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Review

Drug-Coated Balloon for Arteriovenous Access Stenosis in Hemodialysis Patients

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Abstract: Hemodialysis access stenosis is a pervasive problem that occurs due to the physiology of the high-flow circuit. Stenosis occurs due to endothelial and smooth muscle injuries that result in neointimal hyperplasia. Percutaneous transluminal angioplasty is the standard treatment for dialysis access-induced stenosis. Unfortunately, it is also associated with vessel wall trauma, which causes further intimal hyperplasia and restenosis. Data from randomized controlled trials (RCTs) and systematic reviews of the use of drug-coated balloons (DCBs) for dialysis access stenosis have been controversial. While several single-center trials or RCTs have reported safe and effective use of DCBs, conflicting results still exist. Furthermore, paclitaxel is known to be associated with an increased mortality risk. Herein, we review the current evidence on the role of DCBs in the treatment of dialysis access stenosis.

Keywords: hemodialysis access; stenosis; paclitaxel; drug coated balloon; patency; mortality

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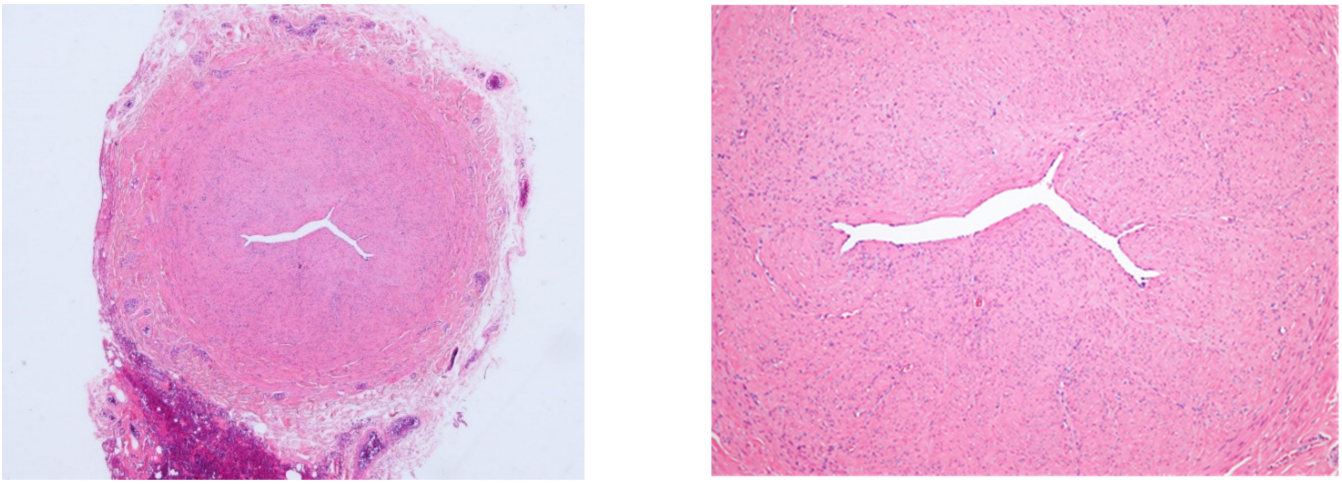
1. Introduction

A well-functioning vascular access is the lifeline for patients with end-stage kidney disease on hemodialysis. Surgically created vascular access, such as arteriovenous fistula (AVF) and arteriovenous graft (AVG), is the method of choice for long-term hemodialysis. However, stenosis and thrombosis most frequently compromise the function of an AVF or AVG. Clinical relapse of stenosis increases the morbidity and medical costs and reduces the quality of life. The etiology of stenosis includes the procedure used to create vascular access; the procedure is accompanied by several inflammatory processes induced by incision, suturing, and wound healing; puncture of the access circuit during dialysis; and the inherent status of these patients, as they often experience oxidative stress and hypoxia [1]. These processes result in inflammation, endothelial dysfunction, and consequently, venous intimal hyperplasia, an aggressive fibromuscular thickening of the vascular wall (Figure 1) [2]. On the cellular level, myofibroblasts and differentiated contractile smooth muscle cells accumulate around the vascular wall and result in an extensive extracellular matrix formation [3]. Endovascular treatment methods can be used to manage stenosis; however, subsequent negative vessel remodeling and neointimal hyperplasia contribute to restenosis, induced mainly by barotrauma and inflammation following angioplasty [4,5]. Therefore, restenosis can be prevented by slowing the proliferative process, which is the target pharmacologic effect of drug-coated balloons (DCBs). These DCBs maintain a sustained release of anti-proliferative drugs without the use of permanent implants.

The use of DCBs were adopted to manage the vascular access following the reports on effective inhibition of intimal hyperplasia and consequent reduction in restenosis of the coronary and peripheral arteries. The mechanism of action of DCBs is based on a combination of angioplasty and local drug delivery using specially designed carriers applied over the balloon's surface; this drug delivery system contributes to the effective delivery and adhesion of a cytotoxic drug, paclitaxel, to the vessel wall [6]. Paclitaxel can slow the process of restenosis by potentially minimizing the cellular component in venous

intimal hyperplasia. In this review, we aimed to provide the current evidence on the clinical effectiveness and safety outcomes of DCB in arteriovenous access for hemodialysis.



