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# Drug Coated Balloon Angioplasty for Dysfunctional Arteriovenous Fistula: A New Standard-of-Care in the Horizon?

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## Abstract

Plain old balloon angioplasty has been a common treatment for arteriovenous fistula (AVF) stenoses; but the latest clinical evidence suggests that drug coated balloons (DCB) significantly increase patency rates and reduce reintervention frequencies.

DCBs delivering the antirestenotic agent paclitaxel have shown to improve outcomes by inhibiting intimal hyperplasia due to the efficient release of the drug into the vessel wall, leading to a diminished proliferation of smooth muscle cells and preventing restenosis. As such, paclitaxel-containing balloons can improve patency rate and reduce reinterventions in hemodialysis vascular access.

Evidence from clinical trials indicates that different brands of paclitaxel DCBs have different associated performance, due to specific design features, different coating technology and a various drug-ligand interactions.

Besides presenting the clinical evidence of different marketed DCBs for AVF dysfunction, this review gives a further insight into the APERTO OTW (Over-The-Wire) paclitaxel DCB, and its novel SAFEPAX coating technology - specifically designed for hemodialysis vascular access stenoses.

As such, this review intends to guide the interventionalist in their decision-making process, knowing that DCBs appear safe when used in arteriovenous access, and seem to provide a benefit in terms of increasing primary patency rates and extending the amount of time between reinterventions.

**Keywords:** Angioplasty; Autogenous Arteriovenous Fistula; Hemodialysis; Drug Coated Balloon; Paclitaxel; Excipient; Coating

## Introduction

In 2017, the Global Burden of Disease Study group estimated the prevalence of Chronic Kidney Disease (CKD) at ~100 million Europeans, among them 55.7 million specifically in European Union (EU) countries alone [1]. In addition, it has been stated that CKD was among the most expensive diseases for health systems, due to a multimorbid population, with an estimated cost of 140 billion EUR annually in the EU. [2]

CKD frequently develops slowly, without initial symptoms, becoming progressively more debilitating at later stages, with kidney replacement therapy (i.e., hemodialysis, or transplantation) being the usual approach to support quality of life. Due to ageing, the incidence and prevalence of CKD increases exponentially, which is mirrored by a year-by-year increase in the age of the dialysis population. [3]

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Since an important cause of morbidity and mortality in hemodialysis patients is complications in vascular access (VA) [4], it is now widely accepted that autogenous arteriovenous fistula (AVF) is the optimal form of VA for better patency and lower infection rates, in comparison with arteriovenous grafts or central venous catheters. [5-7] Guidelines on VA from the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) [8], the Fistula First Initiative [9] and the European Society for Vascular Surgery (ESVS) [10], recommend that AVFs should be considered as the preferred initial access for hemodialysis, particularly in end-stage renal disease (ESRD) patients, where AVFs have proven to have superior clinical and economic advantages. [11]

## Autogenous arteriovenous fistula (AVF) maturation

AVF maturation is a complex process, where the arteriovenous anastomosis reactively enlarge leading to an increase in blood flow, pressure, and vessel wall shear, exposing the veins to an oxygen-rich environment; and as such, promoting a chain-reaction of compensatory outward remodeling, lumen expansion, and wall thickening. [8] Ideally, a mature AVF can easily be punctured during hemodialysis - with a frequency of at least 3 times per week, with a minimal risk of blood leakage, and is able to provide sufficient blood flow throughout the treatment process. [12]

Since publication of the ESVS and KDOQI guidelines, there has been a gradual increase in the application of AVF; and with that, the incidence of vascular access-related complications, such as AVF stenosis or even occlusion, has increased significantly. [13,14] Indeed, due to the physiological nature of the circuit, the maintenance of AVF patency has remained a challenge with several studies showing that 1-year after the initial operation AVF patency rate is only 60-65% [15], and 2-year patency rates are 38-56% [16] – which consequently, leads to a deficient hemodialysis treatment.

