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Paclitaxel-Based Devices for the Treatment of PAD: Balancing Clinical Efficacy with Possible Risk

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Abstract

Purpose of review Paclitaxel-based endovascular devices have become the standard of care in symptomatic, medication-refractory peripheral artery disease (PAD) and in critical limb ischemia (CLI). This review examines the data on the efficacy and safety of these devices relative to standard balloon angioplasty (PTA) and bare metal stents (BMS).
Recent findings Randomized controlled trials (RCTs) have found that peripheral devices coated with paclitaxel result in superior patency rates and decreased target lesion revascularization (TLR) compared with non-drug-coated devices. Recently, a meta-analysis of randomized controlled trials unexpectedly reported an increase in mortality in patients treated with paclitaxel-coated devices (PCDs), resulting in the pausing of ongoing trials and a warning of safety from the FDA. Observational data that has been published since this time has not supported this safety concern.
Summary PAD is a common disease that severely impacts quality and length of life. PCDs are a promising therapy for patients with PAD, offering a more effective and durable intervention when compared with traditional PTA/BMS. A meta-analysis of RCTs identified a signal of harm with these devices which has now been replicated by the FDA. However, there is significant missing data from the trials analyzed by the meta-analysis and FDA, no plausible mechanism linking paclitaxel to death, and no correlation between paclitaxel dose and mortality. Analyses in observational data have found no safety signal. An FDA

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panel evaluating the validity of this late-mortality signal recently adjourned, emphasizing that the available data is incomplete. PCDs will remain on the market, and an active discussion is underway for developing an approach for improved post-market surveillance, device-labeling, and cause of death adjudication.

Introduction

PAD is an underdiagnosed disease with grave consequences for patients. PAD is common, with recent prevalence estimates that are similar to coronary artery disease and stroke. Specifically, weighted mean age-standardized prevalence of outpatient PAD was 11.8% and incidence was 22.4 per 1000 person-years among Medicare beneficiaries in the ARIC study [1]. Additionally, it is estimated that 8–10 million people in the USA have PAD [2]. The prevalence is highest among black patients, and, in particular, black women. Patients with PAD experience significant reductions in quality of life [3]. The primary symptomatic manifestation, claudication, results in limitations to activity and correlates with cost to quality of life. A minority may proceed to develop more severe symptoms, critical limb ischemia (CLI). This condition portends a severe threat of limb loss, with up to 25% of patients requiring amputation within the first year of diagnosis [4]. In addition to adverse effects on limbs, PAD is associated with substantially greater rates of stroke, MI, and cardiovascular death [5]. Patients with PAD have a three- to fourfold increased risk of cardiovascular events, and among those with CLI, nearly 25% will suffer a cardiovascular death within the first year of diagnosis.

An evidence-based treatment approach for claudication includes maximizing medical therapies, participation in a supervised exercise program, and, if symptoms persist, consideration of endovascular intervention. Guideline-directed medical therapies are aimed at reducing symptoms and slowing the progression of PAD, as well as preventing major adverse cardiovascular events (MACE). Medical therapies that confer a mortality benefit include statins [6], blood pressure control with an ACE-inhibitor or ARB [7], single antiplatelet therapy in symptomatic patients [5, 8], low-dose rivaroxaban with aspirin [9], and PCSK9 inhibitors [10]. SGLT2 inhibitors demonstrate a mortality benefit in reducing MACE among diabetics, which involves many patients with PAD, but are currently being evaluated for the possibility of increasing amputations [11]. Cilostazol is the only guideline-recommended anti-claudication therapy that may be used for symptomatic relief, but its use is often limited by prohibitive side effects [12]. Supervised exercise therapy, which is now reimbursed by Medicare, improves symptoms, patient-reported outcome measures, and mortality in PAD [13]. Smoking cessation is a critical lifestyle intervention that reduces progression to CLI and need for amputation [14]. Among patients with CLI, expedited revascularization, either surgically or endovascularly, is often needed to provide limb salvage.

The endovascular-first approach for aortoiliac and femoropopliteal disease is a result of research that has shown that endovascular therapy results in shorter lengths of stay and lower associated morbidity and mortality and comparable patency rates [15, 16]. The 2017 ESC guidelines recommend endovascular therapy as first line for femoropopliteal occlusions < 25 cm [8].

