Drug-Coated Balloons: What's Their Role in AV Access?

The rationale for investigating the use of paclitaxel-coated balloons in vascular access.

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The main disadvantage of endovascular treatment for arterial atherosclerotic occlusive disease is clinical relapse due to neointimal hyperplasia (NIH) formation, induced mainly by barotrauma and inflammation following angioplasty.[1] However, in dialysis access arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs), the pathophysiology of stenosis is different. Various mechanical and biochemical parameters contribute to continuous NIH proliferation. It is believed that ongoing NIH proliferation in AVFs and AVGs is due to nonphysiologic flow dynamics that develop when there is a direct anastomosis of a high-pressure arterial system into a low-pressure venous one. This arterial-to-venous flow circuit generates tangential wall and shear stress, compliance mismatch between arteries and veins, and flow turbulence throughout the circuit. The pathophysiology of vascular access stenosis includes smooth muscle cell (SMC) hyperplasia and angiotensin-mediated, NIH-related augmented pressure.

Mechanical factors contribute to ongoing NIH, including repetitive needle punctures that can lead to both endothelial disruption and fibrotic wall changes. Biochemical mediators of NIH include endothelial dysfunction due to oxidative stress produced by chronic inflammation present in dialysis patients, as well as foreign body reaction (for AVGs).[2,3] Any or all of these factors lead to exaggerated fibromuscular neointimal proliferation—even without endothelial layer disruption. This type of NIH stenosis may have a technically satisfactory result following balloon dilation, but in general, most reports cite poor short-term plain balloon angioplasty and bare-metal stent patency rates in AV access treatment. Although the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines suggest that angioplasty of AV access stenosis should yield at least a 50% 6-month primary patency rate, reported primary patency rates from more-recent publications have found that this patency rate may be well below 50% at 6 months.[4,5]

Although there are scant data for the use of drug-coated balloons in AVFs and AVGs, improved patency following angioplasty with paclitaxel-coated balloons (PCBs) for atherosclerotic arterial stenosis has been validated. A multicenter randomized controlled trial (RCT) demonstrated reduced arterial NIH following treatment of femoropopliteal lesions with PCBs when compared to plain balloon angioplasty.[2] PCB endovascular technology combines the dilating properties of angioplasty with local drug delivery. Balloon surface excipients enable drug elution within the vessel wall, inhibiting cell proliferation and reducing NIH while avoiding the use of permanent metal stents. Paclitaxel is a lipophilic, cytotoxic agent that stabilizes tubulin polymers and prevents their disassembly, thereby halting the progression of mitosis from prophase to metaphase. The end result is that treated cells cannot divide. More specifically, paclitaxel halts SMC proliferation at the angioplasty site and reduces NIH.[6,7]

Studies investigating PCBs in venous or hemodialysis AV animal models are missing. Nonetheless, paclitaxel-coated expanded polytetrafluoroethylene (PTFE) grafts in a porcine model of hemodialysis graft stenosis prevented NIH.[8] Will paclitaxel angioplasty in human AVFs and AVGs reduce NIH and improve patency? These are very interesting and important questions.

CURRENTLY AVAILABLE TECHNOLOGIES AND PUBLISHED DATA

Currently available PCB technologies include a variety of 0.035-, 0.018-, and 0.014-inch platforms developed for the treatment of peripheral arterial disease and smaller-diameter 0.014-inch platforms used in coronary angioplasty. The majority of PCBs use a 3.5-µg/mm^2 drug dose, such as the In.Pact Admiral over-the-wire drug-coated

