Long-term Safety and Efficacy of Paclitaxel-based Endovascular Devices in Femoro-popliteal Intervention: Truth or Myth

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Abstract

Background: Paclitaxel-based devices (PBD) have become the current trend in the treatment of symptomatic femoro-popliteal (FP) arterial disease. This article reviews updated results regarding the safety and efficacy of these devices when compared with standard balloon angioplasty (PTA) and bare-metal stents (BMS) in FP intervention.

Recent findings: Randomized controlled trials (RCTs) have shown that peripheral PBDs have significantly improved vessel patency and decreased the need for target lesion revascularization (TLR) in FP disease as compared to PTA or BMS. Recently, a summary-level meta-analysis unexpectedly reported late excess mortality in patients treated with PBDs, resulting in the pausing or withdrawal of ongoing trials and a safety warning from the FDA. However, publications based on patient-level analysis have not supported this safety concern.

Summary: Lower extremity arterial disease is a widespread atherosclerotic disease that significantly impacts quality of life and survival. PBDs hold promise for patients with symptomatic FP disease, offering the dual advantages of effective and durable intervention, when compared to non-drug devices. A meta-analysis of RCTs found a warning issue of higher late mortality while using these devices, and the FDA has also replicated this alert notice. However, there was found to be significant missing data in this meta-analysis and FDA report; and besides, they did not find a plausible mechanism linking paclitaxel to death, or correlation between paclitaxel dose and mortality. Data analysis from observational patient-level studies did not find a similar safety concern. An FDA panel suspended the validity of this late mortality warning recently, and emphasized that the available data is incomplete. PBDs will remain on the market, and a strategy is actively being developed to improve post-market surveillance, device-labeling, and cause of death adjudication.

Keywords: paclitaxel-based devices, balloon angioplasty, bare-metal stents, symptomatic femoro-popliteal arterial disease

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Introduction

Atherosclerotic lower extremity peripheral arterial disease (LEAD) continues to increase worldwide and is associated with significant morbidity and mortality.[1,2]

In Asia, the burden of LEAD and diabetes mellitus is increasing rapidly,[3,4] and the incidence and prevalence of end-stage renal disease (ESRD) are the highest in the world.[5] Therefore, most Asian patients with LEAD may have diabetes mellitus or ESRD, which has led to an increasing number of chronic limb-threatening ischemia (CLTI) patients, with poor prognosis and increased utilization of health care resources.[6,7]

Claudicants usually present with leg pains and limitations of daily activity. A minority may progress to CLTI, the most severe form of LEAD carrying the threat of limb loss, with up to 25% of patients requiring amputation within the first year of diagnosis.[8] In addition to adverse limb outcomes, patients with LEAD have a 3- to 4-fold higher risk of cardiovascular events, even in the setting of asymptomatic disease.[9] The risk of subsequent cardiovascular events is very high in symptomatic patients, ranging from 20% for 5-year non-fatal events in mild disease to 10% for 1-year fatal events in patients with CLTI.[10,11]

Previous results using the endovascular-centered approach to treat aorto-iliac and FP disease have shown a shorter hospital stay, fewer complications, and acceptable patency rates as compared to open bypass surgery.[12,13] The 2017 European Society of Cardiology guidelines recommend endovascular therapy (EVT) as first-line therapy for FP occlusions < 25 cm.[14] Despite the success of EVTs, initial benefits before PBD technology were short-lived, with a 40-60% restenosis rate for traditional PTA and BMS within one year.[15]

Based on experiences from drug-eluting stents (DES) in percutaneous coronary intervention, the researcher found that paclitaxel was an ideal anti-restenotic agent for LEAD. The characteristic lipophilicity facilitates drug uptake and transferal into tissues and then inhibits smooth muscle proliferation at low concentrations. It maintains a robust anti-proliferative effect over time.[16] Paclitaxel-coated balloons (PCB) and paclitaxel-eluting stents (PES) have been widely adopted in peripheral vascular intervention.

