Title

Update on paclitaxel for femoral-popliteal occlusive disease in the 15 months following a summary level meta-analysis demonstrated increased risk of late mortality and dose response to paclitaxel

Journal

Journal of Vascular Surgery, 73(1)

ISSN

0741-5214

Authors

Schneider, Peter A
Varcoe, Ramon L
Secemsky, Eric
et al.

Publication Date

2021

DOI

10.1016/j.jvs.2020.07.093

Peer reviewed

Published in final edited form as:

J Vasc Surg. 2021 January ; 73(1): 311–322. doi:10.1016/j.jvs.2020.07.093.

Update on paclitaxel for femoral-popliteal occlusive disease in the 15 months following a summary level meta-analysis demonstrated increased risk of late mortality and dose response to paclitaxel

Peter A. Schneider, MD[a], **Ramon L. Varcoe, MBBS, MS, PhD**[b], **Eric Secemsky, MD, MSc**[c], **Marc Schermerhorn, MD**[d], **Andrew Holden, MBChB**[e]

[a]Division of Vascular and Endovascular Surgery, University of California San Francisco, San Francisco [b]The Vascular Institute, Prince of Wales Hospital and University of New South Wales, Sydney [c]the Division of Cardiology, Beth Israel Deaconess Medical Center, Boston [d]the Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center, Boston [e]the Department of Interventional Radiology, Auckland Hospital and University of Auckland School of Medicine, Auckland

Abstract

Background: Peripheral vascular devices (stents and balloons) coated with paclitaxel were developed to address suboptimal outcomes associated with percutaneous revascularization procedures of the femoral-popliteal arteries. In randomized controlled trials (RCT), paclitaxel-coated devices (PCD) provided increased long-term patency and a decreased need for repeat revascularization procedures compared with uncoated devices. This finding resulted in the adoption of their use for endovascular lower extremity revascularization procedures. However, in late 2018 a study-level meta-analysis showed increased all-cause mortality at 2 years or more after

Correspondence: Peter A. Schneider, MD, Division of Vascular and Endovascular Surgery, University of California San Francisco, 400 Parnassus Ave, Ste A583, San Francisco, CA 94143, (peter.schneider@ucsf.edu).

AUTHOR CONTRIBUTIONS

Conception and design: PS, RV, AH
Analysis and interpretation: PS, RV, ES, MS, AH
Data collection: PS, ES, MS
Writing the article: PS
Critical revision of the article: PS, RV, ES, MS, AH
Final approval of the article: PS, RV, ES, MS, AH
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: PS

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

Author conflict of interest: P.A.S. has served as a member of the advisory board for Philips, Boston Scientific, and Medtronic; and as a consultant for Cagent, Cardiovascular Systems, Inc, Intact Vascular, Medtronic, Profusa, Silk Road Medical, and Surmodics. R.V. is a consultant for Abbott Vascular, Medtronic, Boston Scientific, Intact Vascular, Clinlogix, Surmodics, and Intervene. E.S. is a consultant for CSI, Medtronic, and Philips and receives speaking honorarium from BD Bard, Cook, and Medtronic. M.S. is a consultant for Abbott, Cook, Medtronic, and Philips. A.H. is a member of the advisory board for Abbott, Boston Scientific, Endologix, Endospan, Medtronic and Gore and is a clinical researcher for BD-Bard, Cagent, Cook, Intact Vascular, Philips, Reflow, Shape Memory, Surmodics, and Trireme.

the procedure in patients treated with PCDs. This review examines the subsequent data evaluation following the publication of the meta-analysis.

Methods: We review the published responses of physicians, regulatory agencies, and patient advocates during 15-month period after the meta-analysis. We present the additional data gathered from RCTs that comprised the meta-analysis and safety outcomes from large insurance databases in both the United States and Europe.

