Review Article on Endovascular and Surgical Interventions in the End Stage Renal Disease Population

Choosing the right treatment for the right lesion, Part II: a narrative review of drug-coated balloon angioplasty and its evolving role in dialysis access maintenance

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Background and Objective: Drug-coated balloons (DCBs) seek to inhibit restenosis in treated hemodialysis access lesions by delivering an anti-proliferative agent (paclitaxel) into the vessel wall. While DCBs have proven effective in the coronary and peripheral arterial vasculature, the evidence for their use in arteriovenous (AV) access has been less robust. In part two of this review, a comprehensive overview of DCB mechanisms, implementation, and design is provided, followed by an examination of the evidence basis for their use in AV access stenosis.

Methods: An electronic search was performed on PubMed and EMBASE to identify relevant randomized controlled trials (RCTs) comparing DCBs and plain balloon angioplasty from January 1, 2010 to June 30, 2022 published in English. As part of this narrative review, a review of DCB mechanisms of action, implementation, and design is provided, followed by a review of available RCTs and other studies.

Key Content and Findings: Numerous DCBs have been developed, each with unique properties, although the degree to which these differences impact clinical outcomes is unclear. Target lesion preparation, achieved by pre-dilation, and balloon inflation time have proven important factors in achieving optimal DCB treatment. Numerous RCTs have been performed, but have suffered from significant heterogeneity, and have often reported contrasting clinical results, making it difficult to draw conclusions on how to implement DCBs in daily practice. On the whole, it is likely there is a population of patients who benefit from DCB use, but it is unclear which patients benefit most and what device, technical, and procedural factors lead to optimal outcomes. Importantly, DCBs use appears safe in the end-stage renal disease (ESRD) population.

Conclusions: DCB implementation has been tempered by the lack of clear signal regarding the benefits of DCB use. As further evidence is obtained, it is possible that a precision-based approach to DCBs may shed light onto which patients will truly benefit from DCBs. Until that time, the evidence reviewed herein may serve to guide interventionalists in their decision making, knowing that DCBs appear safe when used in AV access and may provide some benefit in certain patients.

Keywords: Hemodialysis (HD); stenosis; drug-coated balloon (DCB); angioplasty; paclitaxel

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Introduction

Hemodialysis (HD) access stenosis is the most common cause of access dysfunction. "Plain old balloon angioplasty" (POBA) is the mainstay of treatment and has excellent short-term success rates, however, the large majority of treated lesions will require repeat intervention due to restenosis. Current 1-year post-angioplasty primary patency rates are disappointingly low, in the range of 40–60% for arteriovenous fistulas (AVFs) and 20–40% for arteriovenous grafts (AVGs) (1-11). This is despite the development of improved equipment, techniques, and therapies tailored to specific lesions locations, as described in part I of this review. The associated morbidity and mortality, ever-rising associated healthcare costs, and effect on quality of life that restenosis, recurrent access dysfunction, and need for repeat interventions has on these patients is significant (10,12).

The ideal stenosis treatment would both treat the culprit lesion and prevent future restenosis and reintervention (13). This can be achieved by pairing angioplasty with a therapy that inhibits post-angioplasty neointimal hyperplasia (NIH) and associated restenosis. Such is the rationale behind drug-coated balloons (DCBs), which are designed to deliver antiproliferative drugs, most commonly paclitaxel, into the vessel wall of a treated stenotic lesion. DCBs have proven effective at preventing restenosis in atherosclerotic coronary arterial disease (CAD) and peripheral arterial disease (PAD), however, the body of evidence for DCB use to prevent restenosis in HD access stenoses has not been as robust (14-19). While a number of randomized controlled trials (RCTs) have sought to evaluate the use of DCBs in arteriovenous (AV) access, they have suffered from significant heterogeneity in terms of study methods and outcome measures, and have often reported contrasting clinical results, making it difficult to draw conclusions on how to implement DCBs in daily practice (20-25).

Recent large-scale RCTs have continued this trend, with some demonstrating a clear clinical benefit of DCBs and others demonstrating no difference in outcomes compared to POBA (26-30). Numerous questions remain regarding which DCBs may be most effective, what technical factors result in best outcomes, and what specific lesions or clinical scenarios may benefit most from DCB use. It is possible that a more precision-based approach will have to be applied in order to realize the true benefit of DCBs, as the one-size-fits all approach taken in many previously performed studies has not always shown DCBs to be of clinical benefit (31). Part two of this review will focus on what has been learned about DCB use in the treatment of AV access stenosis through these studies, and includes an overview of DCB mechanisms, implementation, and design, followed by an examination of the available evidence for their use, emphasizing the numerous RCTs comparing DCBs and POBA, with the ultimate goal of enabling readers to better synthesize the evidence-basis for DCB use. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-497/rc).

Methods

In order to identify relevant RCTs for discussion, a literature search was performed on June 30, 2022 using the electronic databases PubMed and EMBASE from January 1, 2010 to June 30, 2022 including a combination of MeSH terms ("dialysis" OR "hemodialysis" OR "arteriovenous fistula" AND "angioplasty") and non-MeSH terms ("drug" OR "eluting" OR "coated" OR "paclitaxel" AND "random" OR "randomized") (*Table 1*). RCTs published in English were included for specific discussion if the following inclusion criteria were met: (I) randomized-controlled trial, (II) comparison of DCB angioplasty to POBA in the treatment of a stenotic lesion in an AVF or AVG, excluding central venous stenosis, (III) clinical follow-up of at least 6 months, and (IV) at least 30 patients enrolled. Rather than analyzing the identified RCTs in aggregate, as numerous meta-analyses have previously done, this review provides an overview of these RCTs, identifying their unique aspects and discussing them in the context of the overall evidence basis for DCB use. Study reference lists were screened for additional relevant articles. The reference list also includes non-randomized trials, retrospective studies, meta-analyses and additional studies identified manually to provide background and context regarding DCB development.

DCB development and mechanisms of action

Development of DCBs

The underlying concept of DCB use is that of balloon-based local drug delivery, the goal of which is to deliver a biologically-active compound into a vessel wall as part of a single-dose interventional treatment (32). This concept gained traction in the late 1980s in the treatment of CAD, with initial studies using double-chamber balloon systems, which would trap an infused drug between two balloons to allow for local delivery, and porous or channeled balloons, which would allow for direct high-pressure injection of

Table 1 The search strategy summary

Items	Specification
Date of search	6/30/22
Databases and other sources searched	EMBASE, PubMed
Search terms used	MeSH: "dialysis" OR "hemodialysis" OR "arteriovenous fistula" AND "angioplasty"
	Non-MeSH: "drug" OR "eluting" OR "coated" OR "paclitaxel" AND "random" OR "randomized"
Timeframe	January 1, 2010–June 30, 2022
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Study type: randomized controlled trial
	Language restrictions: English language literature only
Selection process	Literature review performed by DM DePietro and SO Trerotola

agents through holes in the balloon into the adjacent vessel walls (33,34). These initial systems suffered from leakage of the applied agent through small collaterals into the systemic circulation in the case of the double-chamber system and local vessel trauma related to high-pressure jets of delivered material in the case of porous balloons (35). In the early 1990s, the first coated-balloons were developed to overcome these limitations. These employed a thin external hydrogel coating, in which various compounds could be incorporated, then deposited into a vessel wall during balloon inflation. Initial studies demonstrated successful deposition of various agents, including genetic material and heparin (36,37).

In the subsequent years, the drug paclitaxel, initially used in oncology due to its anti-mitotic properties, was found to have an anti-proliferative effect on vascular smooth muscle cells (VSMCs) (38). Paclitaxel is a cytostatic agent isolated from the bark of the Pacific yew tree which irreversibly binds to β-tubulin within microtubules, essential components of the cellular cytoskeleton and mitotic spindle (39-41). This binding results in microtubular disorganization, inhibiting the cell's ability to migrate and maintain shape, and arresting the cell in the G0/G1 and G2/M cell cycle phases, thereby halting mitosis and causing cellular apoptosis (14,39-40). Paclitaxel's effects on VSMCs were demonstrated in numerous laboratory and animal models, where it effectively inhibited VSMC proliferation, migration, and subsequent NIH, resulting in lower restenosis rates of treated arterial lesions (14,42,43). Paclitaxel was also found to have multiple properties that would make it an ideal agent for delivery via a DCB—it is highly lipophilic, easily passing through the cell membranes it is in contact with, and is rapidly absorbed by cells within the vessel wall. *In vitro* and animal experiments have demonstrated that very low doses of paclitaxel may result in a sustained anti-proliferative effect on VSMCs despite only brief exposure periods, making it an ideal agent for delivery via balloon coating (38).

In 2004, Scheller *et al.* described the first use of a paclitaxel balloon coating in a porcine model, demonstrating a reduction in NIH in comparison with plain balloons (44). This was followed by the first trial of paclitaxel-coated balloon angioplasty in humans in 2006, where it was found to effectively reduce in-stent restenosis rates in stented coronary arteries (45). In 2008, paclitaxel-coated balloons were applied to femoropopliteal arterial stenoses, demonstrating reductions in late lumen loss (LLL) and target lesion revascularization (TLR) compared to POBA (15). Numerous studies have since confirmed the effectiveness of paclitaxel-coated balloons in preventing restenosis in atherosclerotic occlusive disease in the coronary arterial and peripheral arterial vasculature (16,46,47). The evidence in these areas is consistent and clear: paclitaxel-coated balloons perform better than plain balloon angioplasty alone, specifically in the treatment of in-stent restenosis in the coronary arteries and in *de novo* lesions in the femoropopliteal vasculature, noting all RCTs focusing on femoropopliteal disease have demonstrated the superiority of paclitaxel-coated balloons (43). The success of paclitaxel-coated balloons in these areas would eventually lead to their application in the treatment of AV access stenosis, with the first study of paclitaxel-coated balloons in this application published by Katsanos *et al.* in 2012 (20). In the subsequent decade, numerous RCTs and additional studies have been published regarding their use in AV access, however, their efficacy in this area has been less pronounced than in that of CAD and PAD, as will be

discussed in later sections. All DCBs approved by the US Food and Drug Administration (FDA) for use in AV access at the time of this review's publication, and all that will be discussed in the following sections, contain paclitaxel as the drug component, and paclitaxel-coated balloons will simply be referred to as drug-coated balloons or "DCBs" in the subsequent sections (48).