(**a**) (**b**)

Figure 1. Arteriovenous fistula with intimal hyperplasia and negative remodeling. Extensive cellular proliferation is observed (hematoxylin–eosin stain). (**a**) Section of the vein where stenosis has occurred; (**b**) magnification view.

2. Overview of DCBs

Local drug delivery technology has been used in coronary and lower limb interventions since the 1990s [7]. The currently available DCBs are summarized in Table 1. DCBs include three main components: a standard balloon platform, a drug coated on the external surface of the balloon, and a ligand (excipient) that binds the drug to the balloon (Figure 2) [8]. The primary role of the balloon platform is satisfactory drug delivery; therefore, vessel preparation before the application of a DCB and prolonged inflation time of DCB are important events for a successful outcome [9]. A recently published report confirmed that the procedural details had a significant role in target lesion primary patency (TLPP); pre-dilation before DCB angioplasty (77% with pre-dilation vs. 48.6% without pre-dilation, $p = 0.0005$) or DCB dilation for $\geq$120 s ($p = 0.007$) significantly improved TLPP in a subgroup analysis [10].

Table 1. Drug-coated balloons that are currently available.

Product	Company	Drug	Dose ($\mu g/mm^2$)	Excipient	NP (atm)	RBP (atm)	Diameter (mm)	Length (mm)
IN.PACT AV	Medtronic	Paclitaxel	3.5	Urea	8	9,10,14	4–10,12	40,60,80,120
Lutonix AV	BD	Paclitaxel	2.0	Polysorbate/ sorbitol	6,7	10,11,12	5–8	40,60,80,100
MagicTouch	Concept Medical	Sirolimus	1.27	Phopholipid	6	16	3–10,12	20,40,60,80,100, 120,150,200
SeQuent Please	B. Braun	Paclitaxel	3.55	Iopromide	6	12–16	4–8	40,60,80,120,150

NP, nominal pressure; RBP, rated burst pressure.

The use of a lipophilic excipient results in homogenous transfer of the drugs onto the vessel wall. The commonest drug used on DCBs is paclitaxel. It is a cytotoxic agent with hydrophobic-lipophilic properties that facilitate its cellular uptake. When paclitaxel is absorbed by the cell, it stops the cell cycle in the M-phase of mitosis by inhibiting the disassembly of the microtubular spindle, which prevents neointimal hyperplasia by driving the cells to apoptosis and inhibits the migration of vascular smooth muscle cell and fibroblasts into the intima [11]. Meaningful reduction of restenosis in peripheral arterial

lesions due to paclitaxel's antiproliferative properties was reported, which suggested its potential in patients with dialysis access stenosis [12,13].

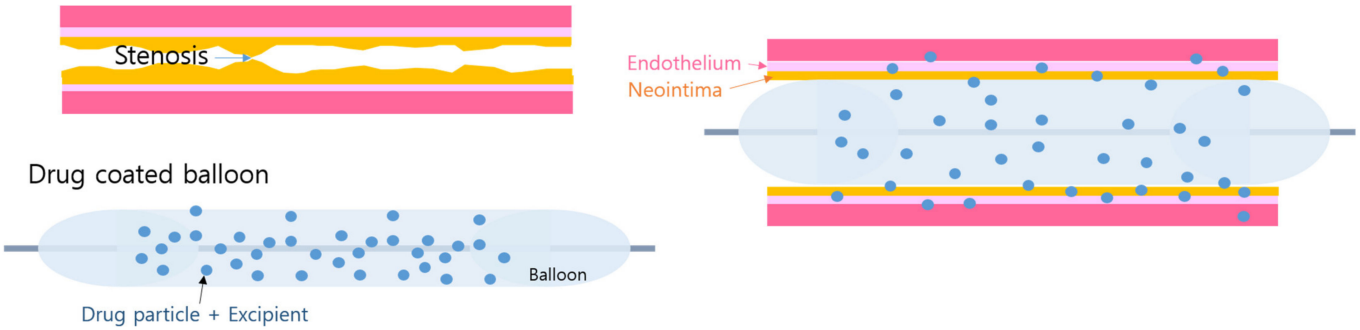


Figure 2. Schematic diagram of a drug-coated balloon (DCB). DCBs include three main components: a standard balloon platform, a drug coated over the external surface of the balloon, and a ligand (excipient), that binds the drug to the balloon. When the DCB is inflated in the stenotic lesion, the drug molecules are absorbed and distributed in the vessel wall.

The currently available paclitaxel DCBs for dialysis access include the Lutonix balloon (Lutonix 035 DCB Catheter; Lutonix, Inc., Maple Grove, MN, USA) and the IN.PACT balloon (IN.PACT 035 DCT Catheter; Medtronic, Dublin, Ireland). The Lutonix balloon uses paclitaxel coating with a drug dose density of 2 μg/mm^2, and the ligand includes sorbitol and polysorbate. In contrast, the IN.PACT balloon is loaded with a higher concentration of paclitaxel (3.5 μg/mm^2) and uses a urea-based excipient [8]. However, the higher density of the IN.PACT balloon does not seem to result in a significant difference in action between the two balloons. Compared to the Lutonix balloon, the IN.PACT balloon has demonstrated greater drug loss with dry handling or inflation and greater downstream embolization, which did not result in a higher dose delivered to the target lesion [14].