## Plain Old Balloon versus Drug Coated Balloon (DCB) Angioplasty

In case of AVF stenosis or occlusion, plain old balloon percutaneous transluminal angioplasty (PTA) is a well-suited intervention for savaging the circuit. [17] Typically, high-pressure balloons (HPB) are the mainstay of treatment when there is an angiographically significant stenosis associated with clinical dysfunction. [8]

However, as reported in systematic reviews and meta-analyses, approximately 50% of patients need a repeated intervention within 6-months. [14,18-20] Following PTA, a combination of upstream and downstream events lead to the development of neo-intimal hyperplasia (IH), and a consequent AVF dysfunction. The pathophysiological mechanism includes pinprick injuries to endothelial cells (ECs), hemodynamic alterations caused by flow turbulence, immune or metabolic stresses, which trigger severe downstream responses such as inflammatory cell adhesion, proliferation and migration of vascular smooth muscle cells (VSMCs), persistent release of extracellular matrix (ECM) proteins, and concomitant vessel lumen remodeling. [21-24]

Due to these factors, the ideal AVF stenosis handling should treat both the culprit lesion and prevent future restenosis. [8,25] With that in mind, the idea of pairing angioplasty with a therapy that inhibits post-angioplasty IH and its associated restenosis, has driven the rationale behind using drug-coated balloons (DCBs). Such devices have been designed to deliver anti-proliferative drugs into the vessel wall of a treated stenotic lesion; and have proven effective at preventing restenosis in atherosclerotic coronary arterial disease (CAD) [26,27] and peripheral arterial disease (PAD). [28,29] In fact, a recent meta-analysis demonstrated that DCBs have a statistically significant higher primary patency rate of target lesions versus PTA at 6- and 12-months timepoints after AVF intervention. [13]

## Paclitaxel Drug Coated Balloons (DCBs): safety concerns

At present, paclitaxel is the most used drug for DCBs. [27]

In late 2018, a meta-analysis by Katsanos et al. published in the Journal of the American Heart Association (JAHA) suggested an increased mortality rate in PAD patients treated with paclitaxel-coated balloons and stents [30], which aroused a widespread concern about the safety of paclitaxel-related endovascular devices. However, device manufacturers collaborated in an updated meta-analysis with the U.S. Food and Drug Administration (FDA) that included additional studies, more complete vital status information, and longer-term follow-up up to 5 years. As such, since the original Katsanos meta-analysis [30], more than a dozen independent analysis failed to associate paclitaxel exposure and short-term survival: loss to follow-up has been incrementally addressed, and signals of harm were reduced to a level of non-significance. [31,32]

In conclusion, in July 2023, FDA clinicians and statisticians determined that with the new updated randomized clinical trial (RCT) meta-analysis, there was no indication that the use of paclitaxel-coated devices was associated with a late mortality risk. [29,32-34]

## Paclitaxel DCBs: basic design considerations

Paclitaxel DCBs are designed to deliver the correct dosage of the drug to the target tissue uniformly and in a time-efficient manner – i.e., avoiding loss of the drug during the numerous procedural steps, like ex-vivo handling, introduction through

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the sheath, manipulation through the vasculature until the target site is reached, while accounting for the loss that might occur. [25,35] With that in mind, DCBs have three primary components: (i) the balloon itself, (ii) paclitaxel, and (iii) an excipient.

The (i) balloon platform apposes the pharmacologically active device surface against the target vessel wall lesion, forming a balloon-coating-to-vessel-wall interface that enables an efficient drug delivery. [25] It is of very importance that the balloon is appropriately sized and able to achieve full inflation, safeguarding a continuous interface for maximal drug exposure to vessel-surface area. [35] Furthermore, it is important to note that the majority of currently marketed DCBs are not designed as HPBs and are not thought to primarily perform high-quality angioplasty on stenotic AVF lesions - rather, most common DCBs are thought to be used as complementary to successful PTA. [25,35] This because, AVF access stenoses often require pressures in excess of 20 atmospheres (atm) to efface the lesion waist, which is greater than what a common DCB is able to produce (i.e., 5-8 atm nominal inflation pressure, 12-14 atm burst pressure). [25]