Endovascular therapy has emerged as a safe and effective treatment for symptomatic PAD. This includes improvements in quality of life, reductions in symptoms, and low rates of procedural complications [15, 16]. Despite the success of endovascular interventions, initial benefits prior to PCD technology were short-lived, with restenosis rates for traditional PTA and BMS as high as 40–60% within 1 year [17]. In response, researchers sought solutions for restenosis following the example of drug-eluting stents for coronary artery disease, a development that changed the long-term success of percutaneous coronary intervention. Studies in cell culture and animal models revealed paclitaxel as an ideal agent for peripheral artery disease as its lipophilicity facilitates rapid drug uptake into tissues, and its efficacy against smooth muscle proliferation at low concentrations allows it to be quickly transferred to tissues, but maintains a robust anti-proliferative effect over time [18].

Paclitaxel has since been incorporated into peripheral vascular intervention in the form of paclitaxel-coated

balloons and paclitaxel-eluting stents. The first paclitaxel-coated stent, the Zilver PTX (Cook Medical) was approved in 2012, and the first paclitaxel-coated balloon, Lutonix 035 (Bard), was approved in 2014. Since then, there has been an expansion in peripheral drug-coated devices, including two additional paclitaxel-coated balloons (IN.PACT Admiral balloon, Medtronic; Stellarex balloon, Phillips) and a second paclitaxel-coated stent (Eluvia, Boston Scientific). Randomized controlled trials of these paclitaxel-coated devices have demonstrated substantial improvement in short- and long-term procedural success, including superior patency and decreased target lesion failure compared with non-drug-coated devices [19]. The first-line use of both paclitaxel-coated balloons and stents for the treatment of femoropopliteal artery disease is supported by a class 1 recommendation in the SCAI consensus guidelines for device selection [20] and the recent ACC/AHA/SCAI/SIR/SVM Appropriate Use Criteria for Peripheral Artery Intervention [21].

Because their use in clinical practice is relatively new, there has not been ample data on the long-term safety of PCDs. The vascular community was taken by surprise when a recent meta-analysis demonstrated an increased risk of mortality in patients treated with paclitaxel-coated devices relative to PTCA/BMS at 2 and 5 years [22••]. This meta-analysis prompted an FDA investigation into the safety of these devices and resulted in two large clinical trials being stopped (SWEDEPAD I,2 and BASIL-3) [23]. The statistical methodologies of this meta-analysis have been called into question however, and multiple studies since this publication have observed no increase in mortality with paclitaxel-coated devices.

Paclitaxel-coated balloons

In contrast to percutaneous coronary intervention, balloon angioplasty is used as the definitive therapy for PAD more often than primary stenting. Peripheral vascular beds, particularly the SFA, pose particular challenges for stents as they are exposed to external and internal mechanical forces, such as compression, flexion, and torsion. This results in stent complications such as stent deformation, in-stent restenosis, and stent fracture. As a result, balloon angioplasty is preferred in many situations as it avoids permanent prosthesis placement.

Paclitaxel is particularly well-suited for use with balloon angioplasty as it rapidly diffuses into tissues due to its lipophilicity and remains in the vessel wall over time, active at low concentrations [18, 24]. Thus, it is effective with delivery of only a single treatment. There are currently three FDA-approved paclitaxel-coated balloons approved for femoropopliteal disease: LUTONIX DCB, IN.PACT Admiral DCB, and Stellarex 035 DCB.

Multiple randomized clinical trials have demonstrated a benefit of PCBs relative to traditional PTA. The first peripheral study of PCBs was a multi-center trial that compared clinical outcomes of 48 patients treated with PCBs with 54 patients treated with PTA for revascularization of superficial femoral and popliteal arteries. They found significant reductions in late lumen loss (0.4 ± 1.2 mm vs. 1.7 ± 1.8 mm, $p < 0.001$) and target-lesion revascularization (TLR) (4% versus 29%, $p < 0.001$) at 6 months. These findings were also present at 24 months [25]. These results were soon replicated in greater numbers of patients. Rosenfield et al. studied a total of 476 patients at 54 sites and demonstrated increased primary patency at 12 months with the Lutonix PCB versus non-drug-coated PTA in femoropopliteal artery disease [26]. Several other randomized controlled trials demonstrated similar findings over 6–24 months periods [27–29].