Another drug used to prevent restenosis is sirolimus. A sirolimus-based DCB is a second-generation DCB that has been successfully used to prevent restenosis in the coronary vessels. Sirolimus is a macrocyclic lactone antibiotic with immunosuppressive and antiproliferative properties. It is different from paclitaxel in terms of its mechanism of action and physicochemical properties. Sirolimus is cytostatic and stops the cell cycle in the G1 phase by inhibiting the mammalian target of rapamycin [15]. The immunosuppressive properties of sirolimus are considered beneficial for the suppression of the local inflammatory response, whereas paclitaxel demonstrated a reduced suppression of inflammation in a preclinical model of a drug-eluting stent [16]. Peak concentrations of paclitaxel are found in the adventitia, whereas all layers of the vascular wall contain similar concentrations of sirolimus [17]. Due to these properties of sirolimus, it was suggested as a treatment option in thrombosed AVGs, and the results of a recent pilot study suggested that a sirolimus-coated DCB may be a feasible option in improving the patency outcomes [18].

3. Effectiveness of DCBs in Preventing Restenosis of Arteriovenous Access According to Randomized Controlled Trials

To date, several clinical trials have reported on the efficacy of DCBs and their superiority over non-DCBs in arterial occlusive diseases; however, the results were conflicting (Table 2). Two recent large multicenter randomized controlled trials (RCTs) have reported promising results. Trerotola et al. compared DCBs to conventional balloons in failing autogenous fistulas accompanied by up to two lesions, with one being a non-target lesion and the other being a target lesion [19]. In this study, these lesions were predilated using balloon angioplasty with high-pressure balloons to achieve an effacement of the waist to <30% of residual stenosis, which was the primary inclusion criterion. Overall, 285/314 (90.8%) met the inclusion criterion of successful pre-dilation and were included in the study. At 6 months, the number of interventions needed to maintain the target lesion patency were significantly fewer in the DCB group than in the conventional balloon group (0.31

vs. 0.44 per patient, respectively; $p = 0.034$). TLPP rates were higher in the DCB group than in the conventional balloon group at 9 months (58% ± 4% vs. 46% ± 4%, respectively; $p = 0.02$) and 12 months (44% ± 5% vs. 36% ± 4%, respectively; $p = 0.04$). However, this difference was not observed subsequently (34% ± 5% vs. 28% ± 4%, respectively; $p = 0.06$ at 18 months; 27% ± 4% vs. 24% ± 4%, respectively; $p = 0.09$ at 24 months).

Table 2. Randomized controlled trials on the effect of drug-coated balloons on vascular access stenosis in hemodialysis patients.

Year	Author	N	Access	Results
2012	Katsanos et al. [21]	40	AVF, AVG	TLPP at 6 mo, 70% DCB vs. 25% POBA ($p < 0.001$)
2015	Kitrou et al. [22]	40	AVF	TLR-free survival: 308 days DCB vs. 161 days POBA ($p = 0.03$)
2015	Kitrou et al. [23]	40	AVF, AVG	TLPP at 12 mo: 35% DCB vs. 5% POBA ($p < 0.001$)
2017	Kitrou et al. [24]	40	AVF, AVG	Median intervention free period (central vein) 179 days DCB vs. 124.5 days POBA ($p = 0.026$)
2018	Irani et al. [25]	119	AVF, AVG	TLPP at 6 mo: 81% DCB vs. 61% POBA ($p = 0.03$) TLPP at 12 mo: 51% DCB vs. 34% POBA ($p = 0.04$) ACPP at 6 mo: 76% DCB vs. 56% POBA ($p = 0.048$) ACPP at 12 mo: 45% DCB vs. 32% POBA ($p = 0.16$)
2018	Trerotola et al. [26]	285	AVF	TLPP at 6 mo: 71% DCB vs. 63% PTA ($p = 0.06$) PP at 3 mo: 88% DCB vs. 80% PTA ($p = 0.43$) PP at 6 mo: 67% DCB vs. 65% PTA ($p = 0.76$) PP at 12 mo: 42% DCB vs. 39% PTA ($p = 0.95$)
2018	Maleux et al. [27]	64	AVF	Mean intervention free period 110 days DCB vs. 193 days POBA ($p = 0.06$)
2019	Bjorkman, et al. [28]	39	AVF	
2020	Lookstein et al. [20] IN.PACT	330	AVF	TLPP at 180 days: 82.2% DCB vs. 59.5% POBA ($p < 0.001$) Adverse event: 4.2% DCB vs. 4.4% POBA ($p = 0.002$)
2020	Trerotola et al. [19] LUTONIX	285	AVF	TLPP at 9 mo: 58% DCB vs. 46% POBA ($p = 0.02$) TLPP at 12 mo: 44% DCB vs. 36% POBA ($p = 0.04$) TLPP at 18 mo: 34% DCB vs. 28% POBA ($p = 0.06$) TLPP at 24 mo: 27% DCB vs. 24% POBA ($p = 0.09$)
2020	Moreno-Sanchez, et al. [29]	136	AVF, AVG	TLPP at 6 mo: 153.0 days DCB vs. 141.7 days POBA ($p = 0.068$) TLPP at 12 mo: 265.8 days DCB vs. 237.8 days POBA ($p = 0.369$) Mortality: 5.7% DCB vs. 9% POBA ($p > 0.05$)
2021	Karuanithy et al. [14] PAVE	212	AVF	TLPP at 6 mo, 71.7% DCB 84.5% POBA TLPP at 12 mo, 52.5% DCB and 58.8% POBA Time to loss of TLPP: DCB compared with the POBA-HR, 1.18; 95% CI, 0.78 to 1.79; $p = 0.440$)

AVF, arteriovenous fistula; AVG, arteriovenous graft; TLPP, target lesion primary patency; DCB, drug-coated balloon; POBA, plain old balloon angioplasty; ACPP, access circuit primary patency; HR, hazard ratio; CI, confidence interval; mo, months; PAVE, paclitaxel-coated balloons and angioplasty of AV fistulas trial.