In terms of the (ii) drug paclitaxel, its active principal is to bind and stabilize □-tubulin micro-polymers protecting them from dismantling and making chromosomes unable to achieve a metaphase spindle configuration – which consequently, blocks migration and also mitosis progression, inhibiting cell proliferation. [36] Additionally, paclitaxel lipophilic properties enable it to easily cross the vessel wall, increasing tissue drug absorption rate even at low concentrations. As such, paclitaxel inhibits VSMC proliferation at concentrations of 1–2 nanograms per gram (ng/g) of tissue and inhibits VSMC migration at 0.4 ng/g of tissue. [27] Since paclitaxel is polymorphous it can be found in multiple different chemical forms, which lead to different solubilities, transfer characteristics, and pharmacokinetics. [37] Also, since the crystalline form has an improved absorption and retention rate in the vessel wall, it has been the preferred form used; although, it has raised concerns of distal embolization due to paclitaxel macro-crystal shedding during interventions. [38,39]

Due to drug solubility issues and molecular kinetics, paclitaxel alone is not enough to inhibit restenosis; as such, an (iii) excipient, or a drug-ligand, needs to be added to the formulation for an improved coat adherence during handling, proper delivery to the target vessel, enhanced bioavailability and more uniform penetration into the vessel wall. [40,41] Numerous organic substrates have been used as excipients, such as iopromide, urea, polysorbate/sorbitol, butyryl trihexyl citrate (BTHC), among others. [25]

## Paclitaxel DCBs: drug-delivery essentials

As we explained above, the dose of paclitaxel that is loaded onto the balloon must account for the various inefficiencies of the delivery process and must ensure that an actual therapeutic dose of paclitaxel remains in the balloon and is delivered in situ. Despite the implementation of various drug-excipient combinations, for most of the available DCBs the amount of drug delivered to the target vessel is only a small fraction of the total dose loaded onto the balloon, typically in the range of 10–15%, with the remainder lost to systemic circulation or staying residual in the balloon. [25,36,40]

Following delivery there is some degree of drug washout; and only afterwards, local tissue levels appear to stabilize, with the retained paclitaxel actually producing the desired restenotic effect. As such, in order to ensure a correct in situ therapeutic dose, a relatively high initial drug concentration is coated onto the balloon (2–3.5 µg/mm$^2$), with a resultant maximum total drug dosage of ~0.5-10 mg delivered locally - i.e., much smaller total systemic dose than what is usually employed in oncologic therapies. [25,35,40] Still, any degree of systemic drug release is undesirable due to harmful off-target effects, and there has been a continuous search for better DCB coating solutions to avoid such transfer inefficiencies.

## Clinical evidence of different brands of paclitaxel DCBs

There are a number of marketed DCBs for the treatment of AVF stenosis, with different design features, excipients and heterogenous clinical outcomes.

The Passeo-18 Lux DCB (Biotronik AG, Buelach, Switzerland) is packaged with a 3.0 µg/mm$^2$ dose of paclitaxel, and a hydrophobic coating of organic excipient BTHC. Recently, the USE of IMplanting the Biotronik PassEo-18 Lux DCB to treat failing hemodialysis arteRiovenous FIstulas and grafts trial (SEMPER FI), a prospective, non-blinded single-arm study, reported that Passeo-18 Lux DCB can be effective and safe in the treatment of failing hemodialysis AVFs [42]. Since no randomized long-term study was performed, the clinical evidence for this device is scarce.

The Lutonix DCB (Becton Dickinson, Franklin Lakes, New Jersey, USA) has a paclitaxel dose density of 2.0 µg/mm2 - on the lower end of available balloons, and uses an excipient combination of polysorbate/sorbitol, although the actual coating form is not publicly known. [25] The Lutonix AV DCB trial published 24-month outcomes assessing long-term safety, while statistically improved outcomes versus PTA were demonstrated only at 9-months, but not at any other measured time points throughout the 2-year study. [43] The TLPP using the Kaplan-Meier analysis through 2-years was 26.9% in the DCB group and 24.4% in the PTA group, showing no statistical superiority of DCB versus PTA (P =.087; note that the significance in this trial was set at P =.025 with a 1-sided test rather than P =.05 with a 2-sided test). [43,44]