In the 5-year follow-up of the THUNDER trial, Tepe et al. found that patency rates and freedom from TLR were durable over time. Specifically, the number of patients requiring TLR was significantly lower in patients receiving PCB versus those receiving PTA (21% and 45%, respectively $p = 0.0005$) [30]. Schneider et al. found similar results in a 5-year follow-up of the IN.PACT. SFA trial in which 331 subjects with symptomatic femoropopliteal lesions were randomized 2:1 to DCB or PTA. Through 5 years, patients treated with DCB demonstrated increased rates of freedom from TLR (Kaplan-Meier estimate of 74.5% versus 65.3%; log-rank $p = 0.020$) [31••].

Of note, the aforementioned studies tested primarily focal lesions of less than 10 cm with low rates of chronic total occlusion (CTO) and in-stent restenosis (Table 1). A small, post hoc analysis in the IN.PACT 5-year analysis favored DCB over PTA in longer lesions, total occlusions, advanced PAD (Rutherford 4), and high-risk patients (age over 75 years) [31••]. Another trial compared DCBs to PTA in 70 patients with symptomatic in-stent restenosis of the SFA [33]. Mean lesions length was 13.9 ± 6.7 cm. They found significantly reduced rates of diameter stenosis and binary restenosis when examined at 6–8 months, as well as reduced rates of TLR at 24 months.

Schmidt et al. retrospectively analyzed registry data of DCBs in longer, more complex lesions over 2 years [37]. They looked at 260 patients with high rates of restenosis (11%), in-stent restenosis (37%), CTO (65%), and intermediate-to-diffuse lesion lengths (24.0 ± 10.2 cm). Primary patency rates were favorable

Table 1. Major randomized controlled trials evaluating the efficacy of drug-coated devices compared with traditional PTA/BMS and compared with each other

Clinical trial	Devices compared	Lesion length (cm)	Restenotic lesions	CTO	Time to follow up	Statistically significant TLR
THUNDER [30]	PCB	7.5 ± 6.2	36%	27%	5 years	PCB
	PTA	7.4 ± 6.7				
IN.PACT. SFA [31]	PCB	8.9 ± 4.8	5%	24%	5 years	PCB
	PTA	8.8 ± 5.1				
Levant 2 [26]	PCB	6.3 ± 4.1	15%	21%	1 year	PCB
	PTA	6.3 ± 4.0				
FEMPAC [32]	PCB	4.0 ± 4.4	34%	16%	18 months	PCB
	PTA	4.7 ± 4.2				
PACIFIER [27]	PCB	7.0 ± 5.3	24%	31%	1 year	PCB
	PTA	6.6 ± 5.5				
ILLUMENATE [29]	PCB	7.2 ± 5.2	8%	19%	2 years	PCB
	PTA	7.1 ± 5.3				
ISAR-PEBIS [33]	PCB	13.2 ± 6.5	100%	–	2 years	PCB
	PTA	14.6 ± 6.9				
Zilver PTX [34]	PES	6.6 ± 3.9	6%	31%	5 years	PES
	BMS/PTA	6.3 ± 4.1				
VIASTAR [35]	PES	19.0 ± 6.3	–	72%	2 years	PES
	BMS	17.3 ± 6.3				
REAL-PTX [36]	PCB	15.0 ± 8.7	–	53%	2 years	No difference
	PES	15.6 ± 8.9				

at 1 year for DCB relative to literature estimates of PTA for comparable lesions (78% and 22–34%, respectively); however, at 2 years, there was a significant drop in primary patency to 49%.

Studies to date show that DCBs present effective, durable interventions that are superior to PTA for focal lesions at 5 years. More studies are needed to define long-term outcomes for more complex lesions, although initial studies support the use of DCB in longer, more complex lesions as well (see Table 1). Head-to-head comparisons are needed to compare DCB to DES for these longer lesions to better define the appropriate populations for these technologies.

Paclitaxel-coated stents

Though stenting is used less frequently than balloon angioplasty in the periphery, stenting is advantageous in more complex lesion anatomy, such as total occlusions and when flow-limiting dissections are present. There are currently two FDA-approved paclitaxel-eluting stents for femoropopliteal disease: the Zilver PTX and the Eluvia. PES have demonstrated improved outcomes compared with both PTA and BMS.