The IN.PACT trial by Lookstein et al. is the second study on the efficacy of DCBs [20]. It is an international RCT that includes centers from USA, Japan, and New Zealand. Currently, 6 months of follow-up results of 330 randomized patients are available. At 6 months, TLPP was significantly higher with DCB than that without DCB (82.2% (125/152) vs. 59.5% (88/148), respectively; $p < 0.001$).

However, a recent trial revealed a contrasting outcome. In 2021, the paclitaxel-coated balloons and angioplasty of AV fistulas (PAVE) trial was conducted with 212 randomized patients [14]. Time to loss of TLPP with DCB was not significantly different from that with the standard balloon (hazard ratio (HR), 1.18; 95% confidence interval (CI), 0.78–1.79; $p = 0.440$) [14]. One possible explanation for the contrasting result between the PAVE and IN.PACT trials is that the trials used different treatment balloons with different drug doses, although this does not refer to the actual doses that reached the target.

There are several reports on the effects of DCBs according to the location of stenosis. Kitrou et al. reported on the use of DCBs in the treatment of symptomatic central venous

stenosis [30]. They conducted a multicenter, single-arm, retrospective analysis; at 6 months, the intervention-free period in the treated segment was 62.7% and the access circuit survival was 87.7%. In comparisons of DCB and conventional balloon on juxta-anastomotic stenosis, TLPP in the DCB group was significantly higher than that in the conventional balloon group at 12 months (81.8% vs. 51.1%, respectively; $p = 0.01$), whereas there was no difference at 6 months (93.1% vs. 81.3%, respectively; $p = 0.14$) [31].

Recently published results of a DCB trial of 392 treatment areas in 320 participants from Europe and Asia who underwent DCB angioplasty included data from the Lutonix AV Global Registry, which is a multicenter, single-arm real-world registry, and suggested that a DCB is a safe and effective treatment option [10]. The access circuit primary patency was 71% at 6 months, and TLPP for stenosis of AVFs was 78.1%. The primary safety endpoint was achieved in 95.5% of participants, and TLPP was 73.9% at 6 months.

So far, the results of systematic reviews have not been conclusive either. There have been eight systematic reviews with meta-analyses; improved outcomes with DCBs were reported in seven [32–38], while similar outcomes between DCB and conventional balloon were reported in one [39]. Even the three most recently published meta-analyses of 2020 have reported contradictory findings [36–39]. A meta-analysis of 10 studies (five randomized controlled trials and five cohort studies) by Yuan et al. included 861 stenoses in AVFs that were treated using DCBs (48.8%) and conventional balloons (51.2%). This study concluded that the primary patency rates for failing hemodialysis access at 6 and 12 months were significantly better in the DCB angioplasty group than those in the conventional balloon group (70% vs. 54% and 59% vs. 37%, respectively) [28]. Another meta-analysis of 12 studies (six randomized controlled trials and six cohort studies) by Cao et al. included 979 stenoses in AVFs that were treated with DCBs (47.9%) and conventional balloons (52.1%). Their pooled results revealed that AVFs treated with DCBs had significantly fewer incidences of target lesion revascularization at 6 months (odds ratio (OR), 0.31; 95% CI, 0.14–0.69, $p = 0.004$) and 12 months (OR, 0.45; 95% CI 0.21–0.97, $p = 0.04$) than did those treated with conventional balloons [36]. Chen et al. summarized 16 studies (12 RCTs and four cohort studies) involving 1086 patients, and they observed a significantly better primary patency in the DCB group than the conventional balloon group (HR, 0.47; 95% CI, 0.33–0.69; $p < 0.001$; $I^2 = 67.3\%$) [38]. However, the results of the meta-analysis by Liao et al. were different [39]. They compared 11 RCTs that included 487 patients treated with DCBs and 489 patients treated with conventional balloon angioplasty and found that the TLPP rates at 6 and 12 months were not significantly different between them (relative risk (RR), 0.75; 95% CI, 0.56–1.01; $p = 0.06$ and 0.89, 95% CI; 0.79–1.00; $p = 0.06$, respectively). The disparity between the meta-analyses could be due to the inclusion of recent large scale multicenter studies, heterogeneity between the types of studies, or the number of patients included. The Kidney Disease Outcomes Quality Initiative was not conclusive regarding the use of specialized balloons (drug coated or cutting) over standard high-pressure balloons in the primary treatment of AVF and AVG stenosis due to the lack of sufficient data regarding the use of DCBs [40].

Therefore, the findings of recent large scale randomized studies, and meta-analyses were in favor of using DCBs for dialysis access, while the evidence in favor of DCBs continues to mount; however, controversies related to the conflicting results have not yet ended.