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The IN.PACT AV balloon (Medtronic, Minneapolis, MN, USA) employs an anhydrous crystalline paclitaxel coating with urea as excipient (FreePac formulation) [44,45], at a dose density of 3.5 µg/mm$^2$ of paclitaxel - the highest dose of commonly available balloons. [25] The IN.PACT AV Access study was a large multicenter RCT for the treatment of dysfunctional fistulae, that demonstrated statistically significant improved target lesion primary patency (TLPP) and access circuit primary patency (ACPP) outcomes at all study time points: 6-, 12-, 24-, and 36-months. [44] TLPP through 36-months was 43.1% in the DCB versus 28.6% in the PTA group (P<.001). [44] Beyond the raw patency data, the median time to reintervention between the DCB group and the control group showed a 14.7-month delay if a participant was treated with DCB, leading to less interruption in hemodialysis treatment and one less intervention. [46] Additionally, through the 3-year trial, AV circuit thrombosis was significantly lower with DCB (8.2%) versus PTA (18.3%) treatment. The PTA group revealed higher access circuit thrombosis at 36-months, significantly impacting the patient's ability to undergo timely and adequate hemodialysis, putting the vascular access at risk. [44]

Practical considerations and technical concerns: With all of the above referred DCBs, an adequate vessel preparation is of utmost importance, with the need to use a HPB for pre-dilation through a period of > 90 seconds prior to DCB treatment. If there is an adequate treatment response (< 30% residual stenosis) on repeat AV fistulography, without evidence of flow-limiting dissection (grade > B) or perforation, then the DCB can be used. [46] The DCB should also cover the entirety of the lesion, with 1-cm extension on each side and inflation maintained for at least 180 seconds. [46]

## APERTO Over the Wire (OTW) paclitaxel DCB balloon and SAFEPAX coating

The APERTO OTW (Cardionovum, Bonn, Germany) is a balloon dilatation catheter with an over-the-wire design, which has a paclitaxel dose density of 3.0 µg/mm$^2$ and uses a unique amorphous in combination with an ammonium salt excipient, named SAFEPAX. [25] As result, the drug-excipient matrix is (i) highly stable – reducing paclitaxel loss during handling; and (ii) non-sticky – leading to a minimal washout effect, protecting the dislodge of particulates and preventing distal embolization. In summa, the SAFEPAX coating conducts to a more efficient and safer in situ drug-release. [48]

Furthermore, the APERTO OTW balloon itself was finely tuned to specifically address unmet clinical needs in the treatment of hemodialysis access stenosis and recanalization of AVF shunt grafts. The dedicated balloon can withstand high-pressures up to 20 bar to ensure an efficient dilatation with a better exposure of the vessel to the coating. Higher pressure DCBs can reinforce the action of vessel preparation and, at the same time, facilitate drug coating contact with the vessel surface, especially in case of fibromuscular thickening of the vascular wall [63].

Clinical Trials and registry data: The efficacy and safety of the APERTO balloon for dysfunctional AVFs and AVGs have been shown in clinical studies. In 2017, a small prospective study conducted by Ierardi et al in Italy, showed an 87.7% TLPP at 8-months. [50]

A registry from Tozzi et al also in Italy with a total of 200 patients, showed TLPP rates of 88%, 64.2%, and 40.6% at 6-, 12-, and 24-months, respectively. Furthermore, in the Tozzi et al registry, circuit patency rates were 99.2%, 92.5% and 84.8% at 6-, 12- and 24-months, respectively. In this registry, primary patency rates were highest in shunts treated de novo with DCBs. Additionally, the risk of restenosis was associated with circuit age (P=0.017), history of treatment with conventional angioplasty (P<0.001) and the kind of balloon used during pre-dilation (P=0.001). [51]

A larger multicenter RCT was conducted in China with a slightly different composite primary endpoint in comparison with previously reported trials. As such, the primary endpoint was target lesion intervention-free survival (TLI-free survival) in conjunction with a peak systolic velocity ratio (PSVR) ≤ 2.0, as determined by duplex ultrasound. [52] The objective was to focus on APERTO OTW effect on the target lesion itself through use of an ultrasound-measurement rather than a clinical event. [25,52] At 6-months, the percentage with TLI-free survival was higher in the APERTO OTW group than in the control group (65% vs 37%, respectively; rate difference, 28% [95% CI, 13%-43%]; P <0.001). The target lesion and target shunt intervention-free survival (TSI-free survival) of the APERTO OTW group were not superior to those of the control group at 6-months (P = 0.3 and P = 0.2, respectively); but were statistically superior at 12-months (TLI-free survival: 73% for DCB vs 58% for control [P = 0.04]; TSI-free survival: 73% for DCB vs 57% for control [P = 0.04]). The average degree of target lesion stenoses at 6-months was not significantly different between the two groups (44% ± 16% for DCB vs 49% ± 18% for control; P = 0.09). [52] In this trial, there was exclusion of anastomotic stenoses and lack of a second angioplasty in the control group, resulting in the DCB group undergoing two angioplasties (pre-dilation and DCB), while the control group underwent one high pressure balloon angioplasty given the different design of the balloons used. [25,52] As a result, compared to conventional High Pressure Balloon angioplasty. APERTO OTW treatment achieved a superior primary patency at 6 months follow-up and TLI-free survival at 12 months.