Differences between stenotic lesion environments

While DCBs have proven effective in the prevention of restenosis in native arterial vessels, there are important biologic differences between arteries and veins that may alter their effectiveness in preventing restenosis in AV access, where lesions typically occur in either an arterialized vein in the case of a fistula, at a vein-graft anastomosis in a graft, or within the venous outflow of either type of access. For example, the vessel wall structure between arteries and veins differs in that native arteries have a well-defined internal elastic lamina separating the media and intima, whereas this lamina is less robust within a vein, enabling VSMCs and fibroblasts to migrate from the media to the intima more easily in veins (19). NIH is characterized by such migration (see discussion of pathophysiology of AV access stenosis in part I of this review), possibly predisposing veins to a more aggressive NIH response. There is also evidence that arterial and venous smooth muscle cells may differ in their response to anti-proliferative drugs (49). Additionally, while restenosis of an arterial lesion is typically due to inflammation and smooth muscle cell proliferation after angioplasty, a number of additional factors contribute to AV access restenosis, including altered flow dynamics and shear stress within the AV circuit (as compared to typical in-line flow within an artery). Veins also tend to produce more nitric oxide and prostacyclin, which may predispose to cellular injury, and the repetitive cannulation injuries that AV accesses undergo cause additional platelet thrombi and cytokine release (19,50,51). Whether these differences explain the difference in outcomes when DCBs are used in AV access compared to CAD and PAD remains unclear, however, it is important to keep in mind these differences when assessing the literature regarding DCBs, as their use in different areas (CAD, PAD, AV access) is often compared and cross-referenced.

DCB design

DCBs are designed with multiple goals in mind—they must deliver a therapeutic drug dose to the target tissue in a uniform distribution and in a time-efficient manner, avoid loss of the drug during numerous procedural steps including *ex vivo* handling, introduction through a sheath, and manipulation through the vasculature to the target site, while accounting for the loss that does occur (43). DCBs consist of three primary components: (I) the balloon itself, (II) the drug to be delivered (paclitaxel in all cases for the purpose of this review), and (III) a drug ligand or excipient (39,43).

Balloon platform

The purpose of the balloon component of the DCB is to appose the pharmacologically-active device surface against the target vessel wall lesion, forming a balloon-coating to vessel wall interface, thus enabling drug delivery. The balloon must be appropriately sized and able to achieve full inflation, ensuring a continuous interface exists with maximal surface area. It is important to note that current balloon components are not designed as high-pressure balloons (HPBs) and are not designed to primarily perform high-quality angioplasty on stenotic AV access lesions—rather, DCBs should be thought of as complementary to successful POBA (43). DCBs are typically compliant, non-HPBs, with nominal inflation pressures on the order of 5–8 atmospheres (atm) and burst pressures 12–14 atm for the most commonly studied DCBs in AV access (43,48). AV access stenoses often require pressures in excess of 20 atm to efface the lesion waist, greater than the DCB is able to produce (52-55). Therefore, pre-dilation using a separate high-pressure or ultra-high pressure plain balloon, termed vessel preparation, should be performed prior to DCB application in order to achieve optimal outcomes. This was not always the case, with early RCTs utilizing a primary DCB strategy, reserving further angioplasty for cases where there was significant residual stenosis after DCB use (20-23,40). The concept of vessel preparation and its rationale will be covered further in a subsequent section.

Drug and excipient coating

While DCBs are relatively similar in terms of their balloon platform, the main difference between the various devices that have been studied is in the design of their drug-coating, with different forms and doses of paclitaxel and various excipient molecules used in combination to create unique drug-excipient formulations. Ultimately, these

design factors control the degree of drug loss, drug transfer, drug adherence to the vessel wall and absorption into the underlying vessel layers, and, ultimately, the ability of the DCB to inhibit NIH. These differences, and the lack of control over certain components, such as the degree of drug loss, make it difficult to determine which design factors contribute most to clinical outcomes and what dose of paclitaxel is optimal (56).

Paclitaxel itself is polymorphous, meaning it can be found in multiple different forms—either as an amorphous solid, in various crystalline forms, or some combination thereof (56,57). These different forms impart different solubility, transfer characteristics, and pharmacokinetics. While similar levels of initial vessel wall adhesion amongst the various forms have been observed, there is significantly improved absorption and retention of the crystalline form within the vessel wall, resulting in more effective inhibition of NIH (56-58). Most common DCBs employ some form of crystalline paclitaxel as a result (57,58).

Early experiments demonstrated that a balloon coating of paclitaxel alone is not effective in inhibiting restenosis, thought to be related to issues with drug solubility and speed of drug release (44,59,60). It was quickly determined that combining paclitaxel with some form of excipient molecule (initially iopromide contrast) solved this issue. Excipient molecules allow for improved coating adherence to the balloon during handling and delivery to the target lesion, enhanced bioavailability and more uniform penetration of the drug into the vessel wall, and, as a result, more effective inhibition of restenosis (44,61,62). Numerous organic substrates have been used as excipients, include iopromide, urea, polysorbate and sorbitol, and butyryl trihexyl citrate (BTHC). The most effective formulation has yet to be determined.

Drug delivery and dosing

The dose of paclitaxel loaded onto the balloon must account for the various inefficiencies in drug transfer, adhesion, and absorption, and must ultimately ensure a therapeutic dose is delivered. Despite the implementation of various drug-excipient combinations, 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 the systemic circulation or remaining on the balloon (32,48). Following delivery, there is some degree of washout that occurs, as not all of the delivered paclitaxel will remain adherent to the vessel wall or be absorbed into the underlying vessel layers (32,42). After this washout period, tissue levels appear to stabilize, and it is likely this retained paclitaxel produces the desired prolonged inhibition of restenosis. Paclitaxel is effective at relatively low concentrations, exhibiting effectiveness at inhibiting VSMC proliferation at concentrations of 1–2 nanograms per gram of tissue and at inhibiting VSMC migration at 0.4 nanograms per gram of tissue (38,62-64). In order to ensure a therapeutic tissue dose, relatively high initial drug concentrations are used in the balloon coating, with most common balloons employing a dose of 2–3.5 μg/mm^2 and resultant maximum total drug doses of approximately 0.5–10 mg (29,43). While this high loading dose is needed to offset the amount of drug lost to inefficient vessel wall delivery and washout, the total systemic dose remains much smaller than that which is delivered systemically in oncologic uses, which may be up to 200–300 times that found on a DCB (40,43). Regardless, any degree of systemic drug release is undesirable, potentially resulting in off-target drug accumulation and harm, and the current degree of delivery inefficiency is a limitation of available DCBs (48).

Most commonly studied DCBs

While there are a number of DCBs on the market, there are two balloons that stand out as the most studied for treatment of AV access stenosis in RCTs. These are the IN.PACT AV balloon (Medtronic, Minneapolis, MN, USA) and the Lutonix DCB (Becton Dickinson, Franklin Lakes, New Jersey, USA). The IN.PACT AV balloon employs an anhydrous crystalline paclitaxel coating in combination with urea as the excipient molecule, in a formulation referred to as FreePac (56). The paclitaxel dose density of the current IN.PACT AV balloon is 3.5 μg/mm^2, the highest dose of commonly available balloons, although versions of the IN.PACT balloon used in earlier trials had a dose density of 3.0 μg/mm^2. The Lutonix DCB has a paclitaxel dose density of 2.0 μg/mm^2, on the lower end of available balloons, and uses a combination of polysorbate and sorbitol as the excipient. The form of paclitaxel used in the coating is not publicly available. Additional balloons that have been studied in RCTs include the Passeo-18 Lux balloon (Biotronik AG, Buelach, Switzerland) and the Aperto balloon (Cardionovum, Bonn, Germany), both of which have a paclitaxel dose density of 3.0 μg/mm^2. The Passeo-18 Lux balloon employs hydrophobic BTHC as the excipient, while the Aperto DCB uses a coating of amorphous paclitaxel in combination with an ammonium salt excipient,

Table 2 Most common drug-coated balloon devices evaluated in randomized controlled trials in AV access stenoses

Device	Company	Paclitaxel dose density (μg/mm^2)	Excipient	Balloon diameters (mm)	Balloon lengths (mm)
IN.PACT	Medtronic, Dublin, Ireland	3.5	Urea	4–12	40, 60, 80, 120
Lutonix	Becton Dickinson, Franklin Lakes, New Jersey, United States	2.0	Polysorbate and Sorbitol	4–12	40, 60, 80, 100, 120, 150, 220
Passeo-18 Lux	Biotronik SE & Co. KG, Berlin, Germany	3.0	Hydrophobic butyryl-tri-hexyl citrate (BTHC)	2–7	40, 80, 120
Aperto	Cardionovum, Bonn, Germany	3.0	Ammonium salt	5–10	20, 40, 60

AV, arteriovenous.

referred to as SAFEPAX. Additional details regarding these three balloons can be found in *Table 2*.

Few comparative studies between different DCBs have been performed and it is unclear whether the aforementioned differences in balloon design result in different clinical outcomes. While the majority of "positive" RCTs to date that have shown a clinical benefit of DCBs compared to plain balloons have used the IN.PACT balloon, and while it has been postulated this is due to the higher drug concentration of the IN.PACT balloon, there are also multiple negative studies using this balloon as well (24). Available animal, *in-vivo*, and *in-vitro* studies comparing the IN.PACT and Lutonix balloons have demonstrated that there is a higher non-target embolic crystalline material when using the IN.PACT balloon as well as greater drug loss during dry handling (30,62,65). Given this, it is unclear whether the higher drug concentration results in greater drug deposition. No direct comparison between these balloons regarding the amount of drug delivered to the vessel wall. Further comparative research is needed to determine whether any clinically significant differences exist between DCB types and what device component (dose density, excipient molecule, etc.) such differences are related to.

DCB procedural considerations

Lesion preparation (pre-dilation)

As mentioned earlier, DCBs are typically compliant or semi-compliant non-HPBs designed for optimal drug delivery, not optimal angioplasty, and many DCBs may not be able to efface the waist of an AV access stenosis. Early RCTs employing DCBs in AV access had high rates of technical failure as a result, requiring post-dilation with HPBs after DCB use. For example, in the 2012 study by Katsanos *et al.* technical success was 45% in the DCB group and 100% in the control group (which used high-pressure plain balloons), with 11/20 DCB-treated lesions having to undergo post-dilation with an HPB because of an unacceptable angiographic result (20). As more experience and knowledge was gained, the importance of adequate vessel preparation in the form of pre-dilation was realized, and it is now recommended by DCB manufacturers (20,66). Successful pre-dilation is defined as ≤30% residual stenosis after dilation in the majority of large RCTs (26,28,30).