Recent consensus guidelines recommend first-line treatment with both PCB and PES for FP artery disease with a class one indication for device selection.[17,18] Because their use in clinical practice is relatively new, data regarding the long-term safety of PBDs are scarce. The vascular intervention community was taken by surprise when a recent meta-analysis demonstrated an excess late mortality in patients treated with PBDs relative to PTA/BMS at 2 and 5 years.[19] This prompted the FDA to investigate the safety of these devices, and two large clinical trials were halted (SWEDEPAD I, 2; and BASIL-3).[20] The statistical methodologies of this meta-analysis have been questioned since then, and several studies after this publication did not observe an increase in mortality with PBDs.

Efficacy of Paclitaxel-coated balloons

Paclitaxel is particularly well-suited for use with balloon angioplasty because it rapidly diffuses into tissues due to its lipophilicity and remains in the vessel wall over time, active at low concentrations.[16,21] Thus, it is an ideal agent for local drug delivery. Prior RCTs have demonstrated a benefit of PCBs over traditional PTA, and therefore the FDA approved the use of PCBs in treating FP disease. The first peripheral multicenter study compared clinical outcomes of 48 patients treated with PCBs with 54 patients treated with PTA for FP revascularization. They found significant reductions in late lumen loss (0.4 ± 1.2 mm vs. 1.7 ± 1.8 mm, $p < 0.001$) and TLR (4% versus 29%, $p < 0.001$) at six months, with favorable outcomes persisting at 24 months.[22] The following RCTs replicated similar findings over 6-24 month periods.[23-25]

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 with a significantly lower rate of TLR in patients receiving PCB versus those receiving PTA (21% and 45%, respectively p = 0.0005)].[26] Schneider et al. found similar results in a 5-year follow-up of the IN. PACT. SFA trial in which 331 subjects with symptomatic FP lesions were randomized 2:1 to PCB or PTA. Through 5 years, patients treated with PCB demonstrated higher rates of freedom from TLR (74.5% vs. 65.3%, p = 0.020).[27] Of note, the studies above focused on shorter lesion lengths (<10 cm), with a low incidence of chronic total occlusion (CTO) and in-stent restenosis (Table 1).

For real-world complex lesions, the 5-year post hoc analysis in the IN. PACT trial still favored PCB over PTA in longer lesions, CTO, advanced PAD (Rutherford 4), and high-risk patients (aged over 75 years).[27] Another trial compared PCBs to PTA in 70 patients with symptomatic in-stent restenosis of the SFA.[29] The mean lesion length was 13.9 ± 6.7 cm. They found significantly reduced rates of diameter stenosis and binary restenosis at 6-8 months, as well as reduced TLR rate at 24 months. Schmidt et al. retrospectively analyzed registry data of PCBs in longer, more complex lesions over two years.[30] They enrolled 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 at one year for PCB relative to literature estimates of PTA for comparable lesions

Table 1. Major trials assessing the efficacy of paclitaxel-coated devices compared with conventional PTA and bare-metal stents

Clinical trial	Device compared	Lesion length (cm)	Restenotic lesions	CTO	Follow-up time	Significantly Reduced CD-TLR
Thunder[26]	DCB vs. PTA	7.5 ± 6.2 7.4 ± 6.7	36%	27%	5 years	DCB 21% vs. 45%
IN.PACT.SFA[27]	DCB vs. PTA	8.9 ± 4.8 8.8 ± 5.1	5%	24%	5 years	DCB 25.5% vs. 34.7%
Levant 2[28]	DCB vs. PTA	6.3 ± 4.1 6.3 ± 4.0	15%	15%	1 years	DCB (PP) 65.2% vs. 52.6%
Pacifier[23]	DCB vs. PTA	7.0 ± 5.3 6.6 ± 5.5	24%	31%	1 years	DCB 7.1% vs. 27.9%
Illuminate[25]	DCB vs. PTA	7.2 ± 5.2 7.1 ± 5.3	8%	19%	2 years	DCB 12.1% vs. 30.5%
ISAR-PEBIS[29]	DCB vs. PTA	13.2 ± 6.5 14.6 ± 6.9	100%	NA	2 years	DCB 19% vs. 50%
Zilver-PTX[31]	DES vs. BMS/PTA	6.6 ± 3.9 6.3 ± 4.1	6%	31%	5 years	DES 16.9% vs. 32.4%
Real-PTX[34]	DCB vs. DES	15.0 ± 8.7 15.6 ± 8.9	NA	53%	2 years	No difference 71.3% 68.9%
IMPERIAL[32]	Zilver PTX vs. Eluvia	8.2 ± 3.7 8.7 ± 3.7	NA	31%	1 year	No difference (PP) 81.5% vs. 86.8%