Results: Immediately after the publication of the meta-analysis, concern for patient safety resulted in less PCD use, the suspension of large RCTs evaluating their use, and the publication of a letter from the U.S. Food and Drug Administration informing physicians that there was uncertainty in the benefit-risk profile of these devices for indicated patients and that the potential risk should be assessed before the use of PCDs. Review of the meta-analysis found that a mortality signal was present, but criticisms included that the evaluation was performed on study-level, not patient-level data, and the studies in the analysis were heterogenous in device type, paclitaxel doses, and patient characteristics. Further, the studies were not designed to be pooled nor were they powered for evaluating long-term safety. Clinical characteristics associated with a drug effect or causal relationship were also absent. Specifically, there was no dose response, no clustering of causes of death, and a lack of signal consistency across geographic regions. As more long-term data became available in the RCTs the strength of the mortality signal diminished and analysis of real-world use in large insurance databases, showed that there was no significant increase in all-cause mortality associated with PCD use.

Conclusions: The available data do not provide definitive proof for increased mortality with PCD use. A key observation is that trial design improvements will be necessary to better evaluate the risk-benefit profile of PCDs.

Keywords

Paclitaxel; Drug-coated balloon; Drug-eluting stent; Femoral-popliteal occlusive disease

Minimally invasive endovascular therapy primarily in the form of percutaneous transluminal angioplasty (PTA) with or without stent placement has become the first line therapy for the treatment for many patients suffering from life-style limiting or limb-threatening peripheral artery disease (PAD).[1,2] Although these mechanical treatments for atherosclerosis are effective at acutely restoring vascular flow, treatment with non-drug-coated devices has limited durability, with 1-year primary patency rates of 30% to 70%.[3,4] Given these suboptimal results and in an effort to decrease the need for repeat revascularization procedures, stents and balloons coated with paclitaxel were developed. Paclitaxel is an antiproliferative drug initially developed for cancer chemotherapy[5] and later applied to coronary stents to prevent the neointimal hyperplasia that led to in-stent restenosis.[6] These new drug-eluting stents (DES) and drug-coated balloons (DCBs) showed a substantial improvement in patency for femoropopliteal interventions when compared with their uncoated counterparts in randomized controlled trials (RCT).[7–10] This process led to approval of these devices and a subsequent rapid adoption of their use.[11]

As long-term data became available from the RCTs, the paclitaxel-treated arm in some studies showed a concerning trend toward late mortality.[7,12–14] To evaluate these concerns,

Katsanos et al[15] conducted a summary-level meta-analysis of all-cause death in 28 RCTs (n = 4663 patients) of paclitaxel-coated device (PCD) use in the femoropopliteal arteries. This pooled analysis of published or presented trials showed that there was no difference in mortality at one year (n = 4432; 2.3% vs 2.3% crude risk of death; risk ratio [RR], 1.08; 95% confidence interval [CI], 0.72–1.61). However, when evaluated over longer timeframes of 2 and 5 years, all-cause death was significantly greater in PCD-treated patients. The 2-year all cause death was evaluated in 12 RCTs and 2316 patients with crude death rates of 7.2% and 3.8% in the paclitaxel and control arms, respectively. The 5-year all cause death was evaluated in three RCTs and 863 patients with crude death rates of 14.7% and 8.1% in the paclitaxel and control arms, respectively. The RRs at 2 and 5 years were 1.68 (95% CI, 1.15–2.47) and 1.93 (95% CI, 1.27–2.93), respectively. The investigators further evaluated a possible paclitaxel dose relationship to mortality using a calculated dose-time product based on the nominal paclitaxel dose on the DCB or DES. Per this analysis, there was a 0.4 ± 0.1% excess risk of death per paclitaxel milligram-year (95% CI, 0.1%−0.6%; $P < .001$).[15]

The late mortality signal observed in this meta-analysis led to a swift reaction of discussion and investigation in the vascular community and initiated a period of uncertainty. The overall clinical use of PCDs declined due to physician concern for patient safety and ambiguity regarding the risk-benefit profile.[16] There was also reaction by the sponsors of some randomized studies (BASIL-3, SWEDEPAD1, and SWEDEPAD2) to discontinue enrollment until the safety of the study devices could be further evaluated.[17] In January 2019, the U.S. Food and Drug Administration (FDA) indicated that they preliminarily identified the signal and using internally available data from pivotal trials, would perform their own complete analysis.[18]