Pre-dilation serves multiple purposes—it modifies the target lesion in a traumatic fashion, which may allow for better drug delivery to deeper vessel wall layers through intimal tears and other traumatic injuries, it facilitates complete DCB expansion, and it promotes maximal DCB surface contact with the vessel wall (48,67). The majority of evidence for the above has come from literature regarding DCB use in atherosclerotic arterial disease, however, the same principles likely hold true in the treatment of AV access stenosis (68-70). Results of a multi-center global registry of DCBs in AVFs and AVGs, published by Karnabatidis *et al.*, demonstrated improved outcomes in target primary lesion patency at 6 months in those who underwent pre-dilation (77%) compared to those who did not (49%), with P=0.0005 (71).

Finally, pre-dilation ensures that the target lesion can be successfully treated using balloon angioplasty. This last point makes sense from a practical and economic standpoint. One would not want to use a DCB in the setting of a resistant or elastic lesion, as such lesions require additional treatments which may include repeat angioplasty, stent placement, or surgical referral. Repeat angioplasty may disrupt the drug that was just delivered to the vessel wall, with unknown implications regarding the effectiveness of the drug that was previously delivered. In the case of a

resistant lesion, the stenosis remains untreated, and use of a DCB would be wasteful and costly. As mentioned earlier, DCBs should be considered an adjunct to successful POBA with the goal of preventing restenosis, not treating the lesion or replacing POBA. Until a lesion has successfully undergone high-quality plain balloon angioplasty, as discussed in part 1 of this review, a DCB should not be considered (72).

Inflation time

Once a target lesion has been adequately pre-dilated, a DCB with adequate lesion coverage and appropriate diameter (typically 1:1 size matching) is chosen and inflated at the site of treatment. The length of time the balloon recommended for balloon inflation varies amongst device manufacturers and has varied across different studies. While some studies have demonstrated that increased drug-coating to vessel wall contact time proportionally increases drug uptake, it has also been demonstrated that the large majority (>90%) of paclitaxel is delivered to the vessel wall within the first 30 seconds of contact (31,58). Typical inflation times are on the order of 60 to 180 seconds, with initial instructions for use of the Lutonix balloon recommending an inflation time of 30 seconds, later increased to a minimum of 120 seconds, and a longer inflation time of 180 seconds recommended for the IN.PACT balloon (30,31). In the aforementioned prospective registry results reported by Karnabatidis *et al.*, a significant difference in 6-month target lesion primary patency (TLPP) was seen between those in whom a DCB was inflated for >120 seconds (68% when inflated 50–120 seconds, 80% when inflated 120–180 seconds, P=0.007). While recent meta-analyses have also suggested that increased duration of inflation may improve outcomes, whether these differences were truly related to inflation time or other factors remains unclear, and additional research is needed to determine optimal inflation time (31,73).

DCB safety

The safety of DCBs, specifically, that of paclitaxel and its potential for downstream, off-target effects when released into systemic circulation as a result of inefficient delivery and washout, as described earlier, deserves specific discussion. In 2018, Katsanos *et al.* published a systemic review and meta-analysis reporting an increased risk of death at 2 and 5 years following the application of DCBs and paclitaxel-coated stents in the treatment of femoropopliteal arterial lesions (74). The validity of these findings has been the subject of much debate and the biological mechanism of potential association between the application of DCBs and mortality remains unclear. Despite this, the FDA responded by issuing a warning letter regarding DCB use, suggesting alternative treatment options be tried, and resulting in a cautious approach to DCBs in the immediate aftermath.

Those with end-stage renal disease (ESRD) requiring dialysis represent a vastly different population, with significant associated morbidity and mortality, compared to those with PAD suffering from claudication highlighted in Katsanos' report. For example, the 5-year life expectancy of those with ESRD is less than 50% for those ≥65 years old, whereas this is somewhere between 70% and 90% for those with PAD (40). Any increased risk of mortality related to DCB use in the ESRD population must be assessed in the context of the patient's life expectancy, which may be shorter than the time at which there would be an observable increased mortality risk related to DCB use, and balanced with the benefits use of a DCB can potentially provide the patient, such as decreased need for repeat interventions. Studies to date have not demonstrated a similar increased risk of mortality following DCB use in the treatment of AV access stenosis. In their meta-analysis assessing mortality after DCB use in dialysis access, Dinh *et al.* found no difference in mortality in those treated with a DCB compared to POBA at 6 months (5.2% *vs.* 4.8%, P=0.55), 12 months (6.3% *vs.* 6.0%, P=0.9), or 24 months (19% *vs.* 13.5%, P=0.14) (40). Additionally, no individual RCT regarding DCB use in AV access has reported an increased risk of mortality (26-30,40). Based on available evidence, the use of DCBs in the ESRD population appears safe.

Evidence for DCBs in AV access stenosis

The following sections discuss the available evidence for DCB use in the treatment of AV access stenosis, with a focus on the numerous RCTs performed in the past 10+ years. To provide an organizational framework, the RCTs are presented in approximate chronological order to demonstrate the development of the evidence basis over time (*Figure 1*). Of note, all studies published prior to 2018 used the IN.PACT balloon, and only in the past 5 years have RCTs utilizing other DCBs been published.

The previously mentioned heterogeneity that exists between the RCTs comes in many forms, and makes interpretation of the evidence basis as a whole particularly

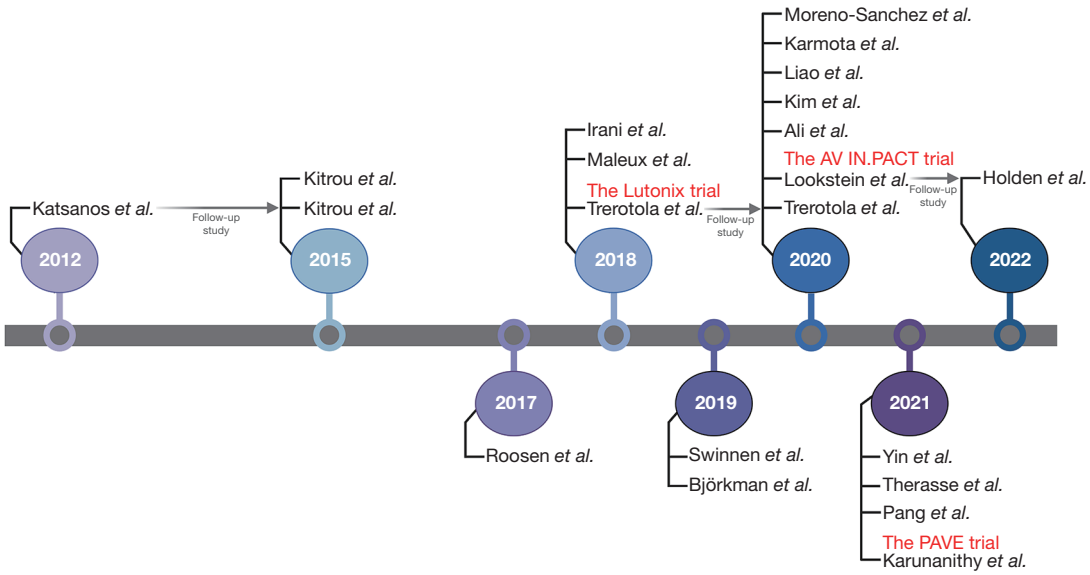

Figure 1 Timeline of published randomized controlled trials comparing drug-coated balloons to plain old balloon angioplasty.

difficult. It includes variable procedural methods, including whether or not pre-dilation was performed, what type of angioplasty balloons were used (standard balloon, HPB, etc.), duration of DCB inflation, whether antiplatelet agents were prescribed, differing inclusion criteria in terms of type of access (AVF, AVG, or both; upper arm and/or forearm, etc.) and lesion location, and whether treated lesions were *de novo* or recurrent, amongst others. One should also note that RCT design often results in control treatments that differ from the standard-of-care (POBA balloon choice, confirmation of <30% stenosis, etc.) and results must be interpreted with this in mind. Details regarding enrollment, certain study methods and inclusion criteria, and DCB and control group angioplasty details are provided in *Table 3*. Details regarding follow-up and study outcomes are provided in *Table 4*. Other salient points are highlighted within the text.

In addition, one of the issues when evaluating the evidence for DCBs is the heterogeneity in terms of primary study endpoints. Therefore, the following terms are defined. TLPP, is defined as freedom from any repeat intervention due to restenosis or thrombosis involving the target lesion, measured from the time of index study intervention to a defined follow-up time (24,26). It is typically described in terms of percentage of lesions that remain patent, without requiring reintervention, during the follow-up period. Time to loss of TLPP is the mean or median time from the index procedure to reintervention for recurrent stenosis or thrombosis, typically measured in days. Access circuit primary patency (ACPP) is defined as freedom from repeat intervention anywhere in entire access circuit, whether the intervention is performed to treat a stenosis, restenosis, or thrombosis related to the target lesion or a different lesion in the circuit. It is described as a percentage of accesses that remain patent, without requiring intervention, during the defined follow-up period (24,25,80). TLR is defined as any reintervention performed to restore patency of the previously treated index lesion, from the time of the index procedure to a defined follow-up time. It is measured in percentage of lesions that required reintervention. TLR can be considered the complement of TLPP and together both should equal 100%. For example, if ten lesions were initially treated and within 6 months four develop restenosis requiring reintervention and six do not, the 6-month TLR is 40% (4/10) and the 6-month TLPP is 60% (6/10). TLR-free survival is the mean or median time between the index intervention and when reintervention for recurrent stenosis or thrombosis is required, and represents the number of days between interventions. TLR-free survival is the same as time to loss of TLPP. Finally, LLL, a quantitative measure of restenosis, has also been used, in which the narrowest part of the index treated area is measured after a specific time from the index procedure (20,75). It is typically measured

