment of stenosis of the venous anastomosis of AVGs.[3,14,15] Most recently, the 6-month results from the AVeVA clinical trial, which studied the COVERA™ Vascular Covered Stent at the graft-vein anastomosis, demonstrated a 71.0% TLPP at 6 months.[16]

Arterial Anastomosis (AVFs and AVGs)

Arterial stenosis is the only case where high-pressure balloon angioplasty is avoided, and a semicompliant balloon such as an ULTRAVERSE® 035 PTA Dilatation Catheter (BD) could be used. In case of residual stenosis, our practice is to consider cutting or scoring balloon angioplasty to avoid increased angioplasty pressures. In case of a successful outcome, our algorithm is to follow with DCB angioplasty. The arterial anastomosis is a no-stent zone. In case of a suboptimal angioplasty result, the case should be discussed in a multidisciplinary

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SUMMARY OF TREATMENT FOR AV STENOSIS

DCB use after every successful angioplasty, excluding the in-AVG stenosis (no tissue present)

TLPP at 6 months:

- Lutonix IDE RCT[10]: 71.4%
- Lutonix Global AV study[12]: 73.5% (78.1% for AVF outflow only)
- Lutonix retrospective study[11]: 72.2%

Covered stent use as a primary/bailout option when angioplasty fails, excluding cannulation zone and arterial anastomosis

TLPP at 6 months:

- AVeVA registry[16]: 71.0%
- AVeNEW RCT[13]: 78.7%

AV, arteriovenous; AVF, arteriovenous fistula; AVG, arteriovenous graft; DCB, drug-coated balloon; IDE, investigational device exemption; RCT, randomized controlled trial; TLPP, target lesion primary patency.

meeting involving a nephrologist and a vascular surgeon to determine whether the patient would need a new access.

SUMMARY

To summarize this treatment algorithmic approach (also see the *Summary of Treatment for AV Stenosis* sidebar[10-13,16]):

- High-pressure balloon angioplasty is used for the treatment of stenosis to "beat" the aggressive fibromuscular thickening.
- Paclitaxel-coated balloons can be used after every successful angioplasty to pharmaceutically decelerate the effect of restenosis.
- Covered stents can be used as a bailout option for the treatment of central venous stenosis and outflow vein stenosis or as a primary option for the treatment of graft-vein anastomotic stenosis.
- When the inflow artery is implicated in the stenotic segment, a DCB could be used; however, the area remains a no-stent zone. ■

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The Use of the Lutonix® 035 Drug Coated Balloon PTA Catheter for Challenging AV Access Stenosis

Formulating a strategy to manage neointimal hyperplasia for dysfunctional AV fistulas in clinical practice.

BY THEODORE F. SAAD, MD

The role of neointimal hyperplasia in the failure of arteriovenous (AV) access has been firmly established over many decades. Conventional balloon angioplasty (percutaneous transluminal angioplasty [PTA]) has long been the standard of care for minimally invasive treatment of stenosis. However, angioplasty does nothing to interrupt the fundamental pathophysiology of neointimal hyperplasia and, in fact, may accelerate the process due to injury-induced mediators of cellular proliferation. Drug-coated balloon (DCB) angioplasty, particularly with the antiproliferative agent paclitaxel, has been shown to reduce neointimal hyperplasia and reduce lesion restenosis in a variety of vascular applications. Clinical studies have demonstrated outcome benefit when DCBs are used to treat stenosis occurring in AV access.[1] The recently completed Lutonix AV clinical trial demonstrated a significant reduction in the frequency of reintervention after DCB PTA, consistent with paclitaxel's known mechanism of action.[2] The Lutonix® 035 DCB (BD) extended the time to reintervention by 114 more days at 24 months when compared to PTA.[3] There was also a signal of improved target lesion primary patency at 6 months (71.4% for DCB vs 63.0% for PTA).[2] However, this did not meet statistical significance at the study-prescribed endpoint. The Lutonix AV study enrolled lesions throughout the access circuit; some of these were likely not responsive to antiproliferative treatment, whereas others may have benefited substantially from reduction in neointimal hyperplasia. Subgroup analysis appears to support this, with superior response in lesions treated for recurrent stenosis; these observations are limited by small sample sizes and statistical challenges of post hoc analysis. Nevertheless, the Lutonix AV trial results can inform a rational strategy for using DCBs in clinical practice.

CLINICAL PARADIGM

Our current paradigm is geared toward identifying lesions most likely to be associated with accelerated neointimal hyperplasia and manifest by rapid restenosis (< 3 months) after previous PTA. Preprocedure ultrasound is a useful tool that can demonstrate a thickened vessel wall at the site of stenosis (Figure 1). Lesions at the arterial anastomosis, juxta-anastomotic segment, needle cannulation areas, and vein transposition swing segments are particularly attractive for DCB PTA treatment. Other sites, such as the cephalic arch or central veins, are more difficult to attribute to hyperproliferative behavior and may have local mechanical factors or elasticity driving stenosis, making other treatment options potentially more attractive.

In my practice, numerous patients appear to have benefited significantly from DCB PTA when managed according to this paradigm. One such example is a 69-year-

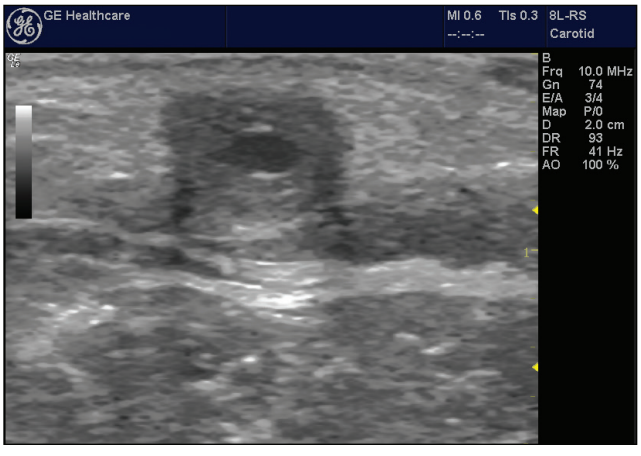

Figure 1. Stenosed AV fistula (AVF) with thickened vein wall indicative of neointimal hyperplasia.

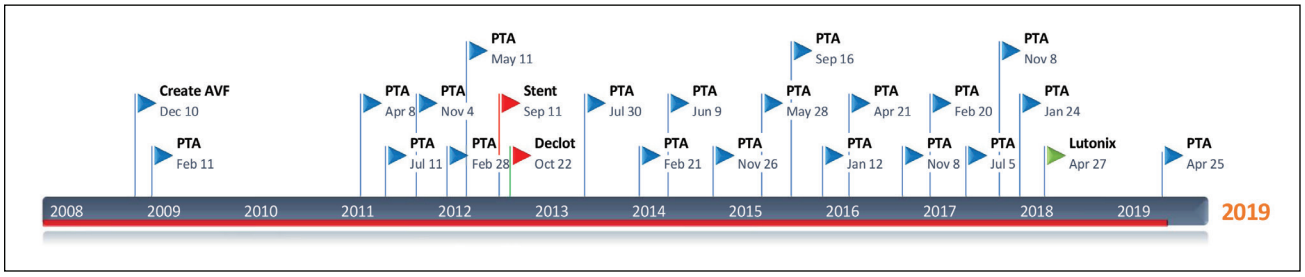

Figure 2. Time of access history and interventions.