In the second quarter of 2019, statements by FDA, Paris Course on Revascularization, and an Expert Advisory Group to the British Medicines and Healthcare Products Regulatory Agency acknowledged that the statistics behind the mortality signal were robust and that the signal was of concern. However, they also acknowledged that there were methodologic limitations in the meta-analysis, including that it was conducted on study-level data, not patient-level data; there was a large variability in the risk estimate; the studies were not designed to be pooled; the studies were not powered for short-term or long-term mortality; and there was no plausible mechanism for increased mortality identified. These statements also suggested that studies that had suspended enrollment should resume.[19–21] In the same timeframe, SWEDEPAD issued a statement that their Data Safety Monitoring Committee had not observed the same mortality association and recommended that the trials restart enrollment.[22] BASIL-3 restarted recruitment in September 2019 based on the Expert Advisory Group analysis.[23]

In June of 2019, a 2-day FDA advisory panel that included industry representatives, patient advocates, and physicians reviewed available data, including updated analyses of PCD efficacy and safety data with patient-level analyses and presentations of newly available data.[24] Based on the review and the advisory panel conclusions, the FDA summarized their findings and recommendations in a statement released August 7, 2019. The FDA noted that PCDs had demonstrated clinically meaningful benefits, but the long-term benefit-risk profile

was less certain. They recommended continued clinical investigation of PCDs with collection of both long-term safety and effectiveness data.[25]

Herein, we summarize the clinical science behind the development of PCDs, provide a summary of what has been learned regarding the safety of PCDs in the 15 months that followed the publication of the meta-analysis, and discuss the expected long-term data that will be available based upon ongoing or planned trials of PCDs.

BIOLOGIC EFFECTS OF PACLITAXEL AND SUMMARY OF EFFECTIVENESS IN FEMOROPOPLITEAL DISEASE

Paclitaxel is highly lipophilic and insoluble in water, which promotes its uptake into and retention in target cells. In the vessel wall, paclitaxel inhibits cellular division and migration by binding cellular tubulin thereby preventing tubulin depolymerization, a key step in mitosis. Paclitaxel diminishes neointimal neoplasia by inhibiting (1) proliferation of smooth muscle cells (SMC) and fibroblasts, (2) migration of SMC, fibroblasts, and lymphocytes, and (3) cellular secretion of extracellular matrix components.[26] There are currently five PCDs approved by the FDA for the treatment for femoropopliteal occlusive disease(Table I). Of these devices, two are stent-based, Zilver PTX (Cook Medical, Bloomington, Ind) and Eluvia (Boston Scientific, Maple Grove, Minn), and three are coated balloons, Lutonix 035 Drug Coated Balloon PTA Catheter (BD Bard, Tempe, Ariz), IN.PACT Admiral (Medtronic Vascular, Santa Rosa, Calif), and Stellarex (Philips, Colorado Springs, Colo). Each device has paclitaxel doses and excipients specific to the device. In addition, the devices differ from each other in both diameter and length. Thus, the potential dose of these devices ranges from 0.1 to 17.0 mg, which is an order of magnitude lower than breast cancer dosing of 236 to 392 mg/infusion (total dose of 1100–1500 mg).[27]

With one exception, the study designs to obtain marketing approval from the FDA required RCTs to compare PCDs to non-drug-coated devices with a primary endpoint of primary patency at 1 year.[7,8,10,28] The Eluvia DES was approved based on a noninferiority trial compared with the Zilver PTX DES.[29] As summarized in Table II, the DCBs had significantly ($P < .02$) greater 1-year patency (range, 65.2%−82.2%) than conventional PTA (range, 52.4%−57.6%).[7,10,28] The 1-year primary patency of the Zilver PTX DES was 83.1% compared with 32.8% for BMS ($P < .001$).[8] Last, the primary patency of ELUVIA DES was noninferior to Zilver PTX 86.8% vs 81.5% ($P < .0001$).[29] Taken together, these results provided strong evidence that PCDs had a significant effect on maintenance of 1-year vessel patency. Further, 5-year follow-up data from two pivotal trials of the Zilver PTX and IN.PACT devices have shown sustained significant superiority ($P < .02$) with PCDs when compared with uncoated devices.[12,30]

SUMMARY OF NEW DATA SINCE DECEMBER 2018

RCT updates.