4. Safety of DCBs in Arterial Diseases

A paclitaxel-based device was first made available as a coronary stent. Paclitaxel-eluting stents were the default control stent in several trials on new-generation drug-eluting stents. An extended follow-up period of 5 years is available for thousands of patients with coronary disease [41]. DCBs have been used in coronary vessels since 2006, and there have been no concerns regarding the use of paclitaxel-coated balloons in the coronary vasculature, which is supported by the findings of registry studies and randomized trials [42]. However, success in maintaining the coronary circulation has

not translated into similar solutions in peripheral artery diseases. Since Katsanos et al. reported an increase in the number of deaths in the DCB group, safety has become a major concern in the use of DCBs [43]. This meta-analysis summarized the data from 28 randomized trials and reported late mortality with a dose–response relationship. The U.S. Food and Drug Administration (FDA) reported similar late mortality based on an analysis of patient-level data; however, there was no definite evidence of a dose–response relationship. Consequently, the FDA has recommended the use of DCBs only for high-risk patients with peripheral arterial diseases. Since the FDA advisory panel proposed their recommendation, several studies have evaluated the association of mortality with paclitaxel but the mortality signal was not replicated in most of them [44–46]. However, one meta-analysis by Rocha-Singh et al. reported an association with an absolute increase in the mortality rate of 4.6% [47] and the exact reason for the mortality signal was reported; therefore, the mortality signal cannot be overlooked.

5. Safety of DCBs in Arteriovenous Access

The increased risk of mortality that was observed with DCBs in peripheral arterial disease has raised concerns for the population on dialysis. To date, there has been no similar signal observed in the population on hemodialysis. The Lutonix trial was the first study to observe mortality specifically in patients on dialysis, and the 2-year data from the Lutonix AV trial demonstrated no increase in mortality with DCB angioplasty [19]. The DCBs achieved a non-inferior safety endpoint (freedom from local or systemic adverse event) in 95% of patients at 30 days, which was unchanged at 6 months. The cause of mortality also did not show any difference between DCBs and conventional balloons. A meta-analysis conducted in 2020 included 16 studies (12 RCTs and four cohort studies) with 1086 patients who underwent endovascular treatment for dysfunctional vascular access [38]. In this meta-analysis, the all-cause mortality rates at 6, 12, and 24 months after the intervention were similar for the DCB and conventional balloon groups (6 months: OR, 1.06; 95% CI, 0.38–2.96; $p = 0.907$; I2 = 19.2%; 12 months: OR, 1.20; 95% CI, 0.66–2.16; $p = 0.554$; I2 = 0%; and 24 months: OR, 1.43, 95% CI, 0.83–2.45; $p = 0.195$; I2 = 0%). Another meta-analysis that included eight studies revealed a similar all-cause mortality in DCBs in comparison with conventional balloons (11.2%; RR, 1.26; 95% CI 0.85 to 1.89; $p = 0.25$; I2 = 0%) [33].

Therefore, there is still no evidence of increased mortality in patients on dialysis with DCBs, and further large studies with long-term follow-up periods are needed.

6. Future Perspectives on Arteriovenous Access

The major studies that are now available provide a high level of evidence; however, the available results of arteriovenous access stenosis are not homogeneous. Dysfunction of vascular access significantly degrades a patient's quality of life. Drug delivering technology that can mitigate the proliferative processes related to the stenosis of vascular access is likely to continue developing despite the mortality concerns raised in the peripheral arteries. Considering that vascular access stenosis frequently occurs in patients on dialysis, the relatively high costs of DCBs should be offset by their apparent superiority in patency and safety. More long-term data regarding the potential role of DCBs in vascular access in terms of the safety and efficacy are needed to validate the findings of the aforementioned studies.