old man with end-stage renal disease (ESRD) due to autosomal-dominant polycystic kidney disease requiring renal replacement therapy for over 30 years. He first initiated treatment with peritoneal dialysis but developed permanent technique failure due to complicated peritonitis. He underwent two successful kidney transplantations, both of which ultimately failed, requiring him to return to hemodialysis in 2007 using a basilic vein transposition AVF. Between 2008 and 2018, this fistula required 21 separate interventions (Figure 2) with conventional angioplasty, including one stent graft and one thrombectomy. He has no other suitable veins for construction of a new AVF and has chronic hypotension, limiting the potential for a successful prosthetic graft. His fistula, although arguably "high maintenance," is a precious vascular access, which embodies the concept of the dialysis patient "lifeline." During 2017 and 2018, he required five angioplasties for stenosis of the fistula inflow and puncture segments (Figure 3A), each time with acceptable immediate result (Figure 3B) using a conventional PTA balloon (Vaccess® or Conquest®, BD). Each angioplasty was followed by rapid, functionally significant restenosis (mean interval, 107 days). He then was considered for DCB PTA. Ultrasound demonstrated a thick ring of tissue, indicating severe intimal hyperplasia (Figure 1), and angiography demonstrated recurrent stenosis at the same fistula segments (Figure 4A). Angioplasty was performed using an 8-mm X 4-cm Vaccess® balloon, followed by an 8-mm X 6-cm Lutonix® 035 Drug Coated Balloon PTA Catheter (Figures 4B and 4C). Over the subsequent 12 months, he experienced no clinically significant AVF dysfunction, with stable monthly access flow measurements and no requirement for re-study or intervention. Ultimately, 363 days after DCB PTA, he was referred back for re-study due to falling access flow and difficulty with needle access, an interval more than three times longer versus previous conventional PTA treatments (Figure 5). Not surprisingly, he was keenly aware of his improved course after DCB PTA and stated, "I want that balloon again!"

Similarly, impressive clinical scenarios have been seen in other patients, lending strong observational support to the efficacy of DCB PTA in AVF stenosis. So, why did the Lutonix AV clinical trial not show a statistically significant improvement in lesion primary patency at 6 months? Based on personal experience, I believe the most likely explanation is that there were at least two distinct patterns of lesion behavior: those that derived little or no benefit from DCB versus those that had substantial benefit, akin

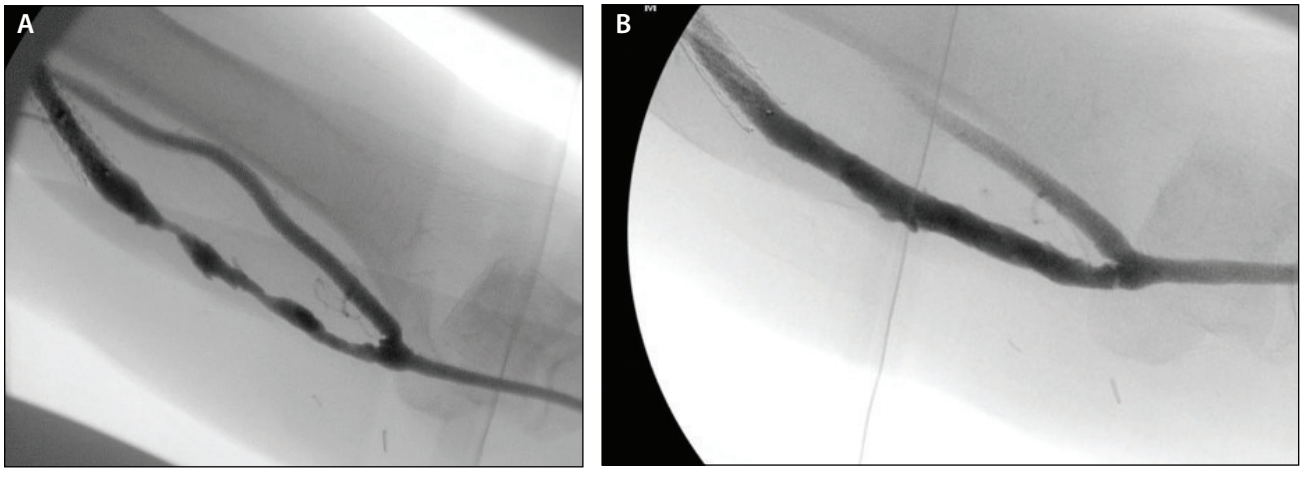

Figure 3. Basilic vein fistula puncture segment stenosis. Preangioplasty (A) and post 8-mm conventional balloon angioplasty (B).

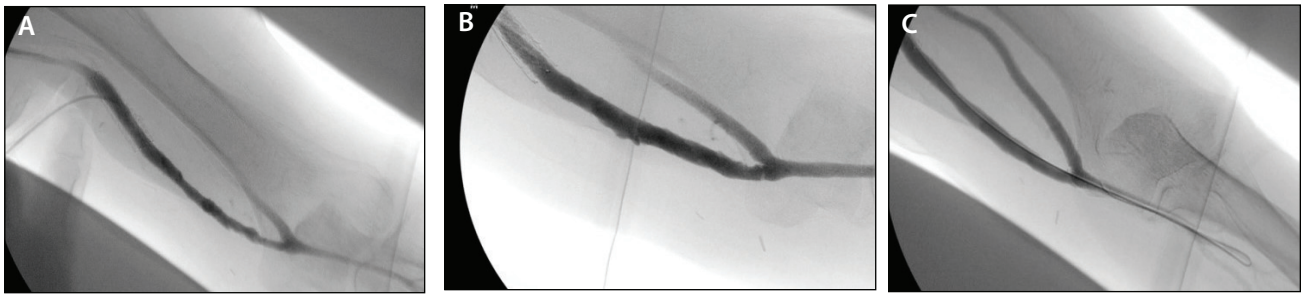

Figure 4. Basilic vein fistula puncture segment restenosis. Preangioplasty (A). Post 8-mm X 4-cm VACCESS® balloon angioplasty (B). Post 8-mm X 6-cm LUTONIX® 035 DCB angioplasty (C).

to the patient presented in this case. Clearly, the next step must be to identify and characterize those subgroups most likely to benefit from DCB. Ultrasound visualization of vessel wall morphologic changes of neointimal hypertrophy is a promising method to identify lesions that are potentially more responsive to paclitaxel's antiproliferative effects.[4]

SAFETY

The Lutonix AV trial was designed to examine safety at 30 days, demonstrating no difference with DCB versus conventional PTA (95.0% and 95.8%, respectively) with regard to freedom from primary safety events.[5] Subsequent analysis at 2 years also demonstrated no significant difference in mortality between the groups (23.4% with DCB vs 18.1% with conventional PTA; $P = .265$).[3] It should also be noted that among FDA-approved paclitaxel-coated balloons, the LUTONIX® 035 DCB Catheter is the only DCB approved for use in AV access in the United States and has a low surface concentration of paclitaxel at 2 µg/mm^2, carried in a polysorbate and sorbitol excipient. In my opinion, it is reasonable to utilize this low effective dose of paclitaxel in AV access applications, where recurrent stenosis and retreatment are likely.

AV access complications contribute disproportionately to morbidity and mortality in these patients. ESRD patients in the United States have exceedingly high mortality, with a 2-year mortality rate of 33.2%.[6] In our practice, we have adopted an approach to consenting for use of DCBs in AV access patients. We disclose the information relative to peripheral artery disease and the absence of clinical evidence for higher risk in AV access; we document this discussion in the consent and/or procedure report. Presented in this way, we have not yet seen a patient with recurrent fistula stenosis decline the opportunity for DCB PTA.