Table 3 Description of methods in reviewed randomized controlled trials

Balloon	First author, year	Enrollment time	Single or multi-center [# of centers]	Blinded?	Number of patients	Type of access	Recurrent or de novo lesions	DCB vessel preparation	DCB details	Control treatment	Inflation time (s)
IN.PACT	Katsanos, 2012, (20) (6-month results); Kitrou, 2015, (21) (12-month results)	3/2010–12/2010	Single	No	DCB: 20; control: 20; total: 40	AVF: 14; AVG: 26	NR	None	IN.PACT (3.0 μg/mm^2)	HPB alone	≥60
IN.PACT	Kitrou, 2015, (22)	3/2011–9/2012	Single	No	DCB: 20; control: 20; total: 40	AVF only	Both	None	IN.PACT (3.0 μg/mm^2)	HPB alone	90
IN.PACT	Roosen, 2017, (23)	NR	Multi [2]	Single	DCB: 16; control: 18; total: 34	AVF: 29; AVG: 5	Recurrent	None	IN.PACT (3.0 μg/mm^2)	Standard balloon alone	60
IN.PACT	Irani, 2018, (24)	1/2012–5/2013	Single	No	DCB: 59; control: 60; total: 119	AVF: 98; AVG: 21	Both	Yes, HPB	IN.PACT (3.0 μg/mm^2)	HPB alone	60
IN.PACT	Maleux, 2018, (25)	1/2013–10/2015	Single	No	DCB: 33; control: 31; total: 64	AVF only	Both	Yes, HPB	IN.PACT (3.0 μg/mm^2)	HPB alone	NR
IN.PACT	Swinnen, 2019, (75)	1/2015–3/2017	Multi [3]	Single	DCB: 70; control: 62; total: 132	AVF only	Recurrent	Yes, HPB	IN.PACT (3.0 μg/mm^2)	HPB + uncoated equivalent of DCB	120
IN.PACT	Björkman, 2019, (76)	8/2013–2/2016	Single	No	DCB: 18; control: 18; total: 36	AVF only	Both	Yes, undersized standard balloon	IN.PACT (3.5 μg/mm^2)	Undersized standard balloon + repeat standard balloon	90
IN.PACT	Kim, 2020, (77)	6/2016–6/2018	Single	Single	DCB: 20; control: 19; total: 39	AVF only	Both	Yes, HPB	IN.PACT (3.5 μg/mm^2) + repeat HPB	HPB + repeat HPB	120
IN.PACT	Liao, 2020, (78)	7/2015–8/2018	Single	Single	DCB: 22; control: 22; total: 44	AVG only	Recurrent	None	IN.PACT (3.5 μg/mm^2)	HPB alone	60
IN.PACT	Lookstein, 2020, (26) (6-month results); Holden, 2022, (27) (12-month results)	4/2017–5/2018	Multi [29]	Single	DCB: 170; control: 160; total 330	AVF only; AVF only	Both	Yes, HPB	IN.PACT (3.5 μg/mm^2)	HPB + standard balloon	>180
IN.PACT	Pang, 2021, (79)	6/2016–4/2018	Single	Single	DCB:20; control: 20; total: 40	AVF: 28; AVG:12	Both	Yes, HPB	IN.PACT (3.5 μg/mm^2)	Semi-compliant balloon alone	180

Table 3 *(continued)*

Table 3 *(continued)*

Balloon	First author, year	Enrollment time	Single or multi-center [# of centers]	Blinded?	Number of patients	Type of access	Recurrent or de novo lesions	DCB vessel preparation	DCB details	Control treatment	Inflation time (s)
Lutonix	Trerotola, 2018, (28) (6-month results); Trerotola, 2020, (29) (24-month results)	6/2015–3/2016	Multi [23]	Single	DCB: 141; control: 144; total: 285;	AVF only	Both	Yes, HPB	Lutonix (2.0 μg/mm^2)	HPB + uncoated equivalent of DCB	>30
Lutonix	Karmota, 2020, (80)	9/2015–12/2017	Multi [2]	NR	DCB: 30; control: 30; total: 60	AVF only	NR	Yes, standard balloon	Lutonix (2.0 μg/mm^2)	Undersized standard balloon + standard balloon	180
Lutonix	Karunanithy, 2021, (30)	11/2015–10/2018	Multi [20]	Single	DCB: 106; control: 106; total: 212	AVF only	Both	Yes, HPB	Lutonix (2.0 μg/mm^2)	HPB + standard balloon	>60
Passeo-18 Lux	Moreno-Sanchez, 2020, (81)	1/2016–7/2017	Multi [4]	Single	DCB: 70; control: 78; total: 148	AVF: 136; AVG: 12	Both	Yes, HPB	Passeo-18 Lux (3.0 μg/mm^2)	HPB + repeat low-pressure inflation (6 atm)	45
Passeo-18 Lux	Therasse, 2021, (82)	3/2014–4/2018	Multi [3]	Single	DCB: 60; control:60; total: 120	AVF: 109; AVG: 11	Both	Yes, HPB	Passeo-18 Lux (3.0 μg/mm^2)	HPB + uncoated equivalent of DCB	60
Aperto	Yin, 2021, (83)	11/2016–7/2017	Multi [10]	Single	DCB: 78; control: 83; total: 161	AVF only	Both	Yes, HPB	Aperto (3.0 μg/mm^2)	HPB alone	120–180
Mixed	Ali, 2020, (84)	10 months (exact dates NR)	Multi [2]	Single	DCB: 40; control: 40; total: 80	AVF: 69; AVG: 11	Both	Yes, HPB	Any available DCB	HPB alone	60

NR = not reported or unspecified/specific details missing in the manuscript; HPB = high-pressure balloon, typically capable of inflation pressure ≥20 atm. A standard balloon refers to a non-high pressure balloon typically capable of inflation pressure <20 atm. NR, not reported; DCB, drug-coated balloon; AVF, arteriovenous fistula; AVG, arteriovenous graft; HPB, high-pressure balloon.

Table 4 Description of follow-up, primary study endpoints, and results in reviewed randomized controlled trials. In cases where a primary study endpoint had a one or multiple specified time points associated with it, these were described, and may differ from total length of follow-up. If the primary study endpoint was not associated with a specific time point in the study methods, the data at the longest follow-up time is provided

Balloon	Author, year	Follow-up time (months)	Follow-up protocol	Primary study endpoint(s)	Results	*Met primary endpoint?
IN.PACT	Katsanos, 2012, (20)	6	Clinical monitoring, angiography every 2 months	TLPP at 6 months	70% (DCB) *vs.* 25% (control), P<0.001	Yes
IN.PACT	Kitrou, 2015, (21)	12		TLPP at 12 months	35% (DCB) *vs.* 5% (control), P<0.001	Yes
IN.PACT	Kitrou, 2015, (22)	12	Clinical monitoring	TLR-free survival	308 days (DCB) *vs.* 161 days (control), P=0.03	Yes
IN.PACT	Roosen, 2017, (23)	12	Ultrasound at 3, 6, 9, and 12 months	TLR-free survival	130 days (DCB) *vs.* 189 days (control), P=0.2	No
IN.PACT	Irani, 2018, (24)	12	Clinical monitoring, angiography at 6 months	TLPP at 6 months	6 months: 81% (DCB) *vs.* 61% (control), P=0.03 12 months: 51% (DCB) *vs.* 34% (control), P=0.04	Yes
IN.PACT	Swinnen, 2019, (75)	12	Ultrasound at 1 week, 6 weeks, 3 months, 6 months, and 12 months	LLL at 6 months	6 months: 0.045 mm/month (DCB) *vs.* 0.23 mm/month (control), P=0.0002 12 months: 0.045 mm/month (DCB) *vs.* 0.23 mm/month (control), P=0.0002	Yes
IN.PACT	Maleux, 2018, (25)	12	Clinical monitoring	ACPP at 3, 6, and 12 months	3 months: 88% (DCB) *vs.* 81% (control), P=0.43 6 months: 68% (DCB) *vs.* 65% (control), P=0.8 12 months: 42% (control) *vs.* 39% (control), P=0.95	No
IN.PACT	Björkman, 2019, (76)	12	Ultrasound at 1, 6, and 12 months	TLR at 12 months	89% (DCB) *vs.* 22% (control), P=0.001	No
IN.PACT	Kim, 2020, (77)	36	Clinical monitoring	TLPP at 12 months	6 months: 90% (DCB) *vs.* 84%(control), P=0.59 12 months: 65% (DCB) *vs.* 68 % (control), P=0.82 24 months: 55% (DCB) *vs.* 57% (control), P=0.90 36 months: 55% (DCB) *vs.* 49% (control), P=0.71	No
IN.PACT	Liao, 2020, (78)	12	Clinical monitoring, angiography every 2 months	TLPP at 6 months	6 months: 41% (DCB) *vs.* 9% (control), P=0.006 12 months: 23% (DCB) *vs.* 9% (control), P=0.013	Yes
IN.PACT	Lookstein, 2020, (26)	6	Clinical monitoring, US at 1, 6, and 12 months	TLPP at 6 months	82% (DCB) *vs.* 60% (control), P<0.001	Yes
IN.PACT	Holden, 2022, (27)	12	Clinical monitoring, US at 1, 6, and 12 months	TLPP at 12 months	64% (DCB) *vs.* 44% (control), P<0.001	Yes
IN.PACT	Pang, 2021, (79)	12	US at 1 week and 3, 6, 9, and 12 months	TLPP at 12 months	65% (DCB) *vs.* 30% (control), P=0.007	Yes
Lutonix	Trerotola, 2018, (28)	6	Clinical monitoring	TLPP at 6 months	71% (DCBs) *vs.* 63% (control), P=0.06	No

Table 4 *(continued)*

Table 4 *(continued)*

Balloon	Author, year	Follow-up time (months)	Follow-up protocol	Primary study endpoint(s)	Results	*Met primary endpoint?
Lutonix	Trerotola, 2020, (29)	24	Clinical monitoring	TLPP at 9, 12, 18, 24 months	9 months: 58% (DCB) *vs.* 46% (control), P=0.02 12 months: 44% (DCB) *vs.* 36% (control), P=0.04 18 months: 34% (DCB) *vs.* 28% (control), P=0.06 24 months: 27% (DCB) *vs.* 24% (control), P=0.09	No**
Lutonix	Karmota, 2020, (80)	12	Clinical monitoring	TLPP at 3, 6, 12 months	3 months: 100% (DCB) *vs.* 100% (control) 6 months: 97% (DCB) *vs.* 90% (control), P=0.3 12 months: 90% (DCB) *vs.* 67% (control), P=0.03	No**
Lutonix	Karunanithy, 2021, (30)	12	Clinical monitoring, 6-month fistulogram	Time to loss of TLPP at 6 months	159 days (DCB) *vs.* 215 days (control), P=0.44	No
Passeo-18 Lux	Moreno-Sanchez, 2020, (81)	12	Clinical monitoring	TLPP in days at 6 and 12 months	6 months: 153 days (DCB) *vs.* 142 days (control), P=0.07 12 months: 266 days (DCB) *vs.* 238 days (control), P=0.37	No
Passeo-18 Lux	Therasse, 2021, (82)	12	Flow monitoring at 3 months, angiography at 6 months, telephone monitoring	LLL at 6 months	0.64 mm (DCB) *vs.* 1.13 mm (control), P=0.08	No
Aperto	Yin, 2021, (83)	12	Clinical monitoring, US at 6 and 12 months	Combined TLR-free survival and PSVR ≤2.0 at 6 months	TLR-free survival: 86% (DCB) *vs.* 78% (control), P=0.3 PSVR ≤2.0: 65% (DCB) *vs.* 37% (control), P=0<0.001	No**
Mixed	Ali, 2020, (84)	12	Clinical monitoring, flow measurement monthly, US every 3 months	Time to loss of ACPP TLR-free survival	Time to loss of ACPP: 287 days (DBP) *vs.* 156 days (control), P=0.04 TLR-free survival: 316 days (DCB) *vs.* 172 days (control), P=0.04	U

*, only if all primary study endpoints at all specified time points were met was this considered to be successfully met and described as "yes"; **, indicates a study that met some, but not all primary endpoints. TLPP, target lesion primary patency; TLR, target lesion revascularization; LLL, late lumen loss; ACPP, access circuit primary patency; PSVR, peak systolic velocity ratio; DCB, drug-coated balloon.

in mm using either ultrasound or fistulography.

