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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.<sup>1</sup> 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.<sup>2</sup>

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).<sup>3</sup> 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.

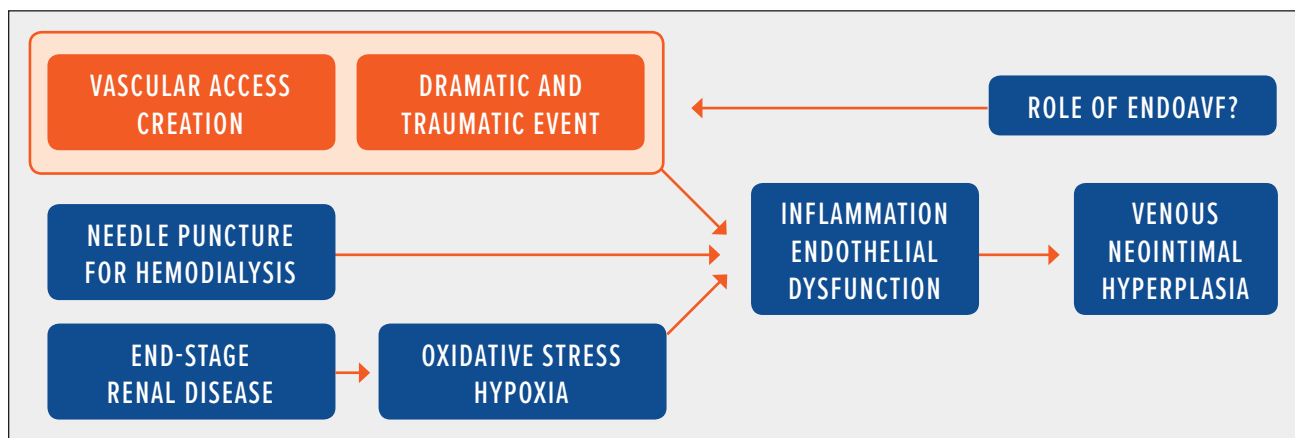


Figure 1. Characteristics of AV stenosis. endoAVF, endovascular arteriovenous fistula.

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.<sup>4</sup>

### 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).<sup>5</sup> Additionally, Swinnen confirmed the increased presence of early elastic recoil after angioplasty.<sup>6</sup> 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.<sup>7</sup>

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.<sup>7</sup> 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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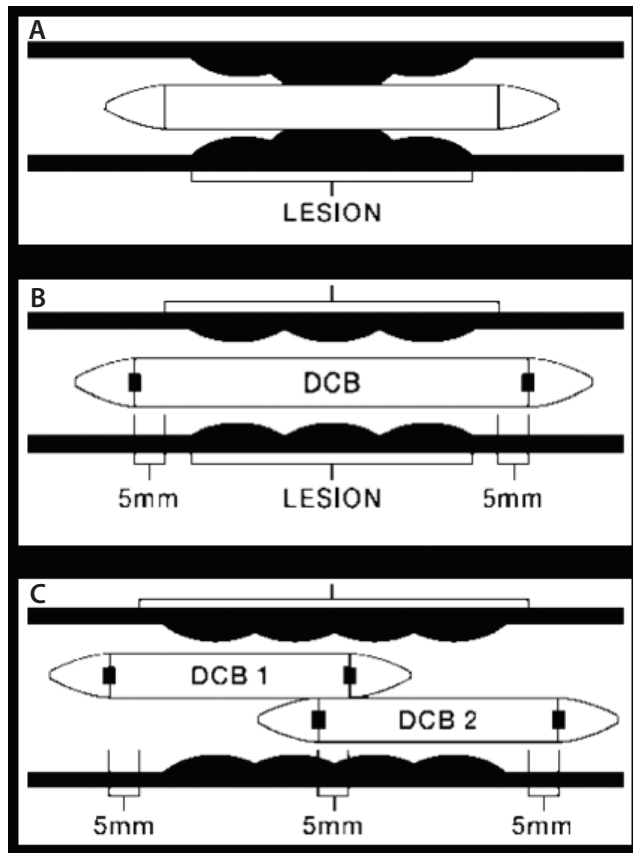


Figure 2. A technique of using DCBs to secure adequate treatment of postangioplasty area. Predilation with high-pressure balloon (A); DCB treatment for vessel preparation injury (B); and dual DCB treatment for predilation/injury segment (C).

**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.<sup>8</sup> If vessel preparation is not successful, a metallic scaffold may be used—covered stents