Since the publication of the Katsanos et al meta-analysis,[15] multiple publications and presentations from various data sources were performed (Fig 1). The FDA conducted an as-treated analysis of mortality based on an evaluation of available data from RCTs of devices

approved for use in the United States. Because of the lack of consistency in capturing the use of PCDs in repeat procedures, the as-treated population was considered by FDA to be the "most relevant cohort" for the primary analysis of the mortality signal. Their initial evaluation included 971 patients with up to 5 years of follow-up (FDA Pre VS) and confirmed a mortality RR of 1.72 (95% CI, 1.22–2.38).[24] As additional data became available, primarily via study sites locating trial patients that were previously lost to follow-up or withdrawn, the patient total increased to 1035 (FDA Post VS) and the RR decreased to 1.57 (95% CI, 1.16–2.13). Katsanos[31] also presented updated data at the 2019 Transcatheter Cardiovascular Therapeutics meeting. The RR for all-cause death was evaluated from five RCTs that included 1429 patients and was lower than the initial analysis, but still significant: 1.64 (95% CI, 1.22–2.20).[31] The independent nonprofit Vascular Interventional Advances (VIVA) group received patient-level RCT data to conduct an evaluation. The analysis included eight RCTs of devices currently approved in the United States and independent Medical Research Organization NAMSA was commissioned to perform the analysis. As with the FDA analysis, the VIVA/NAMSA analysis showed a significant but further attenuated association with mortality: hazard ratio (HR) 1.38 (95% CI, 1.06–1.80).[25] Although the FDA analysis included investigation device exemption studies for devices approved in the United States (which were conducted mostly in the United States), the VIVA analysis included RCTs of devices approved in the United States, including those conducted primarily in countries outside the United States. As additional lost to follow-up patient data were acquired and additional studies were included from outside the United States, the HR was further decreased to 1.27 (95% CI, 1.03–1.58).[32] The absolute increase in mortality among the PCD patients in right RCTs was 4.6%. Albrecht et al[33] published a patient-level subanalysis of 2-year mortality in four RCTs comparing DCB (n = 185) with PTA (n = 184). The 2-year mortality was not significantly different at 7.0% and 8.7% in the PTA and DCB groups, respectively ($P = .55$). There was no discernable pattern in causes of death and the only significant predictor of mortality was patient age 75 years or older.[33]

In addition to updated meta-analyses, cumulative long-term follow-up data from individual device development programs have also been published or presented in 2019. Follow-up periods in each program range from 3 years (Stellarex DCB) to 5 years (Zilver PTX, IN.PACT DCB, Lutonix DCB) and have shown no significant difference in mortality ($P > .05$) between PCDs and their non-drug-coated comparators.[34–37] These studies are summarized in Table III.

Analyses of real-world PCD data.

Additional analyses were conducted from large datasets of real-world use of PCDs. In each study, there was no significant difference in mortality between the PCD and non-drug-treated cohorts. Among the included real-world datasets was a 16,560 patient retrospective analysis of Medicare and Medicaid Services beneficiaries who were admitted for femoropopliteal artery revascularization. The median follow-up in this cohort was 389 days (interquartile range, 277–508 days) and as long as 1573 days. In addition, there was no difference when stratified by DCB, DES, CLI, and non-CLI.[38] Secemsky et al[38] also conducted an analysis of the Medicare database for patients with PAD that were treated with stents. A total of 51,456 patients received stents, and of those, 4105 received a DES.