Dake et al. performed a prospective, multinational randomized-controlled trial in which 474 patients were randomized to PES or PTA. Among patients who experienced initial PTA failure, they underwent secondary randomization to DES or BMS. Relative to PTA, use of a PES was associated with higher 2-year event-free survival (86.6% vs. 77.9%, $p = 0.02$) and primary patency (74.8% vs. 26.5%, $p < 0.01$). The secondary randomization group showed superior 2-year primary patency relative to the BMS group (83.4% vs. 64.1%, $p < 0.01$) [38]. A 5-year follow-up analysis revealed higher patency rates (66.4% vs. 43.4%, $p < 0.01$) and greater freedom from TLR in the PES group versus the PTA group (83.1% vs. 67.6%, $p < 0.01$). Similarly, the secondary randomization group showed superior 5-year primary patency relative to BMS group (72.4% vs. 53%, $p = 0.03$) and freedom from TLR (84.9% vs. 71.6%, $p = 0.06$).

The Eluvia stent is equipped with a polymer coating designed to deliver paclitaxel over a longer period of time than the Zilver PTX, a polymer-free stent. The Eluvia also has the lowest drug-dose density of the PCDs. The Imperial trial compared the Eluvia PES with the Zilver PTX PES. At 1 year, the Eluvia stent demonstrated non-inferiority to Zilver [39]. Primary patency rates were 86.8% in patients receiving the Eluvia and 81.5% in patients receiving the Zilver PTX ($p < 0.0001$).

Further analyses are being done to assess the safety and efficacy of PES in more complex lesions. Cipollari et al. examined outcomes of PES in patients with PAD and no patent tibial runoff [40]. In their retrospective analysis of 900 patients, 54 with no patent runoff vessels and 846 with at least one patent runoff vessel, rates of freedom from TLR, patency, and clinical benefit at 2 years were not significantly different between the groups.

It will be important to better define the roles of DCB relative to DES in more complex lesions. One retrospective propensity score-matched study of 228 patients found comparable 12-month patency and TLR results for DCBs compared with DES in femoropopliteal lesions of greater than 10 cm [41].

Bausbeck et al. published a head-to-head comparison of DCB versus DES in multiple lesion lengths with high lesion complexity through 36 months. They randomly assigned 150 patients with symptomatic femoropopliteal disease to primary DES or DCB with bailout stenting. Average lesion length for PCB was 15.0 ± 8.7 cm and 15.6 ± 8.9 for DES ($p = 0.34$). Greater than half of the lesions were CTOs. At 12 months, primary patency rates were 79% for DES and 80% for DCB ($p = 0.96$), and freedom from TLR was > 90% and not significantly different between groups. At 36 months, primary patency rates decreased to 54% for DES and 38% for DCB ($p = 0.17$) and freedom from TLR was approximately 70% for both groups. The Kaplan-Meier analysis of restenosis in medium to long lesions (> 10 cm) showed a nonsignificant trend favoring DES at 3 years (32.3% DCB, 45.2% DES; rate difference – 12.9; 95% CI – 40.5% to 1.7%; $p = 0.19$). DES did show significantly higher primary patency for stenotic, but not for chronically occluded lesions, at 36 months [36].

Safety of paclitaxel-coated devices

Despite their demonstrated superiority for limb outcomes in the treatment of PAD, the long-term safety of DCB/DES has not been well-established given their limited time in clinical use. Unexpectedly, a recent summary-level meta-analysis by Katsanos et al. found an increase in all-cause mortality associated with DCB/DES relative to PTA/BMS at 2–5 years [22••]. In this study, Katsanos et al. examined 28 randomized controlled trials, 24 that studied PCB and 4 that studied PES. At 1 year (4432 patients), there was no mortality difference between the DCB/DES and PTA/BMS cohorts. At 2 years (12 trials and 2316 patients) and at 5 years (3 trials and 863 patients), they found significant increases in the relative risks of mortality (68% and 93% increased risk, respectively) with DCB/DES compared with PTA/BMS. They reported a positive association between paclitaxel dose and absolute risk of death.

In response to this publication, the FDA issued warnings about the possibility of increased mortality associated with drug-coated devices, even recommending against their use except in cases of high-risk patients. Two large clinical trials were halted (SWEDEPAD 1,2 and BASIL-3), and ongoing trials have experienced lower rates of enrollment. The FDA recently convened an expert panel to review the available data and implications of this mortality signal.