COST-EFFECTIVENESS

No discussion of the clinical application of DCB technology for AV access would be complete without addressing the economic factors involved. For my patient who said, "I want that balloon," we need a system that will cover the additional cost of a DCB, in order to reap the downstream clinical benefits and cost savings of reduced intervention frequency. Unfortunately, in office-based interventional facilities and ambulatory surgery centers, reimbursement for angioplasty is insufficient to support the added cost of a DCB. Therefore, DCB usage is effectively

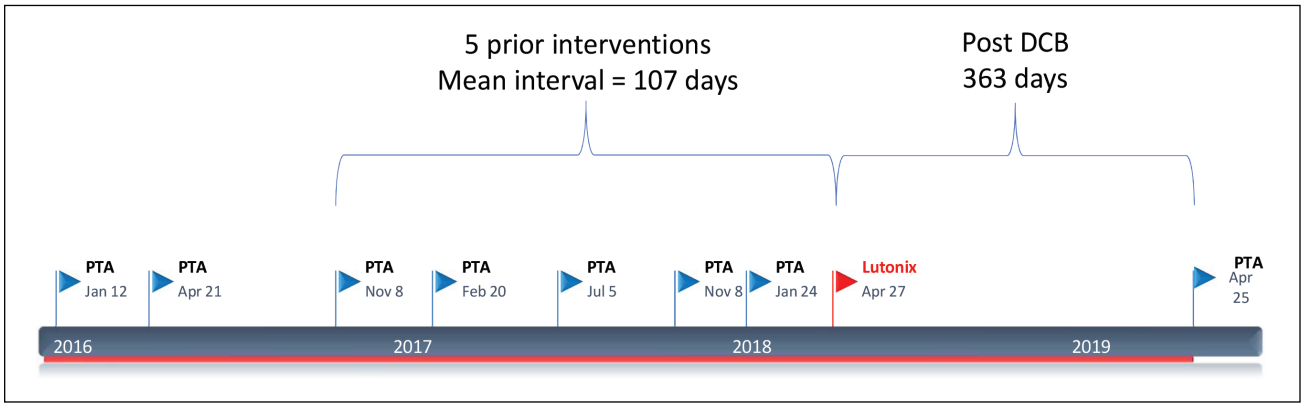

Figure 5. Access timeline: "accelerated phase" of restenosis preceding DCB angioplasty and subsequent extended intervention-free interval.

restricted to hospital-based interventional programs, where higher reimbursement can accommodate the use of this technology. Important "wild cards" in this system are the shared-risk entities, such as ESRD Seamless Care Organizations (ESCOs). There is a mismatch of incentive and reward built into the system, whereby the entity that invests in the DCB reaps no reward on that investment and in fact loses economically, whereas the patient, payer, dialysis facility, and ESCO all benefit from the investment. DCB treatment of AV access stenosis will not achieve its full potential until and unless these economic misalignments are remedied.

CONCLUSIONS AND RECOMMENDATIONS

1. For treating neointimal hyperplasia, which is the fundamental pathophysiology of AV access stenosis and failure, the LUTONIX® 035 DCB is the first and only paclitaxel-coated balloon approved for AV access available in the United States.
2. Use of the LUTONIX® 035 DCB Catheter in the Lutonix AV trial reduced the requirement for subsequent reinterventions by 114 days at 24 months; in my opinion, this statistically significant improvement may be amplified in selected lesions in which exuberant neointimal proliferation results in rapid, repeated restenosis.
3. In my experience, it is useful to monitor individual patient response post-DCB, in terms of need for early or multiple reinterventions. In practice, the patients effectively serve as their own controls for comparison of conventional versus DCB PTA outcomes. Further studies targeted to selected high-risk restenosis patients are needed.
4. DCBs should be preferred for lesions that are unsuitable for treatment with a stent graft and not readily amenable to surgical revision.
5. DCB technology has the potential for significant cost-effectiveness by reducing the requirement for multiple reinterventions. Wider adoption of DCB PTA will require a realignment of medicoeconomic factors, such that the entity investing in a DCB also derives the benefit of future cost savings; most practice in the United States is currently structured with the exact opposite incentives. ■

In August 2019, the U.S. Food and Drug Administration (FDA) issued an updated letter to health care providers noting an increased risk in late mortality (2-3 years post-treatment) with paclitaxel-coated devices when used to treat peripheral arterial disease in the femoropopliteal artery as compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel-coated device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients. BD will continue to work collaboratively with FDA and industry for additional safety data collection and inform labeling as appropriate. These communications as well as information about the FDA Panel meeting can be found at: https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel.

The opinions and clinical experiences presented herein are for informational purposes only. The results from this case study may not be predictive for all patients. Individual results may vary depending on a variety of patient-specific attributes.

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The Evolution of Covered Stents

Improving the outcomes of PTA for hemodialysis access circuit stenosis with the FLAIR® Endovascular Stent Graft, FLUENCY® PLUS Stent Graft, and COVERA™ Vascular Covered Stent.

BY BART DOLMATCH, MD, FSIR

Arteriovenous (AV) access is the lifeline for patients with end-stage renal disease who require chronic hemodialysis. Today, there are nearly 500,000 people with end-stage renal disease in the United States and many thousands more throughout the world who undergo hemodialysis, most of whom dialyze with either an AV graft (AVG) or AV fistula (AVF).[1,2] However, these permanent dialysis access circuits are fraught with problems, particularly the development of flow-limiting stenosis. Dialysis access stenosis reduces dialysis efficiency and can cause secondary dialysis circuit complications, such as bleeding, aneurysms, and pseudoaneurysms. In some cases, stenosis can lead to access circuit thrombosis, necessitating urgent declotting, or abandonment with central venous catheter placement when declotting cannot be achieved.

BACKGROUND

Percutaneous transluminal angioplasty (PTA) has been the mainstay for treating stenosis in AVGs and AVFs. Dialysis access PTA, first described by Glanz et al in 1984,[3] is still widely used to treat stenosis. It is usually performed as an outpatient procedure and is easily arranged, safe, and technically effective in treating stenosis so that the patient can return to dialysis with good AVG or AVF function. However, recurrence of stenosis at the PTA site is frequent, necessitating repeated PTA.

In the early 1990s, there was hope that adding a bare-metal stent (BMS) at the time of PTA would confer better post-PTA patency. There have been only three truly randomized studies comparing PTA with PTA plus a BMS, and the results indicated no clear patency advantage when a BMS was added.[4-6] Therefore, a BMS does not improve patency if PTA has been technically successful and is only recommended for bailout of technically failed PTA.[7]

Covered stents were initially developed to treat abdominal aortic aneurysms (AAAs).[8] Also called stent grafts or endografts, these AAA devices require large-caliber delivery systems, have pins or hooks at the ends of the device to achieve secure fixation, and incorporate graft material to prevent leakage of blood into the aneurysm sac. Concurrent with initial experience using AAA endografts, reports were published describing the use of smaller-diameter covered stents in peripheral blood vessels to treat aneurysms and traumatic AVFs. An early article by Marin et al described successful treatment of a traumatic femoral AVF using a homemade covered stent.[9] Subsequent reports described the use of various types of covered stents to treat a variety of peripheral vascular conditions, including traumatic injuries, pseudoaneurysms, aneurysms, and peripheral artery occlusive disease.[10]

The concept that a stent covered with graft material could prevent or limit the development of restenotic tissue evolved over the ensuing years. There were several areas where post-PTA restenosis was frequently encountered, including coronary artery and peripheral artery interventions, transjugular intrahepatic portosystemic shunts, and dialysis access circuit interventions. Covered stents have limited use in the coronary arteries and are prone to thrombosis.[11] In the peripheral arteries, aortoiliac and femoropopliteal covered stents have been adopted. However, in both the coronary and peripheral arteries, inhibition of restenosis is now often managed with pharmacologic approaches such as drug-eluting stents and drug-coated balloons. Yet, covered stents remain the mainstay for preventing restenosis in transjugular intrahepatic portosystemic shunts and dialysis access circuits.

A BROADER STENT GRAFT APPLICATION

Focusing on hemodialysis access circuit stenosis, early work on AVG and AVF covered stents began in the mid-1990s with in vivo studies of covered stent designs and healing properties.[12-15] Various graft materials were studied, as were constructs where the graft material was on the outside, inside, or both sides of a stent. Different stents were also modeled in the covered stent design. From this work, an understanding of covered stent design and healing in peripheral arteries created the foundation that led to development of the hemodialysis access circuit covered stents we use today.