**Practical recommendations:** With the APERTO OTW, the recommended balloon inflation and deflation time is 90

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seconds. [48] In order to eliminate as far as possible the danger of the balloon rupturing during use, the Rated Burst Pressure (RBP) must never be exceeded [49] Additionally APERTO OTW is indicated not only for AVF and AVG occlusions, but also for the treatment of Central Veins Stenosis (CVS).

## Cost-effectiveness considerations

Because DCBs cost more than plain old balloons, there are economic considerations that need to be taken into account. The costs of maintaining vascular access with PTA has been identified as a significant and growing contributor to the overall costs of hemodialysis, with a substantial share of these costs related to reintervention procedures required to maintain access circuit patency. [53] Two studies using the 12-month outcome data from the IN.PACT AV trial have been conducted and published, showing long-term cost savings in the United States (US), Japan, and South Korea. [44,53,54] The data on these studies suggests that DCBs may lead to meaningful reductions in reintervention costs rendering it cost-saving at 1-year in the case of Korea and US, and between 3- and 5-years in the case of Japan. [53,54] Specifically, in the US Medicare context, there was an estimated per-patient savings of $1,632 at 1-year and $4,263 at 3-years before considering the cost of the DCB (~$1,800). [25,53] After inclusion of cost, there was cost neutrality at 1- and 2-years, and cost savings at 2.5 and 3-years. [25,53]

A small European study evaluating the clinical effectiveness and cost effectiveness of DCB use for the treatment of AVF failure, performed an analysis on the basis of a single institution randomized controlled trial comparing participants treated with DCB or PTA (N = 20 per group). [55] This study found that DCBs were associated with cost-savings and outcome improvement, justifying the added cost of DCBs in a European context. [55]

As such, in general it can be expected that DCBs can be cost saving in AVF dysfunction treatment if further studies are performed, and longer follow-up data confirms its clinical effectiveness.

## Future perspectives

Paclitaxel has ruled the world of DCBs; but Sirolimus – a potent antiproliferative agent, which has been effective in preventing restenosis in the coronary bed [56] and peripheral vasculature [57], is now being tested in Singapore in the Intervention with Selution SLR Agent Balloon for Endovascular Latent Limus therapy for failing AV Fistulas (ISABELLA trial). [58] Recently, early results have been published with data at 6- and 12-months, showing TLPP rates of 72% and 45%, respectively. [59,60] It will be interesting to see the final results, and a comparison study between paclitaxel-coated versus sirolimus-coated balloons in dysfunctional AVFs, although recent results of the TRASFORM I in coronary application indicated Sirolimus DCB Magic Touch failed to demonstrate noninferiority for angiographic net lumen gain at 6 months compared to paclitaxel coated SeQuent Please Neo [64]

Additionally, it has been suggested that a more precision-based approach to DCB AVF stenoses clinical studies is needed in order to maximize efficacy, optimize outcomes, and ensure safe and economic use. [25,61] It is possible that implementing such a precision-based approach may shed light onto which patients truly benefit from DCB use, given the fact that not only CKD patients need hemodialysis, but acute kidney injury can also imply short- and long-term complications that often require maintenance dialysis in subsequent months or years. [62]

## Conclusions

As described previously, although paclitaxel DCBs are commonly portrayed as a single group due to the common drug used, these devices are actually quite technologically different when it comes to dosage, excipient or design. Furthermore, studies on DCBs can be quite heterogenous in terms of fundamental qualitative differences, such as different endpoints, different ways of measuring the same outcome, different target lesions with different characteristics (e.g., de novo/restenotic and in-stent, or prior presence of thrombosis within the vascular circuit). [63]

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