Katsanos et al., 2012 and Kitrou et al., 2015; IN.PACT balloon (20,21)

The first RCT performed to evaluate DCBs in AV access stenosis had its 6-month interim results published in 2012 and its final 12-month results in 2015. This study, performed in Greece and designed as a non-inferiority study, compared the IN.PACT DCB to a variety of HPBs in the treatment of venous outflow stenoses in both AVFs and AVGs. Pre-dilation was not performed, however, post-

dilation with an HPB was performed if there was residual stenosis >30% after DCB use. Initial technical success was 45% in the DCB group and 100% in the control group (P<0.001), which increased to 100% in both groups after post-dilation was performed in the DCB group. At 6-month interim analysis, cumulative TLPP was 70% (DCB) *vs.* 25% (control), with P<0.001, and cumulative patency of the treated dialysis circuit was 65% (DCB) *vs.* 20% (control), with P<0.008. Significantly more procedures were required in the control group (n=13, 65%) compared to the DCB group (n=4, 20%), with P=0.002. Overall dialysis circuit survival was >90% in both groups (P=0.35). On final 12-month analysis, cumulative TLPP was 35% (DCB) *vs.* 5% (control) (P<0.001), with an overall median primary patency of 0.64 years in the DCB group *vs.* 0.36 years in the control group (P=0.0007). Subgroup analysis by access type demonstrated significant improvement in primary patency of AVGs after DCB treatment, but only a trend towards improvement in AVFs. Limitations included small sample sizes, a non-blinded design, and, notably, the lack of pre-dilation with an HPB in the DCB group, with the majority of lesions subsequently requiring post-dilation with a HPB (55%). The effect of this post-dilation, and whether it accounts for some of the differences between groups, is unclear, and represents a common limitation to all subsequently described studies performed without pre-dilation in the DCB group. Despite these limitations, the positive results would pave the way for numerous additional RCTs to be performed.

Kitrou et al., 2015; IN.PACT balloon (22)

An additional RCT was performed by the same group, with similar study design, looking at outcomes in AVFs without specifying the site of stenosis within the access. Pre-dilation was again not performed. Initial balloon inflation was for 90 seconds (compared to >60 seconds in the prior study) and if there was residual stenosis post-dilation was performed with an HBP for another 2 minutes. The primary endpoint, TLR-free survival, also differed from the prior study. The lack of pre-dilation in the DCB arm again resulted in a low initial technical success of 35% compared to 100% in the control arm, with all failures undergoing successful post-dilation after DCB use. TLR-free survival was significantly higher in the DCB group at 308 days compared to 161 days in the control group (P=0.03), as were ACPP rates [270 days (DCB) *vs.* 161 days (control), P=0.04]. Limitations were similar to the prior study.

Roosen et al., 2017; IN.PACT balloon (23)

This small (n=34), two-center RCT from the Netherlands was performed in patients with recurrent stenoses in AVFs and AVGs and results did not support the use of DCBs, marking it as the first RCT in AV access that did not demonstrate benefit of DCB use. TLR-free survival of 130 days in the DCB group *vs.* 189 days in the control group (P=0.2). Notably, pre-dilation was not performed and a standard balloon, rather than HPB, was used in the control arm. Additionally, it is unclear what effect the inclusion of both fistulas and grafts had on study results. The majority of subsequent studies, aside from a 2020 study by Liao *et al.* (78), performed lesion preparation with pre-dilation, with technical success approaching 100% in these studies. While pre-dilation decreases treatment differences between study groups, inclusion of pre-dilation may result in a mismatch in the number of angioplasties a lesion undergoes, with pre-dilated lesions undergoing two angioplasties (pre-dilation + DCB) compared to a control group undergoing single POBA. This could introduce bias regarding the increased number of angioplasties in the treatment arm. Some studies offset this by performing repeat/sham balloon treatment in the control arm, noting that doing so differs from the standard-of-care, as repeat/sham treatment is not performed in the normal clinical setting.

Maleux et al., 2018; IN.PACT balloon (25)

This three-center trial performed primarily in Belgium included 64 patients with AVFs (47% radiocephalic and 41% brachiocephalic), with lesion pre-dilation performed using the same HPB in both the DCB and control groups. No second angioplasty was performed in the control group. The primary endpoint was not met, with no significant difference in patency rates between the DCB and control group at 3 months (88% *vs.* 81%, P=0.43), 6 months (68% *vs.* 65%, P=0.8), or 12 months (42% *vs.* 39%, P=0.95). Additionally, no particular group appeared to benefit from DCB use on subgroup analysis.

The DEBAPTA trial: Irani et al., 2018; IN.PACT balloon (24)

In the same year, this single-center trial performed in Singapore including 119 patients with stenoses in any location within either AVFs or AVGs was published. Patients with multiple sites of stenosis were included, with

DCB treatment reserved for the most severe lesion. The study included a large number of forearm accesses (>50% in both arms. At 6 months, TLPP was 81% for the DCB group and 61% for the control group (P=0.03) and ACPP was also significantly improved (DCB =76% *vs.* control =56%, P=0.48). At 12 months, the improvement in TLPP remained (DCB =51% *vs.* control =34%, P=0.04), however, there was no longer a significant difference in ACPP (DCB =45% *vs.* control =32%, P=0.16). While this study met its primary endpoint, there were significantly more forearm fistulas in the DCB group compared to the control group (75% *vs.* 53%, P=0.02), which typically have improved outcomes compared to upper arm fistulas (5). While TLPP improvement persisted at 12 months, the ACPP did not, noting the large number of patients with multifocal stenoses (not all of which were treated by a DCB) may account for this. Notable sub-group analysis findings from this study include a greater benefit of DCB use in treatment of restenotic lesions compared to *de novo* lesions (14).

The Lutonix AV pivotal trial: Trerotola et al., 2018 and Trerotola et al., 2020; Lutonix Balloon (28,29)

Published in 2018, with long term follow-up results published in 2020, the Lutonix AV trial was the first large-scale multicenter clinical trial assessing DCB use in AV access. The trial included 23 centers in the United States (U.S.) and enrolled 285 patients with dysfunctional AVFs with either *de novo* or non-stented restenotic lesions at any site within AVFs (excluding the central veins) and utilized a core lab. All lesions were initially treated with an HPB, with successful treatment considered full effacement of the balloon waist and <30% residual stenosis. Additionally, there could be no more than one additional non-target lesion in the circuit, which had to be successfully treated prior to randomization. Following successful vessel preparation, lesions were treated with either the DCB or a partially compliant low-pressure control balloon, ensuring similar number of angioplasties were performed in both groups. The recommended duration of balloon inflation was adjusted from at least 30 seconds to at least 2 minutes partway through the trial, based on data regarding DCB use in PAD (85). Importantly, the study analysis was designed to look at 6-month TLPP as the primary end-point, with 180 days representing the predetermined analysis point. In order to allow time for patients to return for the 6-month visit, a protocol-specified window of 30 days was allowed (days 150–210), however, because analysis could only occur at a single time-point, rather than within a window, the 180-day time point was chosen, which may have led to undesirable censoring of subject data between days 180–210.

The primary study endpoint was ultimately not met, with Kaplan-Meier survival analysis at day 180 demonstrating a TLPP rate of 71%±4% in the DCB group and 63%±4% in the control group, with P=0.06. An exploratory analysis performed at day 210 to include censored data between days 180 and 210 did reach statistical significance (DCB =64%±4% *vs.* control =53%±4%, P=0.02). Six-month ACPP did not differ between the two groups in either 180 day or exploratory 210-day analysis. There were significantly fewer interventions required to maintain TLPP in the DCB group (0.31) compared to the control group (0.44), with P=0.03. The study concluded that the DCB was not shown to be superior to a standard balloon when used after successful angioplasty in AVF stenosis using a strict 180-day definition of the 6-month end point, although fewer interventions were needed to maintain target lesion patency. Notably, the DCB outcomes were similar to prior studies, including those by Katsanos and Kitrou *et al.* (20,21), however, the control arm patency was much higher in the current study, owing to high-quality angioplasty using HPBs in both study groups as compared to earlier studies in which vessel preparation was not performed. Maintaining a high standard of pretreatment angioplasty in both arms may serve to decrease the effect size between the DCB and control groups compared to prior studies, but appropriately allows for the true effect of the drug-element of the DCB to be evaluated, rather than its treatment effect as an angioplasty balloon and/or additional angioplasty treatment.

The 2-year trial results represent the largest cohort of 2-year follow-up data available after DCB use (at the time of this review's publication). Numerous additional analyses were performed to assess differences in outcomes regarding lesion location, access age, and residual stenosis, amongst others. In the final analysis, TLPP was statistically better in the DCB group at 9 months (DCB =58% *vs.* control =46%, P=0.02) and 12 months (DCB =44% *vs.* control =36%, P=0.04), but not at other time points including 24 months (DCB =27% *vs.* control =24%, P=0.09). Some DCB benefit was demonstrated, as there was a longer mean time to event for TLPP in the DCB group (DCB =322 days *vs.* control =207 days, P<0.001) and fewer interventions were needed to maintain TLPP in the DCB group at 9 months (P=0.02), but not at other time points. There was no difference in ACPP at any time point and subset analyses

did not demonstrate any additional differences between groups. Overall, while the Lutonix trial did not demonstrate a clear benefit of DCBs in term of TLPP or ACPP, it did demonstrate benefit in prolonging the length of time between interventions on the target lesion, about 4 months on average, a not insignificant amount of time for these patients. Additionally, the study provided reassuring safety information regarding DCB use in the ESRD population, with no difference in safety between the study groups during follow-up.