The FLAIR® and FLUENCY® PLUS Endovascular Stent Grafts

In the late 1990s, covered stents seemed to be a viable approach to limit post-PTA restenosis in AV access circuits.

Based on healing properties with different materials and designs, prototype devices were developed and tested by the collaborative efforts at Impra, Inc. and AngioMed GmbH & Co., which were both acquired by C.R. Bard, Inc., now Becton, Dickinson and Company. This work resulted in the first commercially available AV access covered stent in United States, called the FLAIR® Endovascular Stent Graft (BD). Designed on a self-expanding nitinol stent embedded in a fused internal-external barrier layer of expanded polytetrafluoroethylene (ePTFE), the FLAIR® Stent Graft was specifically developed to treat stenosis at the venous end of an AVG, where recurrent post-PTA restenosis was often seen. One novel attribute of the FLAIR® Stent Graft was the option to select either a tubular or flared configuration depending on the size of the outflow vein. The flared device has a downstream diameter that is 4 mm larger than the rest of the device. This larger flared end of the stent graft was a better match for the size of the outflow veins, which permitted optimized flow patterns that could lead to decreased neointimal hyperplasia formation.

An additional advantage that wasn't recognized during the design of the flared FLAIR® Stent Graft is its ability to support more laminar flow with fewer flow disturbances within the venous outflow, as compared with the straight configuration in the same condition where the outflow vein has a larger diameter than the AVG. As the diameter of the device increases, so does the cross-sectional area, and therefore the velocity of blood flow entering the vein diminishes. Simulated flow models have shown that the typical tubular end-to-side vein/graft anastomosis produces turbulence at the anastomosis, whereas placement of a flared FLAIR® Stent Graft at the anastomosis allows for more laminar flow into the outflow vein.[16] Turbulent flow has been associated with the development of neointimal stenosis, whereas laminar flow is believed to reduce hyperplastic tissue proliferation and may reduce the development of restenosis.

The FLAIR pivotal trial and the subsequent RENOVA postmarket trial demonstrated clinical benefit using the FLAIR® Stent Graft to treat AVG venous anastomotic stenosis. Both trials showed superior treatment site patency and AVG circuit patency compared with PTA alone at 6 months.[17,18] The FLAIR® Stent Graft was approved by the FDA in 2007 for use in the treatment of stenoses at the venous anastomosis of ePTFE or other synthetic AVGs.

The FLUENCY® PLUS Endovascular Stent Graft (BD) was developed at the same time as the FLAIR® Stent Graft on a slightly different self-expanding base stent. The FLUENCY® PLUS Stent Graft was tested for treatment of in-stent restenosis located in the venous outflow of AVGs and AVFs, as well as in-stent restenosis in the central veins. Compared with PTA at 6 months, the FLUENCY® PLUS Stent Graft demonstrated superior patency in both the AV access circuit and central veins.[19] Beyond treatment of in-stent restenosis, the FLUENCY® PLUS Stent Graft was approved by the FDA for use in the venous outflow of AVGs without any previous stent placement. The FLUENCY® PLUS Stent Graft still remains the only proven treatment studied in a clinical trial for treating in-stent restenosis in hemodialysis access circuits and central veins.[20]

Although these stent grafts are superior to PTA for their indicated applications, both the FLAIR® Stent Graft and FLUENCY® PLUS Stent Graft have been in clinical use for more than 10 years without much change. Meanwhile, today's requirements for dialysis circuit intervention have evolved. Whereas the FLAIR® Stent Graft was developed for AVG use, the impact of the Fistula First Breakthrough Initiative has led to fewer AVGs and many more AVFs. Furthermore, with recognition that BMSs do not afford better outcomes than PTA, fewer BMSs are seen in AV circuits, and there is a decreased need for the FLUENCY® PLUS Stent Graft to treat in-stent restenosis. What is needed at this time is a flexible covered stent with a broad sizing matrix that can be accurately delivered to treat not only stenosis in AVGs but also in AVFs.

The COVERA™ Vascular Covered Stent

To meet this need, BD/Bard developed the COVERA™ Vascular Covered Stent, which has a flexible, nitinol base stent that has excellent conformability and is kink resistant and durable. Although it uses a similar ePTFE covering as the FLAIR® Stent Graft and FLUENCY® PLUS Stent Graft, the COVERA™ Vascular Covered Stent is an improvement in several ways. The size matrix of the COVERA™ Vascular Covered Stent is broad and allows treatment of long lesions. The delivery system is triaxial and permits precise implantation, yet it has a smaller diameter than comparable delivery catheters for the FLAIR® Stent Graft and FLUENCY® PLUS Stent Graft.

The COVERA™ Vascular Covered Stent has been approved by the FDA for use in AVGs and AVFs based on data from the ongoing AVeVA and AVeNEW clinical trials. The AVeVA trial is a single-arm nonrandomized clinical study that evaluated the COVERA™ Vascular Covered Stent for treatment of AVG venous outflow stenosis.[21] The 6-month results exceeded the predicted patency goal of 40% at 6 months with a treatment site patency of 71%, which was better than results from both the FLAIR pivotal and RENOVA clinical trials. AVeVA has completed its 12-month data review and will soon complete 24-month follow-up data.

The AVeNEW clinical trial is a prospective, randomized, multicenter study comparing the outcome of intervention in AVFs.[22] Randomized between PTA or PTA with the COVERA™ Vascular Covered Stent, 280 patients were enrolled in the trial and, at 6 months, demonstrated a target lesion primary patency rate of 78.7% for the COVERA™ Vascular

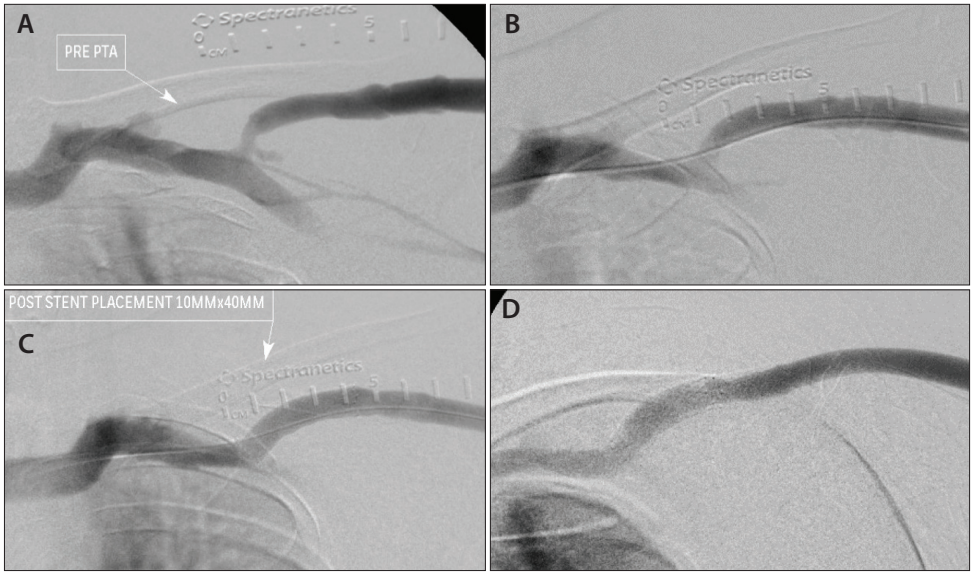

Figure 1. Stenosis > 50% at the terminus of the left cephalic vein arch prior to PTA (A). Post-PTA result with acceptable improvement, although there is some residual stenosis (B). A 10- X 40-mm COVERA™ Vascular Covered Stent was placed at the site of PTA, with no residual stenosis. The COVERA™ Vascular Covered Stent was placed with precision, treating the entire arch, but not extending into the axillary or subclavian vein (C). A look at the COVERA™ Vascular Covered Stent 5 months postprocedure during intervention elsewhere in the AVF. The COVERA™ Vascular Covered Stent remains widely patent (D).