Abbreviation: BMS, bare-metal stent; CD-TLR, clinically driven target lesion revascularization; CTO, chronic total occlusion; DCB, drug-coated balloon; DES, drug eluting stent; NA, not applicable; PP, primary patency; PTA, percutaneous transluminal angioplasty

(78% and 22-34%, respectively); however, at two years, there was a significant drop in primary patency to 49%. Studies to date show that PCBs represent effective, durable interventions for focal lesions at five years. More studies are warranted to define long-term efficacy for complex lesions, although initial studies support the use of PCBs in longer, more complex lesions as well (see Table 1). Furthermore, head-to-head comparisons are needed to compare PCBs to PES, incorporating longer lesions to better define the appropriate populations for these technologies.

Efficacy of Paclitaxel-coated stents

Peripheral stenting provides some advantages over the PTA in more complex lesion anatomy, such as total occlusions and when flow-limiting dissections occur. There are currently two FDA-approved paclitaxel-eluting stents for FP disease: the polymer-free Zilver PTX and the polymer Eluvia. PES has demonstrated improved outcomes compared with both PTA and BMS. Dake et al. reported that 474 patients were randomized to Zilver PTX or PTA. Patients who experienced initial PTA failure, then underwent secondary randomization to Zilver PTX or BMS. Compared 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 also showed superior 2-year primary patency as compared to the BMS group (83.4% vs. 64.1%, p < 0.01).[31] 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 than in the PTA group (83.1% vs. 67.6%, p < 0.01). Similarly, the secondary randomization group showed superior 5-year primary patency in the PES group (72.4% vs. 53%, p = 0.03) and freedom from TLR (84.9% vs. 71.6%, p =0.06). The Eluvia stent has a polymer coating to deliver paclitaxel over one year and has the lowest drug-dose density of PBDs. The Imperial trial compared the Eluvia PES with the Zilver PTX PES. At one year, the Eluvia stent demonstrated non-inferiority to Zilver PTX with one-year primary patency rates of 86.8% and 81.5%, respectively (p < 0.0001).[32] Further analyses have been conducted to assess the safety and efficacy of PES in more complex lesions. Cipollari et al. examined the outcomes of PES in patients with PAD without patent tibial runoff.[33] In their retrospective analysis of 900 patients, 54 of which had no patent runoff vessels and 846 had at least one patent runoff vessel, rates of freedom from TLR, patency, and clinical benefit at two years were not significantly different between groups. Zeller et al. reported a propensity score-matched study of 228 patients and found comparable 12-month patency and TLR results between PCBs and PESs in FP lesions of more than 10 cm.[34]

Bausback et al. published a head-to-head comparison of PCB versus PES in variable lesion lengths with high lesion complexity over 36 months. They randomly assigned 150 patients with symptomatic FP disease to primary PES or PCB with bailout stenting. The average lesion length for PCB was 15.0 ± 8.7 cm and for DES it was 15.6 ± 8.9 cm (p = 0.34). More than half of the lesions were CTOs. At 12 months, primary patency rates were 79% for PES and 80% for PCB (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 PES, and 38% for PCB (p = 0.17), and freedom from TLR was approximately 70% for both groups. The 3-year patency rate in lesion length >10 cm showed a trend favoring PES (32.3% PCB, 45.2% PES; rate difference -12.9; 95% CI -40.5% to 1.7%; p = 0.19). PES showed significantly higher primary patency for stenotic (p = 0.04), but not for CTO lesions (p = 0.93), at 36 months.[35]