Swinnen et al., 2019; IN.PACT balloon (75)

In 2019, a unique RCT from Australia focused on use of DCBs specifically in restenotic lesions, in which an aggressive angioplasty regimen was applied in both study arms. Many of the study methods differ from practice patterns elsewhere, limiting the applicability of study results. Pre-dilation angioplasty and POBA in the control arm was described as "aggressive" in the study protocol, with mention of HPBs, cutting balloons, and angioplasty to the point of fistula rupture, with liberal use of bare metal stents. The effect of this aggressive regimen on the study results is unclear. The primary endpoint was LLL on follow-up ultrasound at intervals up to was performed at intervals up to 12 months. Notably, this measure does not capture whether the restenotic lesion was causing access dysfunction. Additionally, reintervention was not always performed on the basis of a clinical indicator, as luminal diameter <2 mm on ultrasound prompted treatment even in the absence of access dysfunction. This may increase the rate of reintervention beyond what is clinically indicated and is not in line with Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations (13). In total, 132 restenotic lesions (48% of which were in-stent stenoses within bare nitinol stents) were randomized, with 70 in the DCB arm and 62 in the control arm. During the trial, 40 new bare nitinol stents were placed (no difference between study arms, P=0.59). A linear mixed effects model was used to evaluate the primary endpoint, which demonstrated a significant difference in the rate of lumen loss between the DCB group (0.045±0.03 mm per month) and the control group (0.23±0.03 mm per month), with P=0.0002. This finding was also observed at 12 months, and there was improved time to reintervention in the DCB arm compared to the control arm. When restenotic lesions in stented and unstented vessels were evaluated separately, a greater effect of DCB treatment was found in the stented group. The study results were analyzed early, when all follow-up was complete to 6 months, rather than the planned 12 months—a decision reportedly influenced by issues of timeliness and thought that effects should be measurable at this time point as NIH typically occurs between 6 weeks and 6 months (citing a study of coronary arteries restenosis), however, all trial patients were followed to 12 months in an unblinded fashion. Overall, this study suggested DCBs delay restenosis in recurrent lesions, with more of an effect for in-stent restenosis compared to native vessel restenosis, although the findings must be taken in the context of the study methods.

The DRECOREST II study: Björkman et al., 2019; IN.PACT balloon (76)

Another study often specifically discussed, and sometimes excluded from meta-analyses due to its contribution to heterogeneity, is this single-center study of DCBs in AVFs performed in Finland. The main difference in this study compared to others is that fistula age was relatively young (mean access age 0.5 years) and nearly 90% of accesses were forearm radiocephalic fistulas (RCFs) (86). Additionally, while pre-dilation was performed, this was done using a standard non-HPB purposefully undersized 1 mm below the target vessel diameter. No HPBs were used in either study group. Finally, the study was terminated early due to slow recruitment, likely due to the exclusion of perianastomotic lesions (the most common lesion in RCFs). The primary endpoint, TLR, was not met, and results were overwhelmingly negative regarding DCB use. It was postulated that the significant difference between TLR may be related to DCB use in young AVFs created less than 1 year before intervention, as there may be decreased arterialization of the access vein, and the thinner vein wall in the immature fistulae may be more susceptible to over-dosage of paclitaxel and potential toxic side effects. The study concluded that DCB use should be discouraged in recently created or immature accesses.

Kim et al., 2020; IN.PACT balloon (77)

A smaller RCT with a unique population, this Korean RCT focused on treatment of juxta-anastomotic stenosis in RCFs in 39 patients. Pre-dilation was performed in both groups, with those in the DCB group undergoing subsequent DCB angioplasty and repeat POBA (total of 3 angioplasties) while the control group underwent repeat POBA (total of 2 angioplasties). Initial technical success was achieved

in only ~85% in both groups despite HPB use and repeat angioplasty in both groups, with all failures successfully treated with a cutting balloon. Follow-up was longer than most studies, extending to 36 months. TLPP in the DCB and control groups were 90% and 84% at 6 months (P=0.59), 65% and 68% at 12 months (P=0.082), 55% and 57% at 24 months (P=0.9), and 55% and 39% at 36 months (P=0.7), respectively, indicating DCB use did not improve TLPP in juxta-anastomotic stenoses in RCFs.

Liao et al., 2020; IN.PACT balloon (78)

In the same year, a similarly sized study was performed in Taiwan focusing on treatment of venous anastomotic lesions in AVGs, a notoriously difficult lesion to treat. Pre-dilation was not performed in the DCB group, while the control group utilized HPBs. Not surprisingly, initial technical success was only 28% in the DCB group compared to 72% in the control group. Those with residual stenosis underwent repeat angioplasty with a non-compliant ultra-HPB (Conquest, Bard, Crawley, UK), with 15/22 patients in the DCB group requiring this. TLPP was significantly improved in the DCB group (41%) compared to the control group (9%) at 6 months (P=0.006) and at 12 months (23% *vs.* 9%, P=0.013). Significantly improved circuit patency was seen at 6 months, but not at 1 year. Both target lesion and access circuit intervention-free interval were significantly greater at both 6 and 12 months in the DCB group. While these findings suggested improved outcomes with DCBs in the treatment of venous anastomotic stenosis, the confounding effect of the more aggressive POBA performed in the majority of the DCB group may have influenced results. In order to isolate the effect of the DCB on clinical outcomes, identical POBA would have ideally been performed.

The IN.PACT AV access pivotal trial: Lookstein et al., 2020 and Holden et al., 2022; IN.PACT balloon (26,27)

This well-designed multicenter single-blinded trial enrolled 330 patients in the U.S., Japan, and New Zealand with either *de novo* or non-stented restenotic lesions at any site within AVFs (excluding the central veins), utilized a core lab, and represents that largest RCT performed to date assessing the IN.PACT balloon (and any DCB, for that matter). The study prioritized adequate vessel preparation, with all patients undergoing pre-dilation with a non-compliant HPB. Successful pre-dilation, defined as residual stenosis on <30% vessel diameter with absence of perforation or flow-limiting dissection, was achieved in 100% of patients. Thus, all included patients essentially underwent the standard of care (high-quality plain balloon angioplasty) before undergoing treatment with either the DCB or sham-balloon (uncoated non-HPB). All subjects in the DCB group also underwent full 3-minute DCB inflation. The primary endpoint was TLPP at 6 months, defined as freedom from clinically driven TLR or access circuit thrombosis, with events denoting a clinically driven TLR including stenosis of at least 50% vessel diameter in the presence of a clinical indicator of access dysfunction or at least 70% stenosis in the absence of a clinical indicator. Baseline characteristics between the DCB and control groups were similar and there was an even distribution of access locations (upper arm and forearm) as well as lesion locations. The study met its primary endpoint, with a 6-month TLPP of 82% in the DCB group and 60% in the control group (P<0.001), with clinically-driven TLR in the DCB group less than half of that in the control groups (16% *vs.* 39%, respectively). The study met multiple additional secondary endpoints, with significantly decreased mean number of repeat interventions to maintain TLPP (DCB =0.2±0.6 *vs.* control =0.6±0.7, P<0.001) and access-circuit primary patency (DCB =0.3±0.7 *vs.* control =0.6±0.8, P<0.001). ACPP, inclusive of the target lesion, was 73% in the DCB group and 48% in the control group (P<0.001).

Twelve-month follow-up results were published in 2022, and demonstrated sustained effectiveness of the DCB, with 12-month TLPP of 64% in the DCB group compared to 44% in the control group (P<0.001). There was a 35% reduction in reinterventions to maintain TLPP when a DCB was used. Multivariate analysis demonstrated use of a DCB to provide the largest risk reduction regarding loss of TLPP [hazard ratio (HR) 0.45, 95% confidence interval (CI): 0.29–0.64, P<0.001], with additional predictors including access age, target lesion outside of the cephalic arch, and lesion type (de novo *vs.* restenotic). Longer lesions and those with increased number of prior interventions were at higher risk of loss of TLPP. In essence, *de novo* lesions outside of the cephalic arch in more mature accesses had the best outcomes after DCB use, while longer lesions with multiple prior interventions did not fare as well, providing important information in tailoring potential DCB use for specific lesions. Subgroup analysis demonstrated less benefit of the DCB in U.S. participants compared to those elsewhere, with differences in TLPP of 16% between DCB and control groups in the U.S. subgroup compared to a

difference of 32% in the non-U.S. subgroup, thought to be related to the increased number of forearm fistulas outside the U.S. (87).

Overall, the IN.PACT AV access trial had multiple strengths, including a study design that minimized variables and confounders that may affect DCB results, such as consistent vessel preparation, and demonstrated a strong treatment effect when the IN.PACT balloon was used (87). The positive and sustained results demonstrated in this trial are the strongest evidence supporting use of DCBs to date.

Karmota et al., 2020; Lutonix balloon (80)

This small randomized trial from two Egyptian hospitals included 60 patients with solitary AVF stenoses. Some study details, including those regarding blinding, whether lesions were *de novo* or recurrent, and the balloon used for pre-dilation and control angioplasty (high-pressure or not) were not reported. Control patients underwent pre-dilation with an undersized balloon followed by dilation with a standard balloon, while the treatment group underwent pre-dilation with a standard balloon followed by the DCB. No significant differences were seen at 3 months (TLPP 100% in both groups) or 6 months (DCB =97%, control =90%, P=0.03). The primary endpoint was met at 12 months, with a TLPP of 90% in the DCB group *vs.* 67% in the control group (P=0.03). While the study supported the use of DCBs, the 3- and 6-month TLPP in both groups were uncommonly high in this study and the missing data regarding certain study and clinical factors make the findings of this small study difficult to interpret and apply.

Ali et al., 2020; multiple DCBs (84)

In the only study employing more than one brand of DCB, this 80-patient study performed at two centers in Egypt demonstrated improved outcomes with DCB use, although with numerous omissions and inconsistencies in the study methods and results. The DCB group underwent pre-dilation with HPBs followed by DCB angioplasty with any of 5 balloons, dependent upon what was available at the time of procedure. While this may reflect real world practices, it does potentially limit the applicability of the study in that balloons of various different characteristics were used. The primary endpoint of the study was described as TLPP and ACPP at 6 months in the study methods, however, time to loss of ACPP and TLR-free survival at 12 months are reported. It is unclear if the study was blinded in any capacity. Time to loss of ACPP was 287 days for the DCB group and 156 days for the control group (P=0.04) and TLR-free survival was 316 days for the DCB group and 172 days for the control group (P=0.04). No discussion of study limitations or comparison to the literature is found in the discussion. Overall, this study is unique in its inclusion of multiple balloons but the somewhat unclear methods and results reporting, ability to be reproduced, and overall quality of evidence are somewhat limited.

Moreno-Sánchez et al., 2020; Passeo-18 Lux balloon (81)

Representing the first large RCT using the Passeo-18 Lux DCB, this single-blind multicenter study, was performed at four centers in Spain and enrolled 136 patients. All patients were fully heparinized prior to initial treatment with an HPB, followed by treatment with either the DCB or second POBA at 6 atm, inflated for 45 seconds. At 6 and 12 months, time to loss of target lesion patency was 153 and 266 days in the DCB group and 142 and 238 days in the control group, respectively, with Kaplan-Meier analysis demonstrating a trend towards improved patency that did not reach statistical significance at 6 months (P=0.07) and converged at 12 months (P=0.37). Similarly, there was a trend toward improvement in TLPP at 6 months (DCB 73% *vs.* control 58%, P=0.13) and at 12 months (DCB 53% *vs.* control 47%, P=0.29), but these differences were not statistically significant.