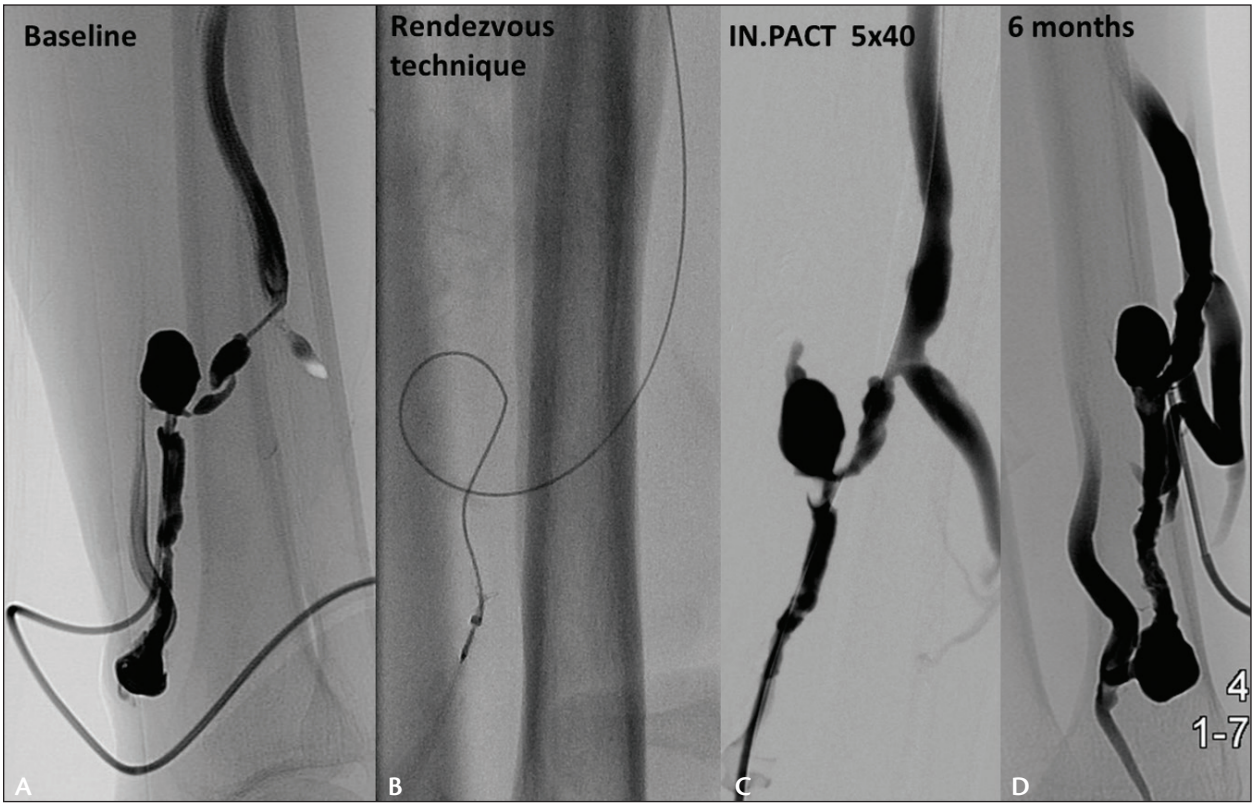

Figure 1. A 68-year-old man with a dysfunctional Brescia-Cimino AVF. Digital subtraction angiography (DSA) revealed significant venous stenoses and aneurysmal dilation approximately 5 cm from the anastomosis (A). The lesion was crossed with the "rendezvous technique," re-entering with a 0.018-inch guidewire from the proximal venous sheath into the distal para-anastomotic sheath (B). Angioplasty with a 5- X 40-mm In.Pact PCB (C). A follow-up fistulagram at 6 months demonstrated vein enlargement (positive remodeling) without target lesion restenosis (D).

balloon catheters (Medtronic), whereas the Lutonix drug-coated balloon catheter (Bard Peripheral Vascular, Inc.), which uses a lower 2-µg/mm^2 dose, is also available in some markets in larger-diameter balloons from > 7 mm and up to 12 mm and is suitable for vascular access and central vein treatment. One dedicated PCB for dialysis access shunt treatment is the novel Aperto OTW paclitaxel-releasing, high-pressure balloon dilatation catheter (Cardionovum GmbH), which has a rated burst pressure of 20 bar; however, this device is not available in diameters larger than 7 mm.