Safety of paclitaxel-coated devices

The long-term safety of these devices has not been well-established, given their limited time in clinical use. A recent summary level meta-

analysis by Katsanos et al. found an increase in all-cause mortality associated with PCB/PES versus PTA/BMS at 2-5 years.[19] This study examined 28 RCTs, 24 for PCB, and 4 for PES. At one year (4432 patients), there was no mortality difference between the PCB/PES and PTA/BMS cohorts. At two years (12 trials and 2316 patients) and 5 years (3 trials and 863 patients), they found significant increases in mortality risk (68% and 93% increased risk, respectively) between PBDs and PTA/BMS. They also reported a positive association between paclitaxel dose and the absolute risk of death. In response to this publication, the FDA issued warnings about the potential risk of increased late mortality associated with PBDs, even recommending against their use except in cases of high-risk patients. Two large clinical trials were halted (SWEDEPAD 1, 2 and BASIL-3). 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 RCTs pooled in the meta-analysis were designed to examine limb-rated outcomes. Thus, they experienced significant attrition from the studies after reaching primary endpoints, the majority of which occurred at one year. Therefore, there was a considerable amount of missing data that may have influenced results. Second, summary-level data combines multiple heterogeneous populations with substantially different baseline characteristics. Pooling heterogeneous patient populations for analysis might result in significant bias. Third, no plausible mechanism for paclitaxel-induced mortality has been proposed. Fourth, the paclitaxel dose-response analysis is challenged by the varying methods to coat each device with paclitaxel, each of which has different biological 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 then arrests the cell cycle in the G2/M phase by preventing microtubule breakdown.[36] At lower concentrations, paclitaxel can reduce restenosis. It inhibits the secretion of extracellular matrix, proliferation and migration of vascular smooth muscle cells and fibroblasts, and white blood cells.[16] Paclitaxel has a long-lasting inhibitory effect even after short exposure time. In cell culture, paclitaxel exposure for 3 min resulted in decreased cell proliferation for up to 12 days.[37] Animal studies have shown the presence of paclitaxel in local vasculature for up to 60 days.[38] 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 after 6-24 h. In humans, plasma levels were undetectable within a few days. The half-life of paclitaxel in plasma is very short (21 ± 14 h, range of 4-65 h), according to the literature for chemotherapeutic dosing.[39] When investigated in LEAD treated with 3 PCBs, paclitaxel was undetectable in the plasma by 24 h, and no paclitaxel-related events occurred.[40] Mean total treatment doses delivered by PCB/PES in clinical trials ranged from 1 mg or less up to 20 mg depending on lesion length, the number of lesions treated, and the technology used.[27] In registry data, there were rare reports of patients receiving up to 70 mg of paclitaxel.[16] When used as a chemotherapeutic agent, average doses of paclitaxel for a single treatment are approximately 230-300 mg, and a total dose of up to 1200 mg for multiple treatments. At chemotherapeutic concentrations, side effects of paclitaxel include neutropenia, neuropathy, hypersensitivity, myalgia, myelotoxicity, anaphylaxis, nausea, and cardiovascular effects such as hypotension/hypertension and bradycardia. The SNAPIST I trial examined paclitaxel administration along with BMS placement for prevention of restenosis at doses of 10, 30, 70,

and 100 mg/m^2. Systemic side effects of moderate neutropenia, sensory neuropathy, and alopecia appeared only with doses of 70 mg/m^2, doses much higher than those delivered with PCB/PES.[41] No plausible mechanism has been put forward to link mortality increase and the use of PBDs. At low concentrations, paclitaxel was hypothesized to potentiate microenvironments of tumor spread; however, analyses of causes of death in the patient-level data from RCTs do not show a consistent modality of death associated with patients receiving PCDs. Importantly, there was no disproportionate increase in malignancies in these patients.[27]