This meta-analysis drew criticism for methodological flaws that may have influenced their results. First, the original randomized controlled-trials pooled in the meta-analysis were designed to examine limb-rated outcomes. Thus, they experienced significant attrition from the studies after primary endpoints were reached; the majority of which occurred at 1 year. Therefore, there was a significant amount of missing data that may have influenced results.

Second, summary-level data combines multiple studies, studies which may have been comprised of heterogeneous populations with substantially different baseline characteristics. Pooling heterogeneous patient populations for analysis can introduce significant bias. Third, there has been no mechanism established for paclitaxel-induced mortality. Fourth, the paclitaxel dose-response analysis is

challenged by varying methods that are used to coat each device with paclitaxel, each of which has different biologic properties and therapeutic half-lives.

Paclitaxel doses and possible mechanisms of harm

Paclitaxel is a cytotoxic agent that is well-established as a chemotherapeutic agent at high concentrations. It inhibits cell division by promoting microtubule assembly and subsequently preventing microtubule breakdown, arresting the cell cycle in the G2/M phase [42].

At lower concentrations, paclitaxel has been found to reduce restenosis. It inhibits secretion of extracellular matrix and proliferation of vascular smooth muscle cells and fibroblasts. It prevents migration of smooth muscle cells, fibroblasts, and white blood cells [18]. Paclitaxel has a long-term inhibitory effect even after very short exposure times. In cell culture, paclitaxel exposure for 3 min resulted in decreased cell proliferation for up to 12 days [43]. Animal studies show the presence of paclitaxel in local vasculature up to 60 days [44].

Paclitaxel is highly lipophilic which mediates its rapid uptake into tissues and high concentrations in the intimal layer of arteries and results in low plasma concentrations. Plasma levels of paclitaxel in animal studies were undetectable by 6–24 h. In humans, plasma levels were undetectable within a few days. The half-life of paclitaxel in plasma is very short and was found to be 21 ± 14 h (range of 4–65 h) in the literature for chemotherapeutic dosing (Rowinsky) [45]. When investigated in PAD after DCB with up to 3 balloons, paclitaxel was undetectable in the plasma by 24 h [46]. No paclitaxel-related events occurred.

Mean total treatment doses delivered by PCB/PES in clinical trials ranged from 1 mg or less up to 20 mg depending on lesion size, number of lesions treated, and technology used [31••]. In registry data, there were rare reports of patients receiving up to 70 mg of paclitaxel [18]. When used as a chemotherapeutic agent, average doses of paclitaxel for a single treatment are approximately 230–300 mg and total dose of up to 1200 mg after multiple treatments is given.

Known side effects of paclitaxel at chemotherapeutic concentrations include neutropenia, neuropathy, hypersensitivity, cardiovascular effects such as hypotension/hypertension and bradycardia, myalgia, myelotoxicity, anaphylaxis, and nausea. The SNAPIST I trial examined paclitaxel administration along with BMS placement for preventions restenosis at doses of 10, 30, 70, and 100 mg/m^2. Systemic side effects of moderate neutropenia, sensory neuropathy, and alopecia were only noted with doses of 70 mg/m^2, doses much higher than those delivered with PCB/PES [47]. There has been no plausible mechanism described for a paclitaxel-mediated increase in mortality associated with PCDs.

It has been theorized that, at low concentrations, paclitaxel could potentiate microenvironments of tumor spread. Analyses of causes of death in the available individual-level data from randomized controlled trials do not show a consistent modality of death associated with patients receiving PCDs. Importantly, there was no disproportionate increase in malignancies in these patients [31••].