Covered Stent compared with 47.9% for standard PTA. The 12-month results show superior patency for the COVERA™ group at all treatment sites, with over 35% greater patency at 12 months (57.5% for COVERA™ Vascular Covered Stent vs 21.2% for standard PTA). At 6 months, half of all stenoses were in the cephalic vein arch, but all stenosis locations had statistically superior patency with the COVERA™ Vascular Covered Stent compared with PTA alone for all subgroups analyzed. Figure 1 shows one of the cephalic arch stenosis cases from the AVeNEW trial. Data collection and analysis will continue to 24 months.

CONCLUSION

Covered stents have consistently improved the results of PTA for treating hemodialysis access circuit stenosis. For more than 10 years, BD/Bard has advanced the science of covered stents. Three different covered stents have been developed, tested, and proven in human clinical trials: the FLAIR® Stent Graft, FLUENCY® PLUS Stent Graft, and now the COVERA™ Vascular Covered Stent. With recent compelling clinical trial data and FDA approval, the COVERA™ Vascular Covered Stent can be used to treat stenosis in both AVGs and AVFs. ■

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PANEL DISCUSSION

How Do Emerging Technologies in AV Access Fit Within the Current Economic Climate of Your Practice?

A discussion of the economic benefit of drug-coated balloons and covered stents and the current economic challenges of treating AV access patients.

WITH TOBIAS M. STEINKE, MD; SCOTT S. BERMAN, MD, MHA, RVT, FACS, DFSVS; AND BART DOLMATCH, MD, FSIR

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Vascular access in hemodialysis patients is regarded as a critical determinant of morbidity and mortality. Studies have shown that native arteriovenous fistulas (AVFs) are associated with better survival, fewer occurrences of mechanical and infectious complications, longer patency, and reduced health care costs compared with AV grafts (AVGs).[1-4] Both options are better than central venous catheters.

The main cause of AVF or AVG dysfunction is the development of stenoses that lead to reduced blood flow, which may reduce the quality/efficacy of hemodialysis.[5-7] If untreated, stenoses could progress and lead to thrombosis and possible access circuit abandonment, with high associated economic burden. The basic management of vascular access stenoses is percutaneous transluminal angioplasty (PTA) with or without stenting. For the last few decades, the standard of care for stenoses has been considered to be PTA alone[8,9]; however, keep in mind that long-term patency is limited, and reinterventions to maintain patency are common.

A randomized controlled trial evaluated the safety and efficacy of the LUTONIX® 035 Drug Coated Balloon (DCB) PTA Catheter (BD) versus PTA alone in treating stenotic lesions of AVFs. The LUTONIX® 035 DCB showed a prolonged reintervention-free interval of 114 more days at 24 months than standard PTA,[10] resulting in a relevant benefit for patients with end-stage renal disease who receive hemodialysis. This is strongly supported by the Lutonix Global AV registry with 73.5% target lesion primary patency and 70.9% access circuit primary patency at 6 months.[11] In addition, an economic model (developed from a United States payer perspective based on 12-month reintervention rates from the Lutonix AV trial) predicted that the LUTONIX® 035 DCB would be cost-effective in the first year, with a reasonable incremental cost savings of $661 per patient compared with PTA.[12]

In my practice (in the German health care system), DCB devices are still reimbursed, which makes sense because it benefits the patients; but there is an ongoing discussion with health insurance companies/payers because general reimbursement of DCBs in AV access would lead to widespread use in hemodialysis patients.

Due to the obvious benefits of DCB in AVF stenoses, de novo lesions in hemodialysis patients at our vascular center are primarily treated with DCBs, because PTA alone is known as a strong risk factor for restenosis.[13,14] The potential lack of reimbursement in different national health care systems could be a hindrance for DCBs, depending on the structure of their specific reimbursement models.

Situations with elastic recoil in AVF/AVG stenoses cannot be addressed by a DCB. Therefore, the approach of a "nothing left behind" strategy must be modified in those patients. Although not indicated for use, bare-metal stents (BMSs) have been used to treat AVF/AVG stenoses despite the inconsistent results in observational studies and absence of randomized controlled trials.[15-17] In-stent restenosis with BMSs will limit long-term patency as well.[18,19] To overcome limitations associated

with PTA and BMSs, stent grafts are a strong option to inhibit restenosis and reestablish a functional AVF. The COVERA™ Vascular Covered Stent (BD) showed superior primary patency when compared with standard PTA at 6 months in AVeNEW, the first level 1 clinical trial on the use of a covered stent in AVFs.[20] In the covered stent group, primary patency was 78.7% versus 47.9% in the angioplasty group. This is a difference of > 30% at 6 months, with a highly significant *P* value at < .001 according to Kaplan-Meier analysis. This is consistent with our clinical experience using the COVERA™ Vascular Covered Stent in our daily routine since 2016. Fortunately, the German diagnosis-related group systems have covered the additional expenses until now, allowing a patient-optimized therapy strategy. An economic model published by Dolmatch et al in 2018 predicted that an increased use of stent grafts for treatment of AVG anastomotic stenosis and AVF/AVG in-stent restenosis can be economically favorable, while providing improved patient care through reduced reinterventions.[21]

I believe that incorporating DCB and stent graft technology, with their proven extension of intervention-free intervals, will change the way we care for patients with AV access dysfunction.

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Despite significant enthusiasm for payment reform over the last 5 years, there has been little practical change to the way most providers of AV access care receive reimbursement (ie, fee for service [FFS]). Few private payers have adopted alternative payment methods (APMs) for care that impact vascular access for hemodialysis. However, cuts have been made to providers based on the site of service, with significant reductions to reimbursement for vascular access maintenance procedures performed in an office-based setting but increases in reimbursement for those same procedures performed in ambulatory surgery centers over the last 2 years.[1] This "shell game" of reimbursement precipitated by the Centers for Medicare & Medicaid Services makes it incredibly difficult for practices to manage their AV access business. The recent trend of either closing office-based facilities or converting them to ambulatory surgery centers will likely continue until the next round of fee adjustments comes from the Centers for Medicare & Medicaid Services, which will then prompt the appropriate compensatory response from access providers in order to remain profitable.

If a provider performs all of their vascular access procedures at a hospital, then these regular adjustments to reimbursement in the ambulatory setting will likely have less impact on your practice. This has been my situation, and because none of my payer contracts involve APMs, my incentive to reduce interventions and maximize longevity of treatments has been motivated only by my commitment to quality care and not mandated through economic pressure. It is important to point out, however, that a FFS payment model rewards volume of care, not value—providers are compensated every time the patient requires an intervention, controlled only by global billing policies and not by clinical outcomes, as would be the case with APMs and other value-based payment models.

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A different way for providers to think about the business side of FFS is that, ultimately, we are consuming a limited resource, and despite economic pressure to the contrary, each provider needs to conserve the resources for the future, including care that they themselves may need.

Given those provisos, any treatment for AV access maintenance that reasonably prolongs uninterrupted use of the access and is not prohibitively expensive has a role in my practice. The LUTONIX® 035 DCB PTA Catheter is one device that fills these criteria. Not only did the balloon provide a 31% improvement in primary patency at 12 months compared with plain old balloon angioplasty, but the improvement in time to first intervention of nearly 2 months translates into a savings per patient of around $600.[2] This savings does not include the cost of missed dialysis occurring with failure after plain old balloon angioplasty.