Mortality through 4.1 years was similar for both DES and BMS-treated patients (51.7% for DES vs 50.1% for BMS; log-rank $P = .16$). Furthermore, there was no association between stent type and mortality after multivariable adjustment (HR, 0.98; 95% CI, 0.93–1.03; $P = .53$).[39] In an updated analysis presented at the FDA safety panel meeting in June 2019 involving 152,473 Medicare beneficiaries treated either as inpatients or outpatients from January 2015 to December 2017, there was no association between drug-coated stents or balloons with mortality through a median follow-up of 799 days and longest follow-up of 1573 days (adjusted HR, 0.94; 95% CI, 0.93–0.96; $P < .001$).[40] Patients were categorized as having received a PCD (n = 61,507) or a plain stent or balloon (n = 90,966), and as having either claudication or chronic limb-threatening ischemia (CLTI). Among those with claudication, mortality at 1500 days was 37.7% in the nondrug group and 36.5% in the group that received paclitaxel. Among patients with CLTI, mortality was 60.1% in those who did not receive paclitaxel and 58.3% among those who received PCDs.

A similar analysis of the Optum claims database evaluated 20,536 patients who underwent either inpatient or outpatient femoropopliteal artery revascularization. These patients were evaluated for a median of 763 days after the procedure and there was no increased mortality signal associated with the use of PCDs (adjusted HR, 1.09; 95% CI, 0.98–1.22).[41] Bertges et al[42] performed a propensity-matched analysis of 4880 patients (n = 2440 PCD; n = 2440 noncoated devices) undergoing endovascular treatment of superficial femoral-popliteal artery occlusive disease in the Vascular Quality Initiative. The mean follow-up was 509 days (range, 0–813 days) and the crude mortality rates were 13.2% and 11.5% for the nondrug and PCD groups, respectively. There was no association between PCDs with all-cause mortality (adjusted HR, 0.87; 95% CI, 0.73–1.04). A subgroup analysis of patients with claudication and with CLTI also showed no mortality difference.[42]

Freisinger et al[43] evaluated data from the 9.2 million-patient German BARMER Health Insurance database on the use of PCDs from their introduction to market until the present time. They identified 64,771 patients who underwent endovascular procedures and 3324 who underwent a procedure with a PCD. They conducted a time-dependent Cox regression analysis that adjusted long-term mortality by PCD use and baseline cardiovascular risk factors and showed no statistical increase in mortality for up to 11 years after the procedure for either DES or DCB use.[43] Behrendt et al[44] also conducted an analysis of patients in the Barmer database. The evaluated sample included 21,456 propensity score matched patients stratified by CLTI or intermittent claudication. Cox proportional hazards models for survival after 5 years favored the patients treated with PCDs in both the CLTI (HR, 0.83; 95% CI, 0.77–0.90) and intermittent claudication (HR, 0.88; 95% CI, 0.80–0.98) cohorts.[44]

Katsuki et al[45] conducted a propensity analysis of patients undergoing femoropopliteal stent placement at four centers in Japan. The analysis cohort included 285 patients treated with Zilver PTX DES and 1250 patients treated with BMS. The median follow-up was 3.4 years (interquartile range, 2.1–5.7 years). At 5 years, there was no difference in the overall survival with 77.5% (95% CI, 72.0%−83.4%) in the DES group and 73.7% (95% CI, 67.2% −80.9%) in the BMS group, ($P = .59$).[45] Liistro[46] presented a propensity-matched analysis from Italy comparing PTA patients (n = 440) and PCD patients (n = 414). The survival at 6 years was not significantly different (log-rank $P = .146$) between the PTA (71.6%) and PCD

(73.9%) cohorts.[46] Donas et al[47] conducted a two-step real-world use analysis of IN.PACT DCB in Europe. The first analysis of the entire patient cohort (n = 84 PTA; n = 121 DCB) showed a significantly greater 5-year mortality for the PTA group (26.2% vs 14.0%; *P* = .02). The second analysis used propensity pair matching, which showed a nonsignificant (*P* = .4) difference in 5-year mortality 26.0% vs 20.8% for the PTA and DCB groups, respectively.[47]