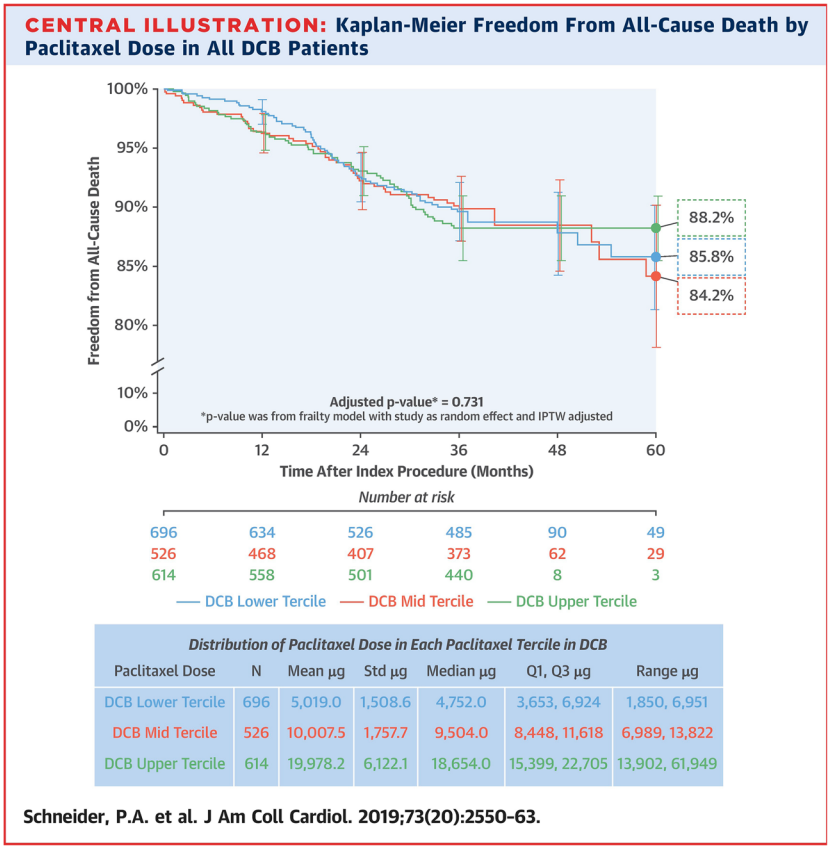

Fig. 1. Schneider et al. divided 1980 patients from four prospective studies into three groups based on paclitaxel doses received. They found no difference in mortality between the groups [31].

A recent study investigated whether an association between paclitaxel dose and mortality exists. They studied 1980 patients from 4 prospective studies of PCB and stratified them into terciles by paclitaxel doses received [31••]. There was no significant difference in all-cause mortality among the terciles at 5 years (see Fig. 1).

Analyses presented since publication of the meta-analysis

In response to this meta-analysis, multiple studies have been published including patient-level meta-analyses, retrospective analyses from Medicare databases, and registries from industry (see Table 2). Schneider et al. performed a meta-analysis using patient-level data from two prospective randomized controlled trials and two prospective single-arm studies [31••]. They examined 1980 patients over 5 years. In addition, they performed a survival analysis on patients treated with DCB stratified by paclitaxel dose and found that there was no difference in all-cause mortality in patients receiving low, middle, and high paclitaxel doses ($p = 0.700$). Albrecht et al. pooled four randomized controlled trials comparing PCB and PTA. They

Table 2. Summary of data evaluating the long-term safety of paclitaxel-coated devices