In the ambulatory care environment, particularly settings owned and managed by physicians, incremental device-related cost increases directly and negatively affect profit margin.[3] The answer to these economic challenges in AV access maintenance may ultimately be found in the outcomes of end-stage renal disease seamless care organizations (ESCOs). ESCOs currently provide coordinated care for patients in renal failure and are a form of APM whereby the integrated network is at risk for the cost of the care it provides.[3] Cost savings appreciated by the ESCO realized over time will be shared with the provider network as will economic losses. More successful treatment decisions will translate into lower resource utilization and, therefore, cost savings. ESCOs are an example of a payment model that requires providers to consider long-term effects of treatment and device costs in their treatment algorithms, because they are financially at risk for treatment failures and subsequent resource utilization associated with reinterventions.[3] This is in stark contrast to FFS whereby providers have little to no financial risk associated with treatment outcomes.

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BD-11452

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Historically, the standard of care for hemodialysis vascular access stenosis has been PTA, but long-term vessel patency has been limited by elastic recoil and the formation of neointimal hyperplasia.[1-4] Post-PTA use of BMSs lacks FDA approval and has limited effectiveness due to development of in-stent restenosis (ISR).[4-7] To overcome limitations of PTA and BMSs, recent treatment options have grown to DCBs and covered stents (also known as stent grafts). Now with a wide body of clinical evidence, covered stents are an attractive, FDA-approved adjunct to PTA that improve clinical outcomes. The nitinol scaffold in a covered stent prevents elastic recoil, and the expanded polytetrafluoroethylene (ePTFE) coating limits neointimal hyperplasia and ISR.[4,8-10] Although clinical and biologic benefits are paramount to the patient, the current health care landscape requires providers and payers to carefully balance benefits with costs when treating hemodialysis vascular access circuits, especially with advanced technologies such as covered stents.

To effectively manage outcomes and costs, the right product must be used. BD offers a range of covered stents for use in dysfunctional hemodialysis circuits. The FLAIR® Endovascular Stent Graft was the first ePTFE-covered stent to receive FDA approval for the treatment of vascular access stenosis in AVGs.[5] The FLAIR® Endovascular Stent Graft is being replaced by the COVERA™ Vascular Covered Stent, which builds on a more flexible stent architecture suitable for use within tortuous vessel segments of the venous outflow. The COVERA™ Vascular Covered Stent is the first ePTFE-covered stent to receive FDA approval for the treatment of stenosis in nonstented AVFs.[11] The FLUENCY® PLUS Endovascular Stent Graft is available for treatment of ISR occurring in AVFs, AVGs, and central veins and has an additional indication to treat nonstented venous outflow stenosis in AVGs.[12]

The efficacy and safety of the FLAIR® Endovascular Stent Graft, the COVERA™ Vascular Covered Stent, and the FLUENCY® PLUS Endovascular Stent Graft are well supported by several clinical trials. The FLAIR® Endovascular Stent Graft was evaluated in the PIVOTAL Study and the RENOVA trial for treatment of AVG stenosis. It demonstrated significantly higher primary patency* compared with PTA through 24 months.[13-15] The COVERA™ Vascular Covered

Stent was also studied in AVG stenosis in the AVeVA trial and demonstrated a primary patency† of 71% at 6 months.[11] In patients with AVF stenosis, the COVERA™ Vascular Covered Stent showed a significantly higher primary patency‡ compared with PTA at 6 and 12 months in the AVeNEW trial.[11] For treatment of ISR within AVGs, AVFs, or central veins, the FLUENCY® PLUS Endovascular Stent Graft was evaluated in the RESCUE trial and exhibited significantly higher primary patency§ compared with PTA at 6 months.[12,16]

In addition to providing improved clinical outcomes compared with PTA, the use of covered stents may have important economic benefits to both payers (eg, Medicare) and points of care (POC) (eg, hospitals and freestanding outpatient centers) due to reduced resource use over 2 years.[17] To highlight this, we recently conducted an economic analysis evaluating the impact of increasing the adoption of covered stents in clinical practice for treatment of AVG stenosis and AVF/AVG ISR from two different United States stakeholder perspectives. Our results highlighted the change in costs between the real-world mix of treatments for vascular access stenosis (88.9% PTA, 5.5% BMS, and 5.5% covered stents, as measured in 2016) to two different projected future treatment mixes where use of covered stents was increased for a hypothetical cohort of 1,000 patients. In the first projected scenario, the amount of PTA remained fixed, with the increased adoption of covered stents resulting from decreased BMS use (88.9% PTA, 2.8% BMS, 8.3% covered stents). In the second projected scenario, the use of covered stents and PTA were assumed to increase, resulting in further decreases in BMS use (90.3% PTA, 1.4% BMS, 8.3% covered stents). This assumption was supported by clinical trial data that found that use of covered stents resulted in reduced stenting relative to PTA reinterventions.[17]

The primary outcomes of our analyses were the costs associated with the index procedure and reinterventions over 2 years. These costs varied by stakeholder perspective (ie, POC or payers). The POC analyses considered the device costs for the index procedure and reinterventions. For the payer analyses, costs for the index procedure and reinterventions were based on 2017 Medicare reimbursement payments for procedures performed in physician office-based labs, ambulatory surgery centers, and hospital outpatient centers.[17]

To inform our reintervention outcomes, we used data from the RENOVA and RESCUE trials for AVG stenosis and AVF/AVG ISR, respectively. These outcomes included reintervention rates at 2 years and the breakdown of reintervention treatments after covered stent and PTA index procedures. Due to a lack of randomized evidence for currently used BMSs in hemodialysis vascular access and no definitive observational evidence supporting the use of BMSs over PTA for the treatment of AVG stenosis at 6 to 12 months, the clinical outcomes for BMSs were assumed to be equivalent to PTA.[17]

From a POC perspective, results of the AVG stenosis population predicted cost savings, with reduced overall spending on devices over 2 years ranging from $4,106 to $34,420 per 1,000 patients. In the AVF/AVG ISR population, the incremental results over 2 years ranged from an additional cost of $17,187 to potential cost savings of $13,159 per 1,000 patients, depending on the breakdown of interventions in the two projected scenarios. From Medicare's perspective, the two projected scenarios anticipated costs savings for the AVG stenosis and AVF/AVG ISR populations over 2 years. The predicted reduction in total Medicare payments per 1,000 patients ranged from $57,401 in the AVG/AVF ISR population to $169,544 in the AVG stenosis population, depending on the projected treatment mix.[17]

The projected economic advantages of covered stents demonstrated in our analyses are primarily driven by two factors. First, covered stents have been shown to reduce reinterventions over 2 years compared with PTA. In the RENOVA trial, use of the FLAIR® Endovascular Stent Graft resulted in less frequent reinterventions over 24 months compared with PTA (3.4 vs 4.3, respectively).[15] In the RESCUE trial, use of the FLUENCY® PLUS Endovascular Stent Graft also led to less frequent reinterventions over 24 months compared with PTA (5 vs 5.5, respectively).[12,16] In the AVeNEW trial, use of the COVERA™ Vascular Covered Stent in AVF stenosis reduced the risk of clinically driven reintervention at the target lesion by 68%¶ and decreased the average number of reinterventions at the target lesion and AV access circuit at 12 months compared with PTA‖.[11]

The second benefit with covered stents is the anticipated reduced cost of reinterventions due to less postprocedural stenting. In the RENOVA and RESCUE clinical trials, a larger proportion of reinterventions after

*Primary patency in the FLAIR pivotal study (n = 190) was defined as treatment area primary patency and was significantly greater for the FLAIR® Endovascular Stent Graft compared with PTA (51% vs 23%, respectively; $P < .001$).
†Primary patency in the AVeVA trial (n = 110) was defined as 6-month target lesion primary patency.
‡Primary patency in the AVeNEW trial (n = 280) was defined as 6-month target lesion primary patency and was significantly greater for the COVERA™ Vascular Covered Stent compared with PTA at 6 months (78.7% vs 47.9%, respectively; $P < .001$) and 12 months (57.5% vs 21.2%, respectively; $P < .001$).
§Primary patency in the RESCUE trial (n = 275) was defined as 6-month access circuit primary patency and was significantly greater for the FLUENCY® PLUS Endovascular Stent Graft compared with PTA (18.6% vs 4.5%, respectively; $P < .001$).
¶Reduction in risk of clinically driven reintervention at the target lesion with the COVERA™ Vascular Covered Stent measured as a hazard ratio (0.322; 95% confidence interval, 0.207–0.503; one-sided $P < .001$).
‖Mean number of AV access circuit reinterventions at 12 months with the COVERA™ Vascular Covered Stent and PTA were 1.74 and 2.10, respectively. Mean number of target lesion reinterventions at 12 months with the COVERA™ Vascular Covered Stent and PTA were 0.76 and 1.71, respectively.

covered stent treatment were PTA, whereas patients with an index PTA treatment had a greater proportion of reinterventions using stents (both BMSs and covered stents).[12-14,16] The difference in distribution of reintervention treatments compounds the economic benefits of covered stents, as the lower rate and reduced costs can offset the increased device costs of index procedure.