The PAVE trial: Karunanithy et al., 2021; Lutonix balloon (30)

The PAVE (Paclitaxel-Assisted balloon Angioplasty of Venous stenosis in haEmodialysis access) trial represents the second large RCT using the Lutonix balloon and enrolled 212 patients in 20 centers in the United Kingdom with AVFs and predominantly solitary stenoses. The study methods are notable for pre-dilation using a HPB in the DCB group and performance of a second angioplasty in the control arm, initial inclusion of patients only with single lesions, later broadened to include >1 lesion if all lesions could be treated with a single balloon (to aid in recruitment), and inclusion of patients who had not yet used their fistula for dialysis. Additionally, the investigators recommended >60 second DCB inflation at the trial start (which exceeded the manufacturer's recommendations at that time), however, in 2018, after 75% of patients had been randomized, the manufacturer increased the recommended

time to 120 seconds. This change was subsequently incorporated into the study protocol. Follow-up consisted of clinical monitoring and 6-month fistulogram, with an intervention performed only if a clinical indicator to suggest access dysfunction was present. In order to decrease bias, efforts were made to have a different physician than that who performed the index procedure perform any repeat procedures, and was achieved in 75% of patients. The primary study endpoint, time to loss of TLPP at 6 months, was not met, with no was significant difference between the control group (median 159 days) compared to the treatment group (median 215 days), with HR 1.18 (95% CI: 0.78–1.79, P=0.44). At 6 and 12 months, TLPP was 85% and 59% in the control group, respectively, compared to 72% and 53% in the treatment group, respectively. No secondary outcomes were different between the two groups, including access circuit patency, mean LLL, and number of interventions, amongst others.

Overall, the PAVE trial provided no evidence of additional benefit from DCBs when they were used after clinically-driven high quality balloon angioplasty. In discussion, the authors noted multiple unique factors of the study that provide additional context for these findings. The outcomes in the control group in the PAVE trial were better than many other studies, with a 6-month TLPP of 85%. The authors noted the value of high-quality plain balloon angioplasty in achieving this, and noted that such results may obviate the benefits that DCBs appeared to provide in other trials, including those in which HPB angioplasty was not performed in all groups. One of the unique strengths of the PAVE trial was its inclusion of only single or tandem lesions that could be treated with one balloon—this differed from the Lutonix trial, in which only the lesion most thought to be causing the access dysfunction was treated with the DCB, while others were treated with HPB angioplasty. In order to maintain this trial requirement, a number of immature fistulas were included in the PAVE study—slightly greater than 20% in both groups. While this may have influenced results—noting prior studies in which DCBs showed neutral to negative effects when used in immature fistulae, the authors note that the majority of these fistulas eventually matured, rather than being abandoned, therefore a high rate of primary fistula failure could not explain the results. Additionally, while there was a change to recommended DCB inflation time during the trial, 97% of patients achieved a greater than 60 second DCB treatment at final analysis, without evidence of any differences between groups who underwent different lengths of inflation.

The PAVE trial was the second large RCT that failed to show a clear benefit of using the Lutonix DCB. While the study by Trerotola *et al.* (28,29) demonstrated positive results at certain timepoints (9 and 12 months) as well as increased time to repeat intervention with DCB use, none of these benefits were demonstrated in the PAVE trial. In fact, there was a trend towards improved outcomes in the control arm in the PAVE trial, without much explanation as to why. The lack of significant clinical benefit in the trials utilizing the Lutonix balloon, as compared to the more robust benefit demonstrated in the IN.PACT trial, has raised questions as to whether the balloon device and associated differences in paclitaxel dose density, excipient, and other factors are the variables that explains these different results (31).

Therasse et al., 2021; Passeo-18 Lux balloon (82)

This Canadian multi-center study represents the second large RCT using the Passeo-18 Lux balloon. The study methods are notable for inclusion of patients with 2 or more lesions that could be contiguous or non-contiguous and treated with 2 separate DCBs, with or without overlap. There was a significant difference in the number of patients with 2 lesions in the DCB group (20%) compared to the control group (7%), with P=0.03. This was the only significant difference between the baseline characteristics of the study groups. Results demonstrated no difference in the primary endpoint, non-adjusted LLL, which measured 0.64±1.20 mm in the DCB group and 1.13±1.51 mm in the control group (P=0.08), although these results were statistically significant after adjustment (P=0.0498). While the degree of LLL was of borderline significance, both access circuit failures (DCB =45 and control =67) and target lesion failures (DCB =33 and control =62) were significantly decreased in the DCB group compared to the control group (P=0.017 and P=0.002, respectively). Additionally, at one year, freedom from access circuit failure was significantly better in the DCB group (50%) compared to the control group (30%), with P=0.02, and freedom from target lesion failure was also significantly better in the DCB group (63%) compared to the control group (35%), with P=0.02. Overall, while there was a nonsignificant improvement in LLL between the two groups, clinical outcomes including access circuit and target lesion failure were significantly improved

at 12 months. This study demonstrates the importance of choosing both the correct primary study endpoint and choosing an endpoint with clinical significance (TLPP, ACPP, TLR, etc.) compared to a measured non-clinical marker (LLL, flow measurement, etc.).

Yin et al., 2021; Aperto balloon (83)

Representing the only large RCT using the Aperto balloon, this multi-center trial performed in China was grossly similar in design to previously described large trials, although with some important differences, namely the use of a composite primary endpoint that had not been previously validated. This endpoint consisted of target lesion intervention-free survival (TLR-free survival) in conjunction with a peak systolic velocity ratio (PSVR) ≤2.0 as determined by duplex ultrasound. The methods are also notable for 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 HPB angioplasty. The study population is notable for the inclusion of a large number of forearm accesses, similar to the study by Lookstein *et al.* (26), as is often the case in studies including Asian sites, where forearm fistulas are more prevalent.

While the authors defend this composite endpoint as a way to focus on DCB effect on the target lesion itself through use of an ultrasound-measurement rather than a clinical event, there are multiple issues with such an endpoint. PSVR ≤2 is a measure that has not been validated for evaluation of stenosis in fistulas, rather, it has been evaluated in grafts (which are more uniform in nature compared to potentially tortuous and aneurysmal fistulas) (88). Additionally, the measurement is reliant on ultrasound, with its associated inter-operator variability. This was evident in the results, which demonstrated significantly more lesions with PSVR ≤2 in the DCB group (65%) compared to the control group (37%) at 6 months (P<0.001), however, without significant difference in TLR-free survival, which was 86% in the DCB group and 78% in the control group (P=0.3). Additionally, the average degree of target lesion stenosis at 6 months was not significantly different (DCB =44%±16%, control =49%±18%, P=0.09). The lack of correlation between the PSVR and the clinical indicator of dysfunction, TLR-free survival, as well as the measured degree of stenosis, makes it difficult to interpret the meaning of the PSVR outcome. While no difference in clinical outcomes was observed at 6 months, there was a significant difference in TLR-free survival at 12 months (DCB =73%, control =58%, P=0.04). Overall, this study highlights the importance of the use of validated patient-centered endpoints throughout the AV access literature, and unfortunately does not add convincing evidence in the support of DCB use (88).

Additional smaller RCTs, non-randomized prospective studies, and retrospective studies

While the numerous described RCTs provide the highest level of evidence in determining the effectiveness of DCBs in AV access, there have been a number of non-randomized prospective and retrospective studies that also contribute to the evidence basis.

For the sake of completeness, a small 40-patient RCT by Pang *et al.*, published in 2021, was not available for review, but available data was included in *Tables 3*,*4*, and an additional RCT not previously mentioned due to its small size (n=23) was terminated prematurely due to safety concerns regarding DCBs in 2018, with no significant difference in outcomes between those treated with DCBs and those in the control arm in this inherently underpowered study (79,89).

The largest of the non-randomized prospective studies performed evaluating DCBs in AV access include prospective registries, which have provided useful "real world" use data. A 200 patient Italian registry of those who underwent 311 angioplasty procedures using the Aperto balloon was published by Tozzi *et al.* in 2019, suggesting favorable long-term patency rates can be achieved. Kaplan-Meier analysis of TLPP demonstrated rates of 88%, 64%, and 41% at 6, 12, and 24 months, respectively, and patency rates were highest when *de novo* lesion were treated with DCBs. Additionally, there was improved patency when lesions were pre-dilated with "focal force" balloons or cutting balloons as compared to normal HPBs (90). The previously mentioned global registry reported by Karnabatidis *et al.* enrolled 320 patients with either AVFs or AVGs treated with the Lutonix DCB, with overall TLPP of 74% at 6 months, and significantly improved patency in those in whom the DCB was dilated for >120 seconds and in those in whom pre-dilation was performed (71).

Remaining studies can be roughly divided into those that focused on particular lesion types and those that took a more general approach. In regards to the latter, Veerbeck *et al.* prospectively treated 70 venous stenoses in 41 patients with

AVFs using the IN.PACT DCB and demonstrated primary patency rates of 81% at 6 months and 60% at 12 months (91). Çildağ *et al.* retrospectively compared 26 patients treated with the Freeway DCB (Eurocor GmbH, Bonn, Germany) to 26 patients who underwent POBA, with no significant difference in in primary patency at 6 months (P=0.45), however, with significantly increased primary patency at 12 months (DCB =65%, POBA =35%, P<0.05) (92). In 2017, Kitrou *et al.* retrospectively reviewed patients with AVFs and AVGs who underwent DCB angioplasty with the Lutonix balloon, with TLPP of 72% at 6 months and no differences found between access type or *de novo vs.* restenotic lesions. In 14 cases where the same lesion was treated with two DCBs at different time points, there was a significant increase in time to loss of TLPP after the second intervention (first intervention 180 days, second intervention 174 days, P=0.03) (93). However, a follow-up study by the same group of 38 patients who had consecutive DCB angioplasties demonstrated no significant difference between first and second DCB interventions, with median primary patency rates of 217 days after first intervention and 280 days after second intervention (P=0.37) (94).