Patient-level data analyses

In response to this meta-analysis, several studies have published 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 RCTs and two prospective single-arm studies.[27] They examined 1980 patients over five years. Besides, they performed a survival analysis on patients treated with DCB stratified by paclitaxel dose. They found that there was no difference in all-cause mortality in patients receiving low, middle, and high paclitaxel doses (p = 0.700) (Figure 1). Albrecht et al. pooled four RCTs comparing PCB and PTA. They found no significant differences in all-cause mortality at 24 months (7.9% vs. 5.5%, respectively; p = 0.317).[42] Patient-level analyses from trials of Lutonix, Stellarex, Zilver PTX, and Ranger PCB were presented at the Linc 2019 Leipzig Interventional Course.[46]

There were no mortality differences between drug-coated or non-drug coated devices across all studies, including the Levant 2 trial (14.3% in Lutonix PCB and 10.6% in PTA, p = 0.198) at five years, ILLUMENATE trials (9.3% in Stellarex PCB versus 9.9% in PTA, p = 0.93) at three years, Zilver PTX trials (18.7% in PES vs. 17.6% in PTA/BMS, p = 0.53) at five years, and RANGER SFA trial (13.8% in Ranger PCB vs. 10.7% in PTA) at three years.[43] Secemsky et al. published two retrospective analyses of all-cause mortality in Medicare data. They studied 16,560 patients who underwent FP therapy over a median follow-up of 389 days (interquartile range 277-508 days).[44] They found lower mortality in the PCB/PES group than in the PTA/BMS group 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]. They analyzed 51,456 patients who underwent FP 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, p = 0.16).[45] This finding remained robust after multivariable adjustment and stratification by ALI and CLTI.

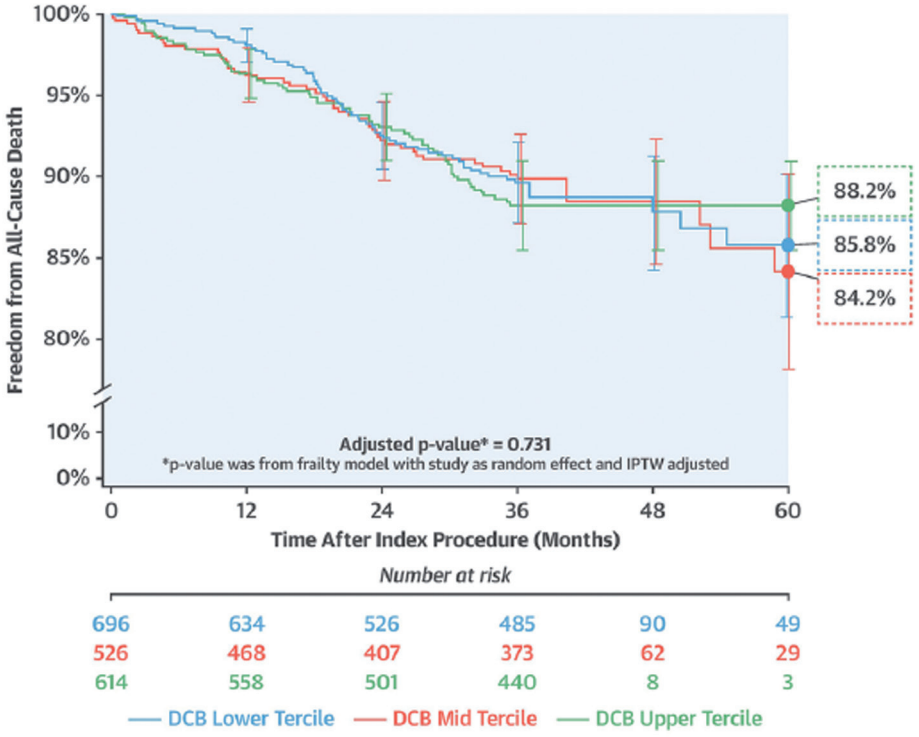
The FDA recently convened a panel investigating the validity of a late mortality signal in PBDs.[47] During this 2-day meeting, the FDA reviewed the internal analysis, which again replicated a late harmful message with PBDs, similar to the original JAHA meta-analysis. However, they found no dose-response relationship between paclitaxel and mortality, no mechanism linking paclitaxel to death, no primary cause of death related to PBD use, and insufficient data for conclusions to be made. Furthermore, more observational data demonstrating the long-term safety of these devices were presented at the meeting. In an expanded analysis of Medicare data, Dr. Eric Secemsky presented data from over 150,000 patients undergoing FP revascularization who were followed for a median of 799 days (longest 1573 days). They found no evidence of harm with PBDs (adjusted HR 0.94, 95% CI 0.93-0.96), including when stratified by DES and DCB, CLTI and non-CLTI, and by inpatient or outpatient. Dr. Robert Yeh presented data from the Optum claims database of over 20,000 patients having FP revascularization over a median 763 days (longest 1028 days). Again, this analysis demonstrated no association of harm with PBDs