Our group at Patras University Hospital in Rio, Greece, investigated the off-label use of PCBs to reduce restenosis and improve patency outcomes in dialysis access in two consecutive single-center, prospective RCTs. The first was a safety and efficacy study that enrolled 40 patients with clinical signs of dysfunctional AVGs or AVFs and one angiographically proven venous outflow stenosis. Patients were randomized on a 1:1 basis to undergo high-pressure balloon angioplasty versus PCB angioplasty for the management of both de novo and restenotic lesions. The PCBs used were the In.Pact drug-coated balloon catheter, which is available in diameters up to 7 mm and lengths up to 120 mm. Six-month interim results were published by Katsanos et al in 2012.[9] No procedure-related complications were noted. Lesion preparation with predilation was not performed, but postdilation was necessary in 65% in the PCB group due to a suboptimal angiographic result versus 0% in the control group ($P < .0001$). This was attributed to the resistant fibrotic nature of the stenoses being unresponsive to normal-pressure PCB angioplasty (12 atm burst pressure). Cumulative target lesion primary patency, defined as the time period without reintervention due to a > 50% stenosis of the previously treated lesion, was significantly superior in the PCB group (70% vs 25%, $P < .001$; hazard ratio (HR), 0.3; 95% confidence interval (CI), 0.12–0.71; $P < .006$). Moreover, cumulative primary patency of the treated dialysis circuit was also significantly improved with PCB treatment (65% vs 20%, $P < .002$; HR, 0.32; 95% CI, 0.14–0.75; $P < .008$) (Figure 1). However, overall dialysis circuit survival (patent and functional vascular access regardless of the number of repeat surgical and/or percutaneous procedures) was similar in both groups.[9]

Final 1-year results recently published by Kitrou et al demonstrated sustained superior patency outcomes in the PCB group.[10] Specifically, cumulative target lesion primary patency was 35% versus 5% ($P < .001$), with an adjusted HR following Cox multivariable regression of 0.23 (95% CI, 0.1–0.5). Again, no device-related complications were noted.

Additionally, according to the cost-effectiveness analysis performed, PCB angioplasty was related to a reasonable incremental cost-effectiveness ratio—calculated as direct extra costs per year of primary patency gained—of approximately €2,250 per primary patency year of dialysis access gained. The incremental net benefit was nearly €1,000 for a willingness-to-pay threshold of €5,000, which is a reasonable extra cost value to pay in order to gain an extra year of dialysis access patency in each patient. However, the specific analysis was limited by the fact that proper cost-utility and quality-of-life information were not available.

Notably, the study was underpowered for valid subgroup analysis, as the number of AVFs treated was small (seven in each group). This motivated the authors to conduct another single-center RCT to investigate the performance of PCBs in stenoses occurring within AVFs. Again, 40 patients with dysfunctional fistulas were randomized on a 1:1 basis in two groups to undergo either high-pressure balloon angioplasty or PCB angioplasty with the In.Pact device. The primary outcome of 1-year survival free of target lesion revascularization was again significantly superior, nearly double, in the PCB group (308 vs 161 days; HR, 0.478; 95% CI, 0.236–0.966; $P < .03$), and access circuit primary patency was significantly improved following PCB treatment as well (270 vs 161 days; HR, 0.479; 95% CI, 0.237–0.968; $P < .04$). No procedure-related complications were reported. Nonetheless, once more, the postdilation rate was significantly higher in the PCB group (65% vs 0%; $P < .0001$), although anatomical and clinical success after postdilation was 100%.[10]

A single-center, prospective, observational study conducted by Lai et al investigated the SeQuent Please coronary PCB (B. Braun Interventional Systems Inc.) compared with plain balloon angioplasty for the management of 20 juxta-anastomotic stenoses in the autologous radiocephalic fistulas of 10 patients.[11] A different lesion in the same patient served as the control. Survival free of target lesion revascularization was significantly longer in the PCB group (251.2 vs 103.2 days; $P < .01$), and 6-month patency was again significantly in favor of PCB angioplasty (70% vs 0%; $P < .01$). However, although numerically superior, significantly improved patency was not sustained at 12-month follow-up (20% vs 0%; $P > .05$).[11]

In a retrospective study published by Massmann et al in 2015, custom-made, large-diameter (> 7–14 mm) PCBs were investigated for the treatment of recurrent symptomatic central stenosis in 27 consecutive patients with hemodialysis fistulas.[12] The PCBs were manufactured using standard over-the-wire balloon catheters coated with polymer-free microcrystalline paclitaxel at a concentration of 2 µg/mm^2 (Elutax SV, Aachen Resonance GmbH). Compared to plain balloon angioplasty, the PCBs performed better, achieving significantly superior freedom from target lesion revascularization rates according to Kaplan-Meier analysis after approximately 18 months mean follow-up. The authors reported that PCB angioplasty prolonged restenosis intervals (median, 9 vs 4 months; $P = .023$).[12] This was the first study to provide data from > 7-mm PCBs for the management of central vein disease, as balloons used in the previously described trials were up to 7 mm in diameter, and dialysis patients with central vein disease were not included.