With recent shifts in the health care landscape, clinical and economic outcomes for the treatment of vascular access stenosis are becoming increasingly important to both payers and hospitals, making the use of covered stents an attractive option. From a payer perspective, the push to reduce costs and maintain clinical outcomes makes the use of covered stents an attractive treatment option compared with historical methods. From a hospital perspective, when moving beyond a traditional FFS model into more value-based global payment systems, the total costs of care—rather than just device/consumable costs—become very relevant because every patient reintervention does not necessarily translate into a separate reimbursement payment by payers. With the increasing shift away from volume-based FFS systems, evidence about strategies that provide the greatest clinical and economic benefit is critical to allow hospitals to remain competitive.[17] In these situations, cost analyses such as ours can be effective tools in helping physicians and other health care stakeholders make decisions that involve trade-offs between benefits and costs. ■

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BD-10752

INDICATIONS FOR USE GLOBALLY

Atlas® Gold PTA Dilatation Catheter

INDICATIONS FOR USE: Atlas® Gold PTA Dilatation Catheter is indicated for use in Percutaneous Transluminal Angioplasty of the iliac arteries and for the treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistulae. This device is also indicated for post-dilatation of stents and stent grafts in the peripheral vasculature. This catheter is not for use in coronary arteries.

CONTRAINDICATIONS: None known.

Conquest® 40 PTA Dilatation Catheter

INDICATIONS FOR USE: Conquest® 40 PTA Dilatation Catheter is recommended for use in Percutaneous Transluminal Angioplasty of the femoral, iliac, and renal arteries and for the treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistulae. This device is also recommended for post-dilatation of stents and stent grafts in the peripheral vasculature. This catheter is not for use in coronary arteries.

CONTRAINDICATIONS: None known.

Dorado® PTA Dilatation Catheter

INDICATIONS FOR USE: Dorado® Balloon Dilatation Catheters are recommended for Percutaneous Transluminal Angioplasty (PTA) of the renal, iliac, femoral, popliteal, tibial, peroneal, and subclavian arteries and for the treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistulae. This device is also recommended for post-dilatation of balloon expandable and self expanding stents in the peripheral vasculature. This catheter is not for use in coronary arteries.

CONTRAINDICATIONS: None known.

Flair® Endovascular Stent Graft

INDICATIONS FOR USE: The Flair® Endovascular Stent Graft is indicated for use in the treatment of stenoses at the venous anastomosis of ePTFE or other synthetic arteriovenous (AV) access grafts.

CONTRAINDICATIONS: There are no known contraindications for the Flair® Endovascular Stent Graft.

Ultraverse® 035 PTA Dilatation Catheter

INDICATIONS FOR USE: The Ultraverse® 035 PTA Dilatation Catheter is intended to dilate stenoses in the peripheral arteries, to treat obstructive lesions of native or synthetic AV fistulae and/or re-expand endoluminal stent graft elements in the iliac arteries. This device is also recommended for post-dilatation of balloon expandable and self-expanding stents in the peripheral vasculature. This catheter is not for use in coronary arteries.

CONTRAINDICATIONS: None known.

INDICATIONS FOR USE IN THE U.S.

Covera™ Vascular Covered Stent

INDICATIONS FOR USE: The Covera™ Vascular Covered Stent is indicated for use in hemodialysis patients or the treatment of stenoses in the venous outflow of an arterio-venous (AV) fistula and at the venous anastomosis of an ePTFE or other synthetic AV graft.

CONTRAINDICATIONS: There are no known contraindications for the Covera™ Vascular Covered Stent.

Fluency® Plus Endovascular Stent Graft

INDICATIONS FOR USE: The Fluency® Plus Endovascular Stent Graft is indicated for use in the treatment of in-stent restenosis in the venous outflow of hemodialysis patients dialyzing by either an arteriovenous (AV) fistula or AV graft and for the treatment of stenosis in the venous outflow of hemodialysis patients dialyzing by an AV graft.

CONTRAINDICATIONS: There are no known contraindications for the Fluency® Plus Endovascular Stent Graft.

Lutonix® 035 Drug Coated Balloon PTA Catheter

INDICATIONS FOR USE: The Lutonix® Catheter is indicated for percutaneous transluminal angioplasty (PTA), after pre-dilatation, for treatment of stenotic lesions of dysfunctional native arteriovenous dialysis fistulae that are 4 mm to 12 mm in diameter and up to 80 mm in length.

CONTRAINDICATIONS: • Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children over the next 2 years. It is unknown whether paclitaxel will be excreted in human milk and there is a potential for adverse reaction in nursing infants from paclitaxel exposure. • Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placements of the delivery system.

WavelinQ™ 4F EndoAVF

INDICATIONS FOR USE: The WavelinQ™ 4F EndoAVF System is indicated for the creation of an arteriovenous fistula (AVF) using concomitant ulnar artery and ulnar vein or concomitant radial artery and radial vein in patients with minimum artery and vein diameters of 2.0 mm at the fistula creation site who have chronic kidney disease and need hemodialysis.

CONTRAINDICATIONS: Target vessels < 2mm in diameter.

INDICATIONS FOR USE IN EU UNDER CE MARK

Covera™ Vascular Covered Stent

INDICATIONS FOR USE: The Covera™ Vascular Covered Stent is indicated for the treatment of stenoses in the upper extremity venous outflow of patients dialyzing with an arteriovenous (AV) access graft or fistula.

CONTRAINDICATIONS: There are no known contraindications for the Covera™ Vascular Covered Stent.

Fluency® Plus Endovascular Stent Graft

INDICATIONS FOR USE: • Residual stenosis with impaired perfusion (pressure gradient) following balloon dilatation, especially in stages III and IV according to Fontaine. • Dissection. • Detached arteriosclerotic plaque material and luminal obstruction following balloon dilatation. • Occlusion after thrombolysis or after aspiration and before dilatation. • Restenosis or reocclusion.

CONTRAINDICATIONS: • Uncorrected coagulopathies. • Functionally relevant obstruction of the inflow path, poor outflow or no distal runoff. • Fresh, soft thrombotic or embolic material. • Placement in the distal superficial femoral artery. • Placement in the popliteal artery.

Lutonix® 035 Drug Coated Balloon PTA Catheter

INDICATIONS FOR USE: The Lutonix® 035 Drug Coated Balloon Catheter is intended for Percutaneous Transluminal Angioplasty (PTA) in the peripheral vasculature and for the treatment of obstructive lesions and decreasing the incidence of restenosis. In addition, the Lutonix® 035 Drug Coated Balloon Catheter is intended for PTA of native dialysis fistulae or synthetic grafts, opening narrowing and immature fistulae, to improve blood flow, and decreasing the incidence of restenosis.