Long-term safety analyses	Devices compared	Time to follow up	Mortality difference
Secemsky et al. JAMA 2019 [48].	DCB/DES versus BMS/PTA	Median 389 days, up to 600 days.	No mortality difference: - unadjusted cumulative incidence through 600 days: 32.5% DCB/DES vs. 34.3% BMS/PTA; $p = 0.007$ - adjusted HR 0.97, 95% CI 0.91–1.04; $p = 0.43$
Secemsky et al. JACC 2019 [49].	DES versus BMS	Median 2 years, up to 4.1 years.	No mortality difference: - unadjusted cumulative incidence through 4.1 years: 51.7% DES vs. 50.1% BMS; $p = 0.16$ - adjusted HR 0.98; 95% CI 0.93–1.03; $p = 0.53$
Secemsky, Medicare data from FDA Panel June 19, 2019 [52].	DCB/DES versus BMS/PTA	Median 799 days, up to 1573 days.	No mortality difference: - unadjusted cumulative incidence through 1573 days: 43.1% DCB/DES vs. 47.6% BMS/PTA; $p < 0.001$ - adjusted HR 0.94, 95% CI 0.93–0.96
Yeh, OPTUM Claims data from FDA Panel, June 20, 2019 [52].	DCB/DES versus BMS/PTA	Median 763 days, up to 1028 days	No mortality difference: - unadjusted cumulative incidence through 1028 days: 14.9% DCB/DES vs. 14.9% BMS/PTA; $p = 0.11$ - adjusted HR 1.09, 95% CI 0.98–1.22
Bertges, Vascular quality initiative data from FDA panel, June 20, 2019 [52].	DCB/DES versus BMS/PTA	Median 12.4 months	No mortality difference: - unadjusted cumulative incidence: 8.5% DCB/DES vs. 11.5% BMS/PTA - adjusted HR 0.82, 95% CI 0.68–0.98
Schneider et al. JACC 2019 [31]. (IN.PACT)	IN.PACT DCB versus PTA	5 years	No mortality difference: - cumulative incidence through 5 years: 9.3% DCB vs. 11.2% PTA; $p = 0.399$
Albrecht et al. 2019 [50]. (THUNDER, FEMPAC, PACIFIER, CONSEQUENT)	DCB versus POBA	2 years	No mortality difference: - cumulative incidence through 2 years: 8.6% DCB vs. 7.0% PTA; $p = 0.55$
Mauri, MD from the FDA panel, June 19, 2019 [52].	IN.PACT DCB versus PTA	5 years	No mortality difference: - cumulative incidence through 5 years: 15.7% DCB vs. 11.2% PTA; $p = 0.24$ - HR 1.48, 95% CI 0.77–2.85
Meler, MD. from the FDA panel, June 19, 2019 [52].	Lutonix DCB versus PTA	5 years	No mortality difference: - cumulative incidence through 5 years: 15.5% DCB vs. 13.4% PTA; HR 1.01, 955 CI 0.68–1.52
Gray, MD. from the FDA panel, June 19, 2019 [52].	Stellarex DCB versus PTA	3 years	No mortality difference: - cumulative incidence through 3 years: 9.3% DCB vs. 9.9% PTA; $p = 0.93$

Table 2. (Continued)

Long-term safety analyses	Devices compared	Time to follow up	Mortality difference
Dake, MD from the FDA panel, June 19, 2019 [52].	Zilver PTX DES versus BMS/PTA	5 years	No mortality difference: - cumulative incidence through 5 years: 18.9% DES vs. 15.6% BMS/PTA; $p = 0.46$
William Gray, MD. Linc 2019 Leipzig Interventional Course 2019 [51]. (Ranger SFA)	Ranger DCB versus PTA	3 years	No mortality difference: - cumulative incidence through 3 years: 13.8% DCB vs. 10.7% PTA
Katsanos et al. JAHA 2018 [22].	DCB/DES versus BMS/PTA	2 and 4–5 years	Higher mortality with DCB/DES: - absolute risks at 2 years: 7.2% DCB/DES vs. 3.8% BMS/PTA; risk ratio 1.68; 95% CI, 1.15–2.47) - absolute risks at 5 years: 14.7% DCB/DES vs. 8.1% BMS/PTA; risk ratio 1.93; 95% CI, 1.27–2.93)
FDA Internal Analysis, FDA panel June 19, 2019 [52].	DCB/DES versus BMS/PTA	5 years	Higher mortality with DCB/DES: - risk ratio 1.57, 95% CI 1.16–2.13
VIVA patient-level meta-analysis, FDA panel June 19, 2019 [52].	DCB/DES versus BMS/PTA	5 years	Higher mortality with DCB/DES: - risk ratio 1.38, 95% CI 1.06–1.80

analyzed all-cause death at 24 months and found no significant differences in mortality (7.9% vs. 5.5%, respectively; $p = 0.317$) [50].

Patient-level analyses from trials of Lutonix, Stellarex, Zilver PTX, and Ranger PCB were presented at the Linc 2019 Leipzig Interventional Course. The Levant 2 trial (Lutonix) examined patients treated with PCB versus PTA at 5 years and found no difference in mortality (14.3% and 10.6%, respectively; $p = 0.198$). Data from Stellarex pooled data from 2351 patients (ILLUMENATE trials) and found no difference in all-cause death at 3 years for PCB versus PTA (9.3% vs. 9.9%; $p = 0.93$). A 5-year-mortality analysis was performed using data from the Zilver PTX trials showing no difference in mortality at 5 years between PES and PTA/BMS (18.7% vs. 17.6%; $p = 0.53$). RANGER SFA trial of the Ranger PCB showed no difference in mortality over 3 years with PCB compared with PTA (13.8% vs. 10.7%) [51].