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References

1. Kitrou, P.; Papasotiriou, M.; Katsanos, K.; Karnabatidis, D.; Goumenos, D.S.; Papachristou, E. Recent developments in endovascular interventions to sustain vascular access patency in haemodialysis patients. *Nephrol. Dial. Transpl.* **2019**, *34*, 1994–2001. [CrossRef]
2. Viecelli, A.K.; Mori, T.A.; Roy-Chaudhury, P.; Polkinghorne, K.R.; Hawley, C.M.; Johnson, D.W.; Pascoe, E.M.; Irish, A.B. The pathogenesis of hemodialysis vascular access failure and systemic therapies for its prevention: Optimism unfulfilled. *Semin. Dial.* **2018**, *31*, 244–257. [CrossRef] [PubMed]
3. Roy-Chaudhury, P.; Sukhatme, V.P.; Cheung, A.K. Hemodialysis vascular access dysfunction: A cellular and molecular viewpoint. *J. Am. Soc. Nephrol.* **2006**, *17*, 1112–1127. [CrossRef]
4. Lee, J.M.; Park, J.; Kang, J.; Jeon, K.H.; Jung, J.H.; Lee, S.E.; Han, J.K.; Kim, H.L.; Yang, H.M.; Park, K.W.; et al. Comparison among drug-eluting balloon, drug-eluting stent, and plain balloon angioplasty for the treatment of in-stent restenosis: A network meta-analysis of 11 randomized, controlled trials. *JACC Cardiovasc. Interv.* **2015**, *8*, 382–394. [CrossRef]
5. Roy-Chaudhury, P.; Kelly, B.S.; Miller, M.A.; Reaves, A.; Armstrong, J.; Nanayakkara, N.; Heffelfinger, S.C. Venous neointimal hyperplasia in polytetrafluoroethylene dialysis grafts. *Kidney Int.* **2001**, *59*, 2325–2334. [CrossRef]
6. Krokidis, M.; Spiliopoulos, S.; Katsanos, K.; Sabharwal, T. Peripheral Applications of Drug-Coated Balloons: Past, Present and Future. *Cardiovasc. Interv. Radiol.* **2013**, *36*, 281–291. [CrossRef] [PubMed]
7. Lincoff, A.M.; Topol, E.J.; Ellis, S.G. Local drug delivery for the prevention of restenosis. Fact, fancy, and future. *Circulation* **1994**, *90*, 2070–2084. [CrossRef] [PubMed]
8. Boitet, A.; Massy, Z.A.; Goeau-Brissonniere, O.; Javerliat, I.; Coggia, M.; Coscas, R. Drug-coated balloon angioplasty for dialysis access fistula stenosis. *Semin. Vasc. Surg.* **2016**, *29*, 178–185. [CrossRef]
9. Trerotola, S.O.; Roy-Chaudhury, P.; Saad, T.F. Drug-Coated Balloons in Dysfunctional Arteriovenous Fistulas: Is it Time? *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* **2021**, *77*, 820–822. [CrossRef] [PubMed]
10. Karnabatidis, D.; Kitrou, P.M.; Ponce, P.; Chong, T.T.; Pietura, R.; Pegis, J.-D.; Ko, P.-J.; Lin, C.H.; Karnabatidis, D.; Ponce, P.; et al. A Multicenter Global Registry of Paclitaxel Drug-Coated Balloon in Dysfunctional Arteriovenous Fistulae and Grafts: 6-Month Results. *J. Vasc. Interv. Radiol.* **2021**, *32*, 360–368. [CrossRef]
11. Ng, V.G.; Mena, C.; Pietras, C.; Lansky, A.J. Local delivery of paclitaxel in the treatment of peripheral arterial disease. *Eur. J. Clin. Invest.* **2015**, *45*, 333–345. [CrossRef]
12. Laird, J.A.; Schneider, P.A.; Jaff, M.R.; Brodmann, M.; Zeller, T.; Metzger, D.C.; Krishnan, P.; Scheinert, D.; Micari, A.; Wang, H.; et al. Long-Term Clinical Effectiveness of a Drug-Coated Balloon for the Treatment of Femoropopliteal Lesions. *Circ. Cardiovasc. Interv.* **2019**, *12*, e007702. [CrossRef]
13. Dake, M.D.; Ansel, G.M.; Jaff, M.R.; Ohki, T.; Saxon, R.R.; Smouse, H.B.; Machan, L.S.; Snyder, S.A.; O'Leary, E.E.; Ragheb, A.O.; et al. Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in the Femoropopliteal Artery: 5-Year Results of the Zilver PTX Randomized Trial. *Circulation* **2016**, *133*, 1472–1483. [CrossRef]
14. Karunanithy, N.; Robinson, E.J.; Ahmad, F.; Burton, J.O.; Calder, F.; Coles, S.; Das, N.; Dorling, A.; Forman, C.; Jaffer, O.; et al. A multicenter randomized controlled trial indicates that paclitaxel-coated balloons provide no benefit for arteriovenous fistulas. *Kidney Int.* **2021**. [CrossRef] [PubMed]
15. Marx, S.O.; Marks, A.R. Bench to bedside: The development of rapamycin and its application to stent restenosis. *Circulation* **2001**, *104*, 852–855. [CrossRef]
16. Finn, A.V.; Kolodgie, F.D.; Harnek, J.; Guerrero, L.J.; Acampado, E.; Tefera, K.; Skorija, K.; Weber, D.K.; Gold, H.K.; Virmani, R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* **2005**, *112*, 270–278. [CrossRef] [PubMed]
17. Wessely, R.; Schömig, A.; Kastrati, A. Sirolimus and Paclitaxel on polymer-based drug-eluting stents: Similar but different. *J. Am. Coll. Cardiol.* **2006**, *47*, 708–714. [CrossRef]
18. Tan, C.W.; Tan, R.Y.; Pang, S.C.; Tng, A.R.K.; Tang, T.Y.; Zhuang, K.D.; Chua, J.M.E.; Tay, K.H.; Chong, T.T.; Tan, C.S. Single-Center Prospective Pilot Study of Sirolimus Drug-Coated Balloon Angioplasty in Maintaining the Patency of Thrombosed Arteriovenous Graft. *J. Vasc. Interv. Radiol. JVIR* **2021**, *32*, 369–375. [CrossRef] [PubMed]
19. Trerotola, S.O.; Saad, T.F.; Roy-Chaudhury, P. The Lutonix AV Randomized Trial of Paclitaxel-Coated Balloons in Arteriovenous Fistula Stenosis: 2-Year Results and Subgroup Analysis. *J. Vasc. Interv. Radiol. JVIR* **2020**, *31*, 1–14. [CrossRef]
20. Lookstein, R.A.; Haruguchi, H.; Ouriel, K.; Weinberg, I.; Lei, L.; Cihlar, S.; Holden, A. Drug-Coated Balloons for Dysfunctional Dialysis Arteriovenous Fistulas. *N. Engl. J. Med.* **2020**, *383*, 733–742. [CrossRef]
21. Katsanos, K.; Karnabatidis, D.; Kitrou, P.; Spiliopoulos, S.; Christeas, N.; Siablis, D. Paclitaxel-coated balloon angioplasty vs. plain balloon dilation for the treatment of failing dialysis access: 6-month interim results from a prospective randomized controlled trial. *J. Endovasc. Ther. Off. J. Int. Soc. Endovasc. Spec.* **2012**, *19*, 263–272. [CrossRef] [PubMed]
22. Kitrou, P.M.; Spiliopoulos, S.; Katsanos, K.; Papachristou, E.; Siablis, D.; Karnabatidis, D. Paclitaxel-coated versus plain balloon angioplasty for dysfunctional arteriovenous fistulae: One-year results of a prospective randomized controlled trial. *J. Vasc. Interv. Radiol. JVIR* **2015**, *26*, 348–354. [CrossRef]
23. Kitrou, P.M.; Katsanos, K.; Spiliopoulos, S.; Karnabatidis, D.; Siablis, D. Drug-eluting versus plain balloon angioplasty for the treatment of failing dialysis access: Final results and cost-effectiveness analysis from a prospective randomized controlled trial (NCT01174472). *Eur. J. Radiol.* **2015**, *84*, 418–423. [CrossRef]