Two studies have looked specifically at restenotic lesions. A retrospective review of 27 patients who underwent DCB treatment of recurrent stenoses with the Freeway DCB (Eurocor GmbH, Bonn, Germany) were evaluated and the time to loss of TLPP of the prior POBA treatment was compared to that after DCB treatment. Time to loss of TLPP was 4.8 months after POBA leading into DCB treatment, and 7.6 months after DCB treatment (P<0.001). Two-year primary patency rates were 32% after DCB treatment (95). In a 2015 study which pre-empted their RCT, Swinnen *et al.* retrospectively reviewed 37 cases in which a DCB (IN.PACT) was used to treat in-stent restenosis, with a significant difference in "re-intervention free percentage at 12 months" before and after DCB use, determined using the disease-free interval prior to DCB use and comparing it to the disease free-interval after DCB use. This was found to be 19% at 12 months prior to DCB use and 69% after DCB use, suggesting DCBs reduce re-intervention on in-stent restenoses (96).

In a unique study retrospectively assessing outcomes after venous outflow stenoses were pre-dilated with a cutting balloon followed by application of a DCB (Aperto), Ierardi *et al.* with a patency rate of 88% at a median follow-up of 8 months (97).

Finally, numerous studies have focused on inflow lesions in RCFs. A 2014 study by Lai *et al.* included 10 patients two short, separate inflow stenoses (n=20) and separately randomized each lesion to undergo DCB (SeQuent Please; B Braun, Berlin, Germany) or plain balloon angioplasty. There was improved TLPP at 6 months (DCB =70%, control=0%, P<0.01), but this difference did not persist at 12 months (DCB =20%, control=0%, P<0.47) (98). In a prospective study of 26 patients with treated with the IN.PACT DCB published in the same year, Patanè *et al.* reported TLPP of 96% at 6 months, 91% at 12 months, and 58% at 24 months (99). In 2018, Lučev *et al.* compared 31 patients with predominantly inflow lesions (94%) were treated with DCBs (IN.PACT) and compared with a history PCB control group, with improved patency rates at 6, 12, and 24 months (DCB =45% *vs.* control =16% at 24 months, P=0.026) (100). Following this, Gulcu *et al.* reported long term results (mean follow-up 27 months) in 38 patients with RCFs and inflow stenoses treated with the IN.PACT and Elutax-SV (ab medica, Dusseldorf, Germany) DCBs, demonstrating patency rates of 81% at 12 months, 61% at 24 months, and 53% at 48 months (101). In a similarly sized study, Kocaaslan *et al.* retrospectively reviewed 43 patients with treated with the IN.PACT DCB and 44 patients who under POBA during the same time period. No significant difference in TLPP was identified at 6 months (DCB =93%, POBA =81%, P=0.14), however, there was a significant difference at 12 months (DCB =82%, POBA=51%, P=0.01) (102).

Summary of studies and meta-analyses

Overall, 7 studies using the IN.PACT balloon enrolling nearly 750 patients (range, 40–330) have reported improved clinical outcomes after DCB use, while 4 studies using the IN.PACT balloon enrolling nearly 175 patients (range, 34–64) did not demonstrate a clinical benefit. None of the 3 studies using the Lutonix balloon, enrolling over 550 patients (range, 60–285), demonstrated a clear benefit of DCB use, with one study meeting no primary endpoints and two others meeting their endpoints only at certain follow-up intervals, but not at others. Neither of the two RCTs using the Passeo-18 Lux balloon, enrolling 120 and 148 patients, demonstrated a benefit of DCB use. The one RCT using the Aperto balloon, enrolling 161 patients, did not demonstrate a strong clinical benefit of DCB use, noting the limitations previously described. The aforementioned non-randomized studies generally suggest improved outcomes with the DCB when compared to historical POBA treatment, however, these studies have

the limitations inherent of prospective single-arm studies, registries, and retrospective studies. Numerous themes are identified throughout: (I) inconsistencies between pre-dilation protocols, balloon choices, and performance of a "sham" second angioplasty in the control arm introduce numerous confounding variables that are difficult to account for and difficult to compare between studies; (II) different RCTs have used a wide variety of inclusion criteria, including access type, lesion location, and whether a lesion was recurrent or *de novo*, increasing heterogeneity between study populations; (III) utilizing similar patient-driven and clinically-driven outcome measures as study endpoints is important, and studies with similar endpoints and easier to compare, and (IV) long-term follow-up is needed, as some studies saw 6-month benefits disappear at 12 months, and vice versa, with significant differences in outcomes identified only after 12 months from the index procedure. As a whole, the variation in available RCT evidence in terms of whether DCBs provide clinical benefit is somewhat inexplicable and this lack of consistent results somewhat discouraging, leaving interventionalists without a clear sense as to whether one should be using a DCB in their daily practice.

Given the lack of clarity provided by the available RCTs, numerous systematic reviews and meta-analyses have been performed over the years. However, these have also been unable to provide a clearer sense of the effectiveness of DCB us in AV access, noting conflicting conclusions likely related to differences in the meta-analyses, including their unique inclusion criteria, availability of RCTs and other studies for inclusion based on time of publication, and different analytic methods (14,66,76,103-107).

For example, a 2020 meta-analysis by Cao *et al.* including 6 cohort studies and 6 RCTS demonstrated a benefit of DCBs when these were combined and when cohort studies were analyzed separately, but not RCTs were analyzed separately, noting high heterogeneity in the RCTs (103). In the same year, Tripsianis *et al.* published a meta-analysis of 11 RCTs demonstrating superiority of DCBs compared to POBA, while Liao *et al.* published a meta-analysis including 11 RCTs which demonstrated no benefit of DCBs at 6 or 12 months, noting wide variations in patency outcomes across the included studies (66,104). A 2021 meta-analysis by Fong *et al.* included 12 RCTs and employed numerous types of analyses, with the majority suggesting a benefit associated with DCB use (105). Similarly, a 2021 meta-analysis by Liu *et al.* included 18 RCTs and suggested DCBs improved TLPP and ACPP compared to POBA (106). However, this was followed by a 2022 meta-analysis by Luo *et al.* including 14 RCTs which demonstrated no clear advantage of DCBs compared to POBA (73). An umbrella review evaluating the numerous meta-analyses available by Lazarides *et al.* summarized the available data (108). No significant differences in TLPP were identified in meta-analyses providing data from AVFs alone. When AVFs and AVGs were mixed, benefits to TLPP and ACPP were identified at 3, 6, and 12 months, however, the majority of predictive intervals included the null value. Overall, the umbrella review concluded a modest benefit to DCBs compared to POBA.

Sub-group analyses performed within some of these meta-analyses have provided some guidance for procedural technique regarding DCBs and raised questions that may be answered in future studies. Both Fong *et al.* and Luo *et al.* suggested that higher-dose DCBs (3.0–3.5 μg/mm^2) were associated with improved outcomes, indicating a higher paclitaxel dose may be of value (73,105). Additionally, Luo *et al.* found that 6- and 12-month TLPP rates were significantly higher in those who underwent a DCB inflation >120 seconds, consistent with other studies that have suggested that a prolonged inflation may improve patency rates (73,109).

Cost

The cost of using a DCB must also be considered when considering their clinical use. DCBs are more expensive than plain balloons, and may not be reimbursed by health systems (43). Additionally, any benefit in terms of patency must be considered in the context of the added cost of the DCB. This, however, may be balanced out by the overall decrease in costs associated with prevention of restenosis and reintervention. Few studies have included a cost-effectiveness analysis (5,21,110). The largest performed to date is the economic analysis performed as part of IN.PACT AV access trial, published in 2022 by Pietzsch *et al.* in tandem with the 12-month trial results. Assuming the benefits of DCB use compared to POBA demonstrated in the trial, 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 (approximately $1,800). After inclusion of cost, there was cost neutrality at 1 and 2 years, but in all analyses performed there were cost savings at 2.5 and 3 years (110). As DCBs continue to be studied it will be important to continue to perform such analyses to determine the overall value to patients and healthcare systems.

Future

It has been over 10 years since the first RCT involving DCBs in AV access, and while evidence continues to be gathered regarding their use, other technologies continue to be developed and studied. In light of the 2018 reports regarding potential paclitaxel-associated mortality, DCBs and stents employing sirolimus as an anti-proliferative gained traction. Tan *et al.* treated 20 patients with vein-graft anastomotic stenoses using a sirolimus DCB (MagicTouch, Concept Medical, India), with results demonstrating a 6-month ACPP of 65% and mean patency of 285 days (111). Twelve-month follow-up results demonstrated a ACPP of 40%. Tang *et al.* treated 43 lesions in 39 patients as part of an ongoing trial evaluating the Selution SLR DCB (M.A. MedAlliance, Nyon, Switzerland), with 6- and 12-month TLPP rates of 72% and 45%, respectively (112,113). No studies have been performed comparing paclitaxel-coated balloons and sirolimus-coated balloons. Paclitaxel-eluting stents have been studied in AVFs as part of a pilot study in which 12 were deployed in 10 patients, with primary patency rates of 78% at a mean of 202 days' follow-up. Two stents thrombosed in the setting of recently stopping dual antiplatelet therapy, requiring salvage with angioplasty (114). While no therapy has proven to be the silver bullet in the treatment of AV access stenosis, future therapies, such as biodegradable stents and stem-cell delivery systems, remain on the horizon (39,115).

Conclusions

As the vascular access community continues to work towards the goals identified in the 2019 KDOQI, namely to prevent access dysfunction and decrease the number of interventions to maintain AV access, the allure of DCBs in both treating stenotic lesions, the most common cause of access dysfunction, and preventing their recurrence remains high (13). The pathophysiologic mechanisms behind DCBs, as explained in this review should function to decrease NIH and subsequent restenosis. However, while there have been glimpses of evidence in favor of DCB use in AV access, these are tempered by numerous studies that suggest the opposite. This is despite a mounting body of literature including numerous large, well-designed RCTs, meta-analyses, and other studies, none of which have provided a clear answer as to whether DCBs should be implemented into daily practice or how to do so. Similarly, no national guidelines, including the 2019 KDOQI, make recommendations regarding their use, citing inadequate evidence (13).

Given the lack of clear signal when considering all-comers with AV access stenosis, and the numerous studies that do demonstrate benefit of DCBs, it is likely that there are groups of patients who benefit from their use. To date, available RCTs and meta-analyses have yet to identify exactly who this group is within their sub-group analyses, however, research in these areas continues. It has been suggested that a more precision-based approach to DCB study and use in AV access stenoses be taken in order to maximize efficacy, optimize outcomes, and ensure their safe and economic use (31). It is possible that implementing such a precision-based approach to DCBs may shed light onto which patients will truly benefit from DCBs, as the one-size-fits all approach has yet to provide a clear answer. Until that time, the available evidence reviewed herein may serve to guide the interventionalist in their decision making, knowing that DCBs appear safe when used in AV access and may provide some benefit in terms of increasing primary patency rates and extending the amount of time between interventions in certain patient populations.

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