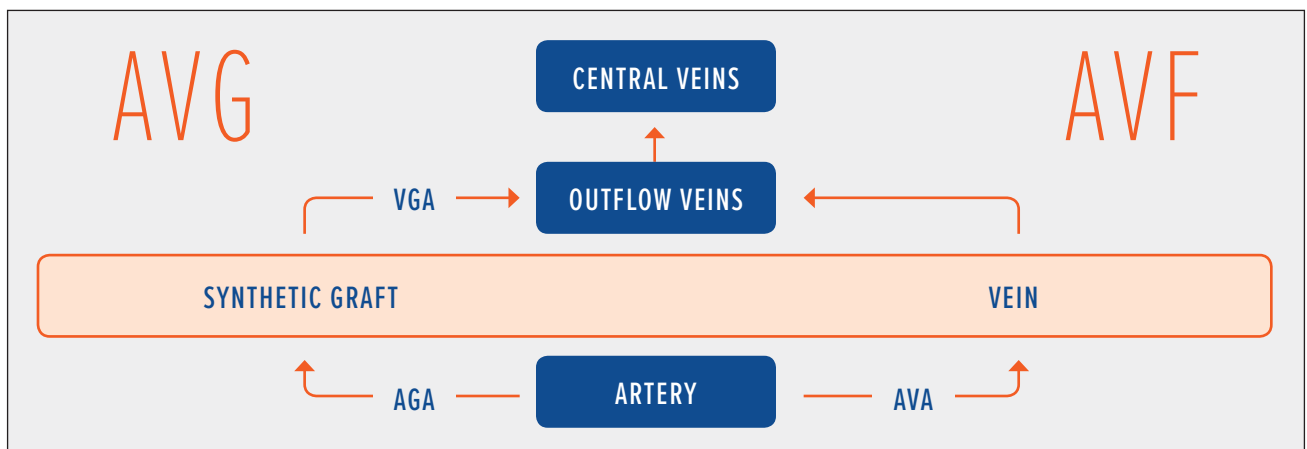


Figure 3. Different segments of AV circuits. The difference between AVGs and AVFs lies in the cannulation zone and the different anastomoses. AGA, arterial-graft anastomosis; AVA, arteriovenous anastomosis; VGA, venous-graft anastomosis.

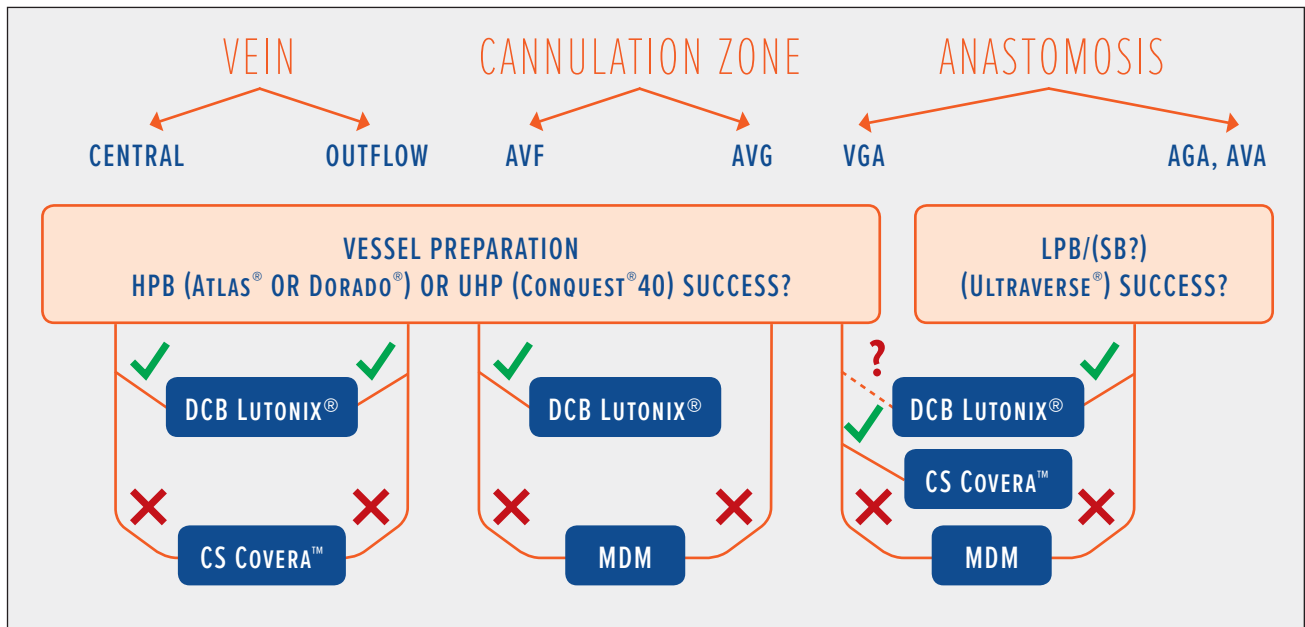


Figure 4. Algorithm of the authors' general treatment approach to AV access stenosis. AGA, arterial-graft anastomosis; AVA, arteriovenous anastomosis; CS, covered stent; HPB, high-pressure balloon; MDM, multidisciplinary meeting; LPB, low-pressure balloon; SB, scoring balloon; UHP, ultra-high-pressure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

are preferred, as they have been shown to have better patency rates compared to bare-metal stents.<sup>9</sup>

### Outflow Veins

Our treatment algorithm for outflow vein stenosis is to incorporate ultra high pressure with a CONQUEST<sup>®</sup> 40 Catheter. Successful angioplasty is then followed by a LUTONIX<sup>®</sup> 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.<sup>10</sup> Kitrou et al reported a TLPP of 72.2% at 6 months in their retrospective analyses,<sup>11</sup> 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.<sup>12</sup> If vessel preparation fails, use of the COVERA<sup>™</sup> 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.<sup>13</sup>

### 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<sup>™</sup> 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<sup>®</sup> 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.<sup>3,14,15</sup> Most recently, the 6-month results from the AVeVA clinical trial, which studied the COVERA<sup>™</sup> Vascular Covered Stent at the graft-vein anastomosis, demonstrated a 71.0% TLPP at 6 months.<sup>16</sup>

### 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<sup>®</sup> 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<sup>10</sup>: 71.4%
- Lutonix Global AV study<sup>12</sup>: 73.5% (78.1% for AVF outflow only)
- Lutonix retrospective study<sup>11</sup>: 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<sup>16</sup>: 71.0%
- AVeNEW RCT<sup>13</sup>: 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<sup>10-13,16</sup>):

- 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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