Currently, results from two trials documented on clinicaltrials.gov are awaited. The DEBAPTA (Prospective Randomized Trial Comparing DEB Versus Conventional PTA for the Treatment of Hemodialysis AVF or AVG Stenoses) is a single-center, prospective, randomized trial designed to compare PCB angioplasty versus conventional balloon angioplasty for the treatment of AVGs and AVFs stenoses and was completed in March 2014 (NCT01544907). The primary outcome measure was 6-month late luminal loss. The interim results from 30 patients were presented at the Society of Interventional Radiology's annual meeting in 2013 and did not demonstrate significantly better results with the PCB, although late luminal loss was less in the PCB group (mean late luminal loss, 29%; standard deviation, 25.2; range, 0–68) versus conventional balloon angioplasty (mean late luminal loss, 44%; standard deviation, 19.4; range, 0–70; $P = .162$). Anatomic success was similar in both groups.[13] The final results are awaited.

Additionally, an international, parallel assignment, open-label, randomized safety/efficacy trial (Local Delivery of Paclitaxel for Prevention of Restenosis in Hemodialysis Access) was launched to compare the 6-month patency rates after angioplasty with the Passeo-18 Lux paclitaxel-coated balloon (Biotronik) versus a conventional balloon (NCT01001676). The study was recently completed in November 2014, and outcomes are awaited. Finally, Bard obtained US Food and Drug Administration approval for a multicenter trial designed to investigate the performance of the Lutonix drug-coated balloon catheter in vascular access stenosis treatment. The study design will soon be available at clinicaltrials.gov.

FUTURE CONSIDERATIONS

According to the initial experience, PCB angioplasty of vascular access stenoses is safe and effective, providing superior reintervention-free intervals compared to plain balloon angioplasty by reducing restenosis without any