24. Kitrou, P.M.; Papadimatos, P.; Spiliopoulos, S.; Katsanos, K.; Christeas, N.; Brountzos, E.; Karnabatidis, D. Paclitaxel-Coated Balloons for the Treatment of Symptomatic Central Venous Stenosis in Dialysis Access: Results from a Randomized Controlled Trial. *J. Vasc. Interv. Radiol. JVIR* **2017**, *28*, 811–817. [CrossRef]
25. Irani, F.G.; Teo, T.K.B.; Tay, K.H.; Yin, W.H.; Win, H.H.; Gogna, A.; Patel, A.; Too, C.W.; Chan, S.; Lo, R.H.G.; et al. Hemodialysis Arteriovenous Fistula and Graft Stenoses: Randomized Trial Comparing Drug-eluting Balloon Angioplasty with Conventional Angioplasty. *Radiology* **2018**, *289*, 238–247. [CrossRef] [PubMed]
26. Trerotola, S.O.; Lawson, J.; Roy-Chaudhury, P.; Saad, T.F. Drug Coated Balloon Angioplasty in Failing AV Fistulas: A Randomized Controlled Trial. *Clin. J. Am. Soc. Nephrol. CJASN* **2018**, *13*, 1215–1224. [CrossRef] [PubMed]
27. Maleux, G.; Vander Mijnsbrugge, W.; Henroteaux, D.; Laenen, A.; Cornelissen, S.; Claes, K.; Fourneau, I.; Verbeeck, N. Multicenter, Randomized Trial of Conventional Balloon Angioplasty versus Paclitaxel-Coated Balloon Angioplasty for the Treatment of Dysfunctioning Autologous Dialysis Fistulae. *J. Vasc. Interv. Radiol. JVIR* **2018**, *29*, 470–475. [CrossRef] [PubMed]
28. Björkman, P.; Weselius, E.M.; Kokkonen, T.; Rauta, V.; Albäck, A.; Venermo, M. Drug-Coated Versus Plain Balloon Angioplasty In Arteriovenous Fistulas: A Randomized, Controlled Study With 1-Year Follow-Up (The Drecorest Ii-Study). *Scand. J. Surg. SJS Off. Organ Finn. Surg. Soc. Scand. Surg. Soc.* **2019**, *108*, 61–66. [CrossRef]
29. Moreno-Sánchez, T.; Moreno-Ramírez, M.; Machancoses, F.H.; Pardo-Moreno, P.; Navarro-Vergara, P.F.; García-Revillo, J. Efficacy of Paclitaxel Balloon for Hemodialysis Stenosis Fistulae After One Year Compared to High-Pressure Balloons: A Controlled, Multicenter, Randomized Trial. *Cardiovasc. Interv. Radiol.* **2020**, *43*, 382–390. [CrossRef]
30. Kitrou, P.M.; Steinke, T.; El Hage, R.; Ponce, P.; Lucatelli, P.; Katsanos, K.; Spiliopoulos, S.; Spinelli, A.; Bisdas, T.; Stavroulakis, K.; et al. Paclitaxel-Coated Balloons for the Treatment of Symptomatic Central Venous Stenosis in Vascular Access: Results From a European, Multicenter, Single-Arm Retrospective Analysis. *J. Endovasc. Ther. Off. J. Int. Soc. Endovasc. Spec.* **2021**. [CrossRef]
31. Kocaaslan, C.; Oztekin, A.; Bademci, M.S.; Denli Yalvac, E.S.; Bulut, N.; Aydin, E. A retrospective comparison analysis of results of drug-coated balloon versus plain balloon angioplasty in treatment of juxta-anastomotic de novo stenosis of radiocephalic arteriovenous fistulas. *J. Vasc. Access* **2020**, *21*, 596–601. [CrossRef] [PubMed]
32. Khawaja, A.Z.; Cassidy, D.B.; Al Shakarchi, J.; McGrogan, D.G.; Inston, N.G.; Jones, R.G. Systematic review of drug eluting balloon angioplasty for arteriovenous haemodialysis access stenosis. *J. Vasc. Access* **2016**, *17*, 103–110. [CrossRef] [PubMed]
33. Dinh, K.; Limmer, A.M.; Paravastu, S.C.V.; Thomas, S.D.; Bennett, M.H.; Holden, A.; Varcoe, R.L. Mortality After Paclitaxel-Coated Device Use in Dialysis Access: A Systematic Review and Meta-Analysis. *J. Endovasc. Ther. Off. J. Int. Soc. Endovasc. Spec.* **2019**, *26*, 600–612. [CrossRef]
34. Kennedy, S.A.; Mafeld, S.; Baerlocher, M.O.; Jaberi, A.; Rajan, D.K. Drug-Coated Balloon Angioplasty in Hemodialysis Circuits: A Systematic Review and Meta-Analysis. *J. Vasc. Interv. Radiol. JVIR* **2019**, *30*, 483–494. [CrossRef] [PubMed]
35. Yan Wee, I.J.; Yap, H.Y.; Hsien Ts'ung, L.T.; Lee Qingwei, S.; Tan, C.S.; Tang, T.Y.; Chong, T.T. A systematic review and meta-analysis of drug-coated balloon versus conventional balloon angioplasty for dialysis access stenosis. *J. Vasc. Surg.* **2019**, *70*, 970–979. [CrossRef]
36. Cao, Z.; Li, J.; Zhang, T.; Zhao, K.; Zhao, J.; Yang, Y.; Jiang, C.; Zhu, R.; Li, Z.; Wu, W. Comparative Effectiveness of Drug-Coated Balloon vs. Balloon Angioplasty for the Treatment of Arteriovenous Fistula Stenosis: A Meta-analysis. *J. Endovasc. Ther. Off. J. Int. Soc. Endovasc. Spec.* **2020**, *27*, 266–275. [CrossRef] [PubMed]
37. Yuan, Y.; Cheng, W.; Lu, H. Drug-Eluting Balloon Versus Plain Balloon Angioplasty for the Treatment of Failing Hemodialysis Access: A Systematic Review and Meta-analysis. *Ann. Vasc. Surg.* **2020**, *64*, 389–396. [CrossRef] [PubMed]
38. Chen, X.; Liu, Y.; Wang, J.; Zhao, J.; Singh, N.; Zhang, W.W. A systematic review and meta-analysis of the risk of death and patency after application of paclitaxel-coated balloons in the hemodialysis access. *J. Vasc. Surg.* **2020**, *72*, 2186–2196. [CrossRef]
39. Liao, M.T.; Chen, M.K.; Hsieh, M.Y.; Yeh, N.L.; Chien, K.L.; Lin, C.C.; Wu, C.C.; Chie, W.C. Drug-coated balloon versus conventional balloon angioplasty of hemodialysis arteriovenous fistula or graft: A systematic review and meta-analysis of randomized controlled trials. *PLoS ONE* **2020**, *15*, e0231463. [CrossRef]
40. Lok, C.E.; Huber, T.S.; Lee, T.; Shenoy, S.; Yevzlin, A.S.; Abreo, K.; Allon, M.; Asif, A.; Astor, B.C.; Glickman, M.H.; et al. KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* **2020**, *75*, S1–S164. [CrossRef]
41. Borhani, S.; Hassanajili, S.; Ahmadi Tafti, S.H.; Rabbani, S. Cardiovascular stents: Overview, evolution, and next generation. *Prog. Biomater.* **2018**, *7*, 175–205. [CrossRef]
42. Scheller, B.; Vukadinovic, D.; Jeger, R.; Rissanen, T.T.; Scholz, S.S.; Byrne, R.; Kleber, F.X.; Latib, A.; Clever, Y.P.; Ewen, S.; et al. Survival After Coronary Revascularization With Paclitaxel-Coated Balloons. *J. Am. Coll. Cardiol.* **2020**, *75*, 1017–1028. [CrossRef]
43. Katsanos, K.; Spiliopoulos, S.; Kitrou, P.; Krokidis, M.; Karnabatidis, D. Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Am. Heart. Assoc.* **2018**, *7*, e011245. [CrossRef]
44. Secemsky, E.A.; Kundi, H.; Weinberg, I.; Jaff, M.R.; Krawisz, A.; Parikh, S.A.; Beckman, J.A.; Mustapha, J.; Rosenfield, K.; Yeh, R.W. Association of Survival With Femoropopliteal Artery Revascularization With Drug-Coated Devices. *JAMA Cardiol.* **2019**, *4*, 332–340. [CrossRef] [PubMed]