Secemsky et al. published two retrospective analyses of all-cause mortality in Medicare data. First, they examined patients receiving PCB/PES versus PTA/BMS. They studied 16,560 patients who underwent femoropopliteal artery revascularization over a median follow-up of 389 days (interquartile range 277–508 days) [48•]. They found that treatment with PCB/PES was associated with a lower mortality than with PTA/BMS through 600 days (32.5% vs. 34.3%, respectively; $p = 0.007$). There was no association between drug-coated devices and all-cause mortality in multivariate analyses [HR 0.97 (95% CI, 0.91–1.04); $p = 0.43$]. Second, they looked at DES versus BMS in the Medicare population. They analyzed 51,456 patients who underwent peripheral stenting over a median follow-up time of 2 years and found no difference in mortality through

4.1 years (51.7% for DES vs. 50.1% for BMS; log-rank p value = 0.16) [49•]. This finding remained robust after multivariable adjustment and stratification by ALI and CLI.

The FDA recently convened a panel investigating the validity of a late mortality signal in paclitaxel-coated devices [52]. During this 2-day meeting, the FDA reviewed their own internal analysis, which again replicated a signal of late harm with PCDs, similar to the original JAHA meta-analysis. However, they found no dose-response relationship between paclitaxel and mortality, no mechanism linking paclitaxel to death, no primary cause of death related to PCD use, and insufficient data for conclusions to be made. Furthermore, more observational data were presented at the meeting demonstrating the long-term safety of these devices. In an expanded analysis of Medicare data, Dr. Eric Secemsky presented data from over 150,000 patients who underwent either inpatient or outpatient femoropopliteal artery revascularization and were followed for a median 799 days and as long as 1573 days. Dr. Secemsky found no evidence of harm with PCDs (adjusted hazard ratio 0.94, 95% CI 0.93–0.96), including when stratified by DES and DCB, CLI, and non-CLI, and inpatient or outpatient. Dr. Robert Yeh presented data from the Optum claims database of over 20,000 patients who underwent either inpatient or outpatient femoropopliteal artery revascularization over a median 763 days (longest 1028 days). Again, this analysis demonstrated no association of harm with PCDs (adjusted HR 1.09, 95% CI 0.98–1.22). Last, Dr. Bertges presented data from the Vascular Quality Initiative Peripheral Vascular Interventon Registry involving more than 8000 patients followed for a median 12.4 months and again found no association between PCDs with all-cause mortality (adjusted HR 0.82, 95% CI 0.68–0.98). The panel concluded that there is evidence of signal of harm with PCDs, but there is no clear mechanism or cause of death. As such, the decisions moving forward will be centered on what future studies will be needed to evaluate the safety of these devices, as well as what additional changes are needed to the device labeling.

Conclusions

It is an exciting time in the field of vascular disease as there are many innovative, disease-altering technologies under development. As clinicians in an evolving field, we have a responsibility to carefully analyze data surrounding these novel treatments, both to protect patients from interventions that may cause unintended harm and to ensure that beneficial interventions are used to their fullest potential.

Paclitaxel-based therapies offer a clear advantage over standard PTA and BMS as they decrease rates of restenosis, target-lesion revascularization, and claudication. A late mortality signal found in a recent meta-analysis has, however, alarmed the vascular disease community, prompting noticeable declines in the use of these therapies since March, 2019. Although this signal of harm has been replicated in multiple patient-level meta-analyses, presented both by the FDA and VIVA physicians, there remains a question of whether this harm signal is truly related to paclitaxel. No singular cause or dose-relationship assessment can clearly link exposure with mortality. In addition, there was significant missing data which may have biased results. Analyses in large observational datasets have not found a late-mortality signal.

A June, 2019 FDA panel concluded that our understanding of the late mortality signal associated with PCDs is incomplete. It has charged the vascular disease community with increasing long-term follow-up and improving cause of death adjudication for patients treated with PCDs.

Compliance with Ethical Standards

Conflict of Interest

Anna K. Krawisz declares no potential conflicts of interest.
Eric A. Secemsky reports grants and modest consulting fees given by Medtronic.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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