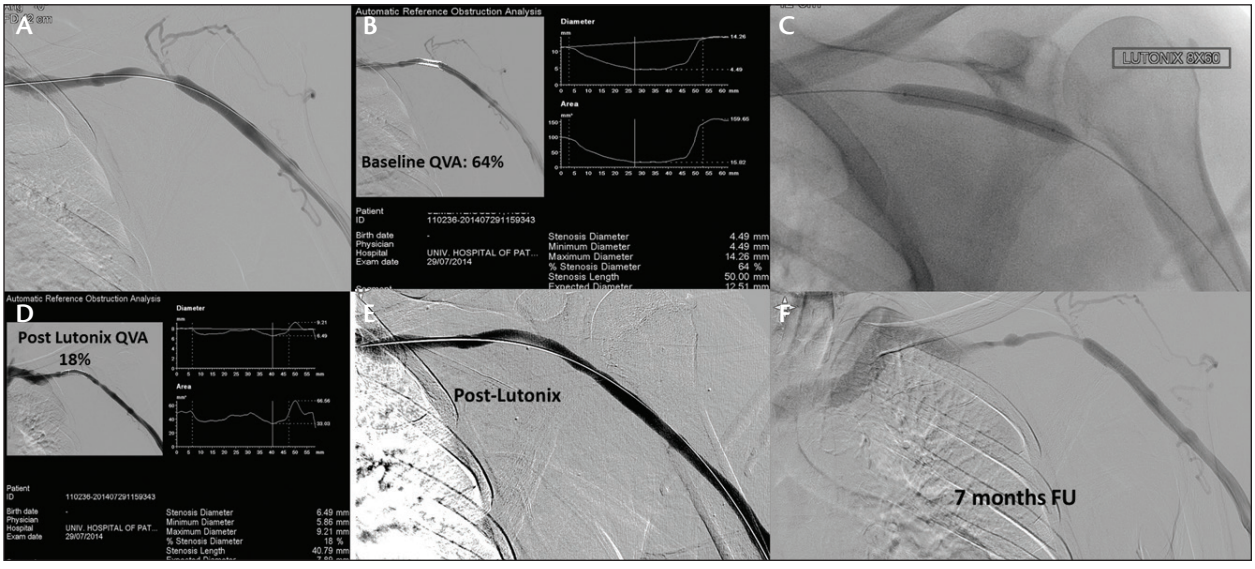

Figure 2. A 61-year-old man was referred to our department due to a dysfunctional AVF. Baseline DSA demonstrated a significant stenosis at the cephalic arch (A). Quantitative vessel analysis using integrated semiautomated software indicated a 64% stenosis (B). Angioplasty was performed using an 8- X 60-mm Lutonix PCB (predilation with a 7- X 40-mm high-pressure balloon not shown; C). Quantitative vessel analysis demonstrated 18% remaining stenosis (D). The final angiographic result (E). Note the disappearance of collateral circulation compared to baseline (F). After 7 months, the patient was again referred to our department due to suboptimal dialysis. DSA revealed significant target lesion restenosis. Nonetheless, the reintervention-free interval exceeded 6 months.

device-related complications. Still, the reported number of dialysis patients treated with PCBs is low, and several issues remain to be determined.

First of all, it is not clear which lesions will benefit from this technology, as not all lesions are the same. The pathophysiology of vascular access stenosis depends on biomechanical properties, which differ between various anatomical sites of the access and on vessel histological type and caliber. These specific lesion characteristics may influence endovascular treatment outcomes. For instance, shear stress within thin-walled veins, as well as periodic punctures at the same site, triggers fibromuscular hyperplasia, causing fibrotic venous lesions that are more resistant to percutaneous transluminal angioplasty and susceptible to recoil compared to nonfibrotic lesions.[3]

It is also widely acknowledged that 3-month patency after angioplasty of central stenoses and cephalic arch lesions remains extremely poor (Figure 2). Fibrotic, platelet-based stenosis developed within PTFE grafts may not benefit from PCB angioplasty, as the paclitaxel mechanism of action is mainly based on SMC cycle inhibition. In analogy to peripheral arterial disease, in which different devices are indicated for diverse arterial segments (eg, carotid, iliac, femoropopliteal, or infrapopliteal arteries), vascular access treatment involving arterial, inflow, main body ("arterialized" vein or PTFE), and large-caliber venous outflow lesions should not be considered a "one-treatment-fits-all" area and should also include different indications for various devices. Furthermore, PCBs could improve patency for in-stent restenosis or in-segment stent graft restenosis. Phenomena such as neoatherosclerosis (eg, continuous atherosclerotic process within neointimal hyperplasia) after stenting could also affect treatment, and the effect of antiplatelet therapy on outcomes after dialysis access percutaneous transluminal angioplasty or stenting remains "terra incognita."[14]

Lesion preparation is another issue that merits further investigation. Manufacturing companies recommend predilation to facilitate drug diffusion within the deeper layers of the vessel wall and to optimize the antirestenotic effect. However, in both RCTs published so far, predilation was not performed. As PCB technology was developed to attain uniform drug coating and delivery to the vessel wall, normal pressure-compliant balloons were employed, and therefore, a limitation of PCB angioplasty is the necessity to postdilate with a high-pressure balloon in the majority of the cases in order to accomplish an acceptable immediate angioplasty outcome. Perhaps newly developed high-pressure PCBs could surpass the need for additional postdilation and even predilation, decreasing procedural cost and time. Nonetheless, technical improvements in new-generation

PCBs to ameliorate outcomes and address current limitations are awaited.

Finally, although the long-term safety of PCBs in dialysis access treatment has been reported, preclinical, experimental studies in animal models are missing, and therefore, information on the pathology demonstrating the effect, diffusion, and duration of paclitaxel within the venous wall is not available. Of note, preclinical data could also provide information regarding the safety time margin of reusing PCB angioplasty in the same lesion.

CONCLUSION

The initial results indicate that PCB angioplasty for dysfunctional vascular accesses could improve clinical outcomes and treatment cost effectiveness by significantly reducing restenosis. However, several issues remain to be determined as research advances, and results from large, multicenter RCTs are awaited to validate the beneficial effect of PCB angioplasty in dialysis access stenoses and establish specific indications according to high-quality evidence. ■

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