45. Böhme, T.; Noory, E.; Beschorner, U.; Jacques, B.; Bürgelin, K.; Macharzina, R.; Gebauer, E.; Cheung, F.; Lechner, P.; Nührenberg, T.; et al. Evaluation of Mortality Following Paclitaxel Drug-Coated Balloon Angioplasty of Femoropopliteal Lesions in the Real World. JACC. *Cardiovasc. Interv.* **2020**, *13*, 2052–2061.
46. Heidemann, F.; Peters, F.; Kuchenbecker, J.; Kreutzburg, T.; Sedrakyan, A.; Marschall, U.; L'Hoest, H.; Debus, E.S.; Behrendt, C.A. Long Term Outcomes after Revascularisations below the Knee with Paclitaxel Coated Devices: A Propensity Score Matched Cohort Analysis. *Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg.* **2020**, *60*, 549–558. [CrossRef] [PubMed]
47. Rocha-Singh, K.J.; Duval, S.; Jaff, M.R.; Schneider, P.A.; Ansel, G.M.; Lyden, S.P.; Mullin, C.M.; Ioannidis, J.P.A.; Misra, S.; Tzafriri, A.R.; et al. Mortality and Paclitaxel-Coated Devices: An Individual Patient Data Meta-Analysis. *Circulation* **2020**, *141*, 1859–1869. [CrossRef]