CONTRAINDICATIONS: The Lutonix® Catheter is contraindicated for use in: • Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy. • Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and there is a potential for adverse reaction in nursing infants from paclitaxel exposure. • Pediatric patients. The safety and effectiveness of the Lutonix® Catheter in pediatric patients has not been established. • Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system. • This product should not be used in patients with known hypersensitivity to paclitaxel or structurally related compounds.

WavelinQ™ 4F EndoAVF System

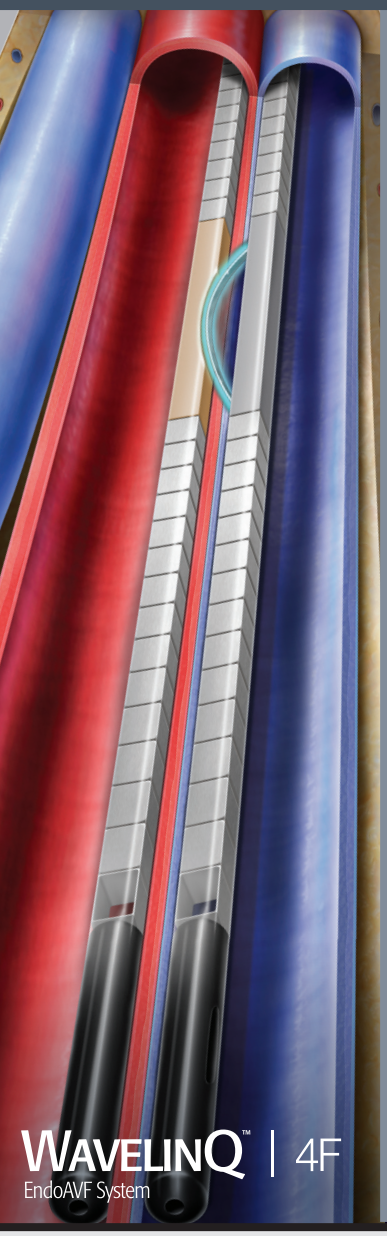
INDICATIONS FOR USE: The WavelinQ™ 4F EndoAVF System is intended for the cutting and coagulation of blood vessel tissue in the peripheral vasculature for the creation of an arteriovenous fistula used for hemodialysis.

CONTRAINDICATIONS: • Known central venous stenosis or upper extremity venous occlusion on the same side as the planned AVF creation. • Known allergy or reaction to any drugs/fluids used in this procedure. • Known adverse effects to moderate sedation and/or anesthesia. • Distance between target artery and vein > 1.5 mm. • Target vessels < 2 mm in diameter.

Create a Complete AV Access Program

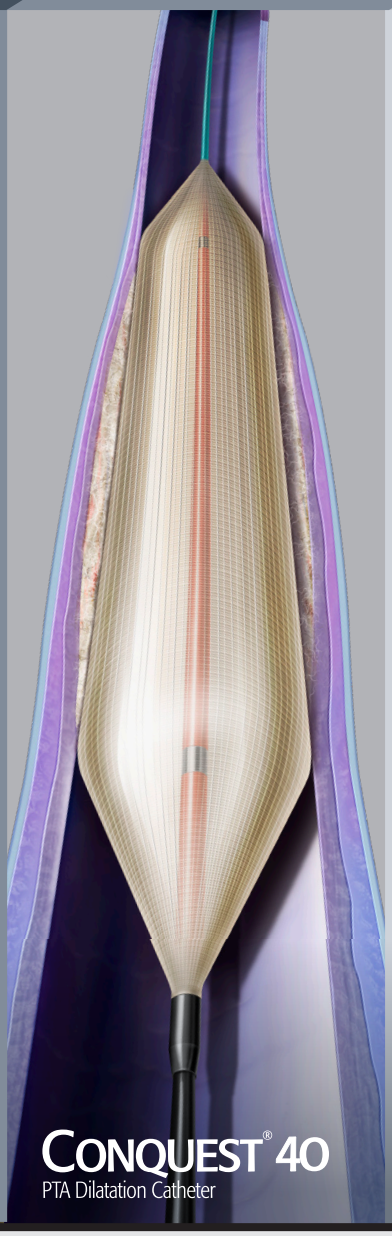
BD offers a comprehensive product portfolio of devices and innovative solutions for creating, restoring and maintaining a patient's AV access. When you reach for an innovation in AV access care, it is important that it is backed by a company that you have trusted for many years. It means that you will have the expert service and support, trusted data, and the leading medical devices that you can count on to deliver care to your patients every day.

CREATE



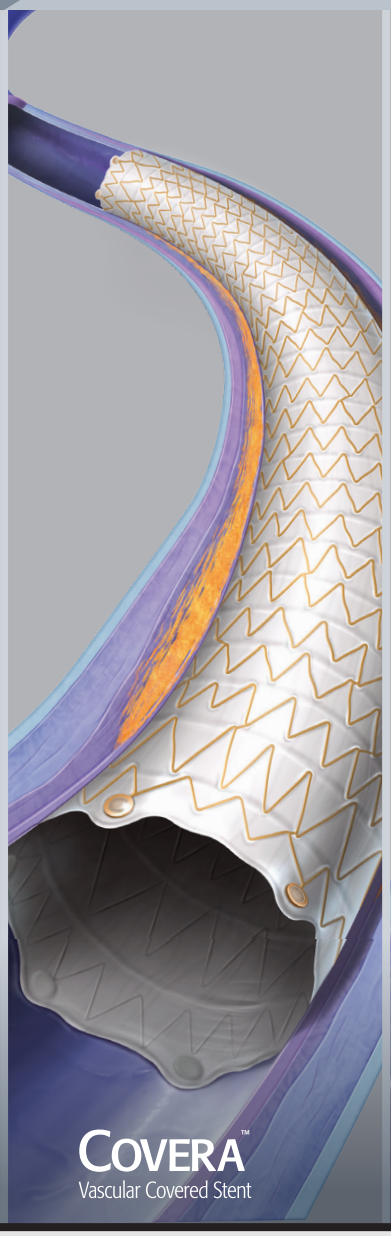
WAVELINQ™ | 4F
EndoAVF System

RESTORE



CONQUEST® 40
PTA Dilatation Catheter

MAINTAIN



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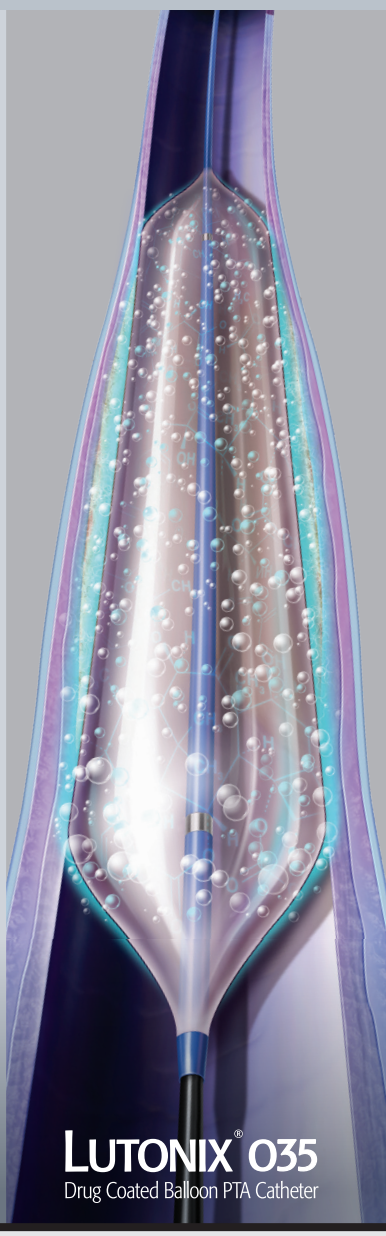
Vascular Covered Stent



LUTONIX® 035
Drug Coated Balloon PTA Catheter

Please refer to previous page for product indications and contraindications.

Please consult product labels and instructions for use for indications, contraindications, hazards, warnings and precautions.

BD

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