Table 2. Literature reporting the long-term safety of paclitaxel-coated devices

Long-term Safety Analyses	Devices comparison	Follow-up duration	Mortality difference
Secemsky et al. JAMA, 2019[44]	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[45]	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
Schneider et al. JACC 2019[27] (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[42] (THUNDER, FEMPAC, PACIFIER, CONSEQUENT)	DCB versus PTA	2 years	No mortality difference: - cumulative incidence through 2 years: 8.6% DCB vs. 7.0% PTA; p = 0.55
Dake MD, from the FDA panel, June 19, 2019[47]	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[46] (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[19]	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[47]	DCB/DES versus BMS/PTA	Five 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[47]	DCB/DES versus BMS/PTA	Five years	Higher mortality with DCB/DES: - risk ratio 1.38, 95% CI 1.06-1.80

Abbreviation: BMS, bare-metal stent; CD-TLR, clinically driven target lesion revascularization; CTO, chronic total occlusion; DCB, drug-coated balloon; DES, drug eluting stent; HR, hazard ratio; CI, confidence interval; PP, primary patency; PTA, percutaneous transluminal angioplasty

CENTRAL ILLUSTRATION: Kaplan-Meier Freedom From All-Cause Death by Paclitaxel Dose in All DCB Patients



Distribution of Paclitaxel Dose in Each Paclitaxel Tercile in DCB

Paclitaxel Dose	N	Mean µg	Std µg	Median µg	Q1, Q3 µg	Range µg
DCB Lower Tercile	696	5,019.0	1,508.6	4,752.0	3,653, 6,924	1,850, 6,951
DCB Mid Tercile	526	10,007.5	1,757.7	9,504.0	8,448, 11,618	6,989, 13,822
DCB Upper Tercile	614	19,978.2	6,122.1	18,654.0	15,399, 22,705	13,902, 61,949

Schneider, P.A. et al. J Am Coll Cardiol. 2019;73(20):2550-63.

Figure 1. Schneider et al. stratified 1980 patients into three groups according to paclitaxel doses of exposure. There is no difference in mortality among the three groups[27].

(adjusted HR 1.09, 95% CI 0.98-1.22). Last, Dr. Bertges presented data from the Vascular Quality Initiative Peripheral Vascular Intervention Registry involving more than 8000 patients, followed for a median 12.4 months, and again found no association between PBDs with all-cause mortality (adjusted HR 0.82, 95% CI 0.68-0.98). The panel concluded that there is evidence of a signal of harm with PBDs, but there is no precise mechanism or cause of death. The future decision-making will center on how to assess the safety of these devices in upcoming studies, and whether the device labeling needs additional changes or not.

Conclusions

Paclitaxel-based therapies provide a clear advantage regarding vessel patency and the need for TLR in FP intervention. Excess late

mortality from a recent meta-analysis has alarmed the vascular community, prompting noticeable declines in the therapeutic use since March 2019. The analysis by the FDA and VIVA physicians replicated this alarming issue; however, there remains a question of whether this harm signal is genuinely associated with paclitaxel. No singular cause or dose-relationship assessment can link paclitaxel exposure with mortality. Also, there was significant missing data in the meta-analysis, which may have biased results. Analyses in large observational datasets have not found a late-mortality signal. 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 responses reach their fullest potential.

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