The real-world data available on this issue are voluminous and will likely be followed by even longer term reports on these patients. The disadvantage is the lack of randomization and the presence of selection bias in treatment decisions by the medical team. This factor can be mitigated only partially by propensity weighting. Conversely, loss to follow-up for an outcome such as all-cause mortality, which was a challenge in the RCTs, is less problematic when using claims data, because it is critical to the enterprise that beneficiary deaths be recognized. The Centers for Medicare and Medicaid services uses a number of sources to identify the deaths of its beneficiaries, with nearly 99% of deaths validated. Observational claims data also contain specific device codes for femoropopliteal artery revascularization, including *International Classification of Diseases*, 10th edition Procedure Coding System and Current Procedural Terminology/Healthcare Common Procedure Coding System codes specific to drug-coated devices, which assists in accurate identification of patients.

CONFOUNDING FACTORS IN ASSESSING A CAUSAL RELATIONSHIP BETWEEN PACLITAXEL AND MORTALITY

As the real-world and long-term follow-up studies of PCDs were being presented to the public, the medical community continued to research the scientific validity of the harm signal by conducting a variety of subanalyses to evaluate potential mechanisms. Specifically, there was uncertainty as to whether the increased mortality signal was causally related to paclitaxel or artefactual owing to issues associated with the design and follow-up of the RCTs. Several features of the RCTs included in the meta-analysis made them less reliable for pooling data and evaluating the long-term mortality signal associated with PCD use.

First, there was substantial heterogeneity between the studies. Patient characteristics, device types, paclitaxel doses and formulations, and geographic regions in which the studies were conducted varied from trial to trial. Second, the studies were primarily designed and powered to assess effectiveness in the form of primary patency at 1 year, not all-cause death at periods of 2 years or longer. As such, several issues associated with longer term follow-up became apparent as patient-level data from the RCTs were evaluated more closely. Third, the trials had relatively small sample sizes and five of the larger studies included in the meta-analysis used 2:1 and 3:1 randomization schemes,[15] which decreased the number of patients in the nondrug cohort. Fourth, none of the trials used blinding of the healthcare team, the very individuals tasked with determining whether a patient was deceased or simply lost to follow-up. This factor could have led to biases in patient treatment, assessment of mortality, and patient retention and follow-up.

Finally, a substantial number of patients withdrew or were lost to follow-up in the RCTs. In an analysis of three large RCTs presented at the FDA panel, 25% and 23% of the PCD and

nonpaclitaxel device patients, respectively, did not have long-term data. After a search for the missing patients, vital status was obtained on an additional 83 PCD patients and 37 PTA or BMS patients. These additional patient data were used for the second FDA analysis described elsewhere in this article. As the previously missing patients were accounted for, the mortality signal was decreased, suggesting that although the patients were randomized upon entry to the trial, they withdrew or were lost to follow-up in a manner that was not random and was influenced by other factors.

In addition to the potential trial design and conduct issues that may have led to the mortality signal associated with PCD use, there remains the quest to identify whether there is a mechanism between device use and patient death, which is integral to the causal investigation for evaluating harm. In 1965, Sir Austin Bradford Hill published a set of criteria to identify whether an observed medical phenomenon was caused by an inciting agent or if the observed condition occurred in the same timeframe but without causation and was simply an association. Among the elements of the Bradford Hill criteria that can be applied to the potential causal relationship between PCDs and mortality are temporality, consistency, biologic gradient, and specificity.[48]

Temporality was established as a part of the original and updated meta-analyses that showed that there was an increased mortality incidence at 2-plus years after the use of PCDs.[15] However, temporality is not supported to this point by the real-world data. Consistency of signal would indicate that PCD-associated mortality would have a similar incidence regardless of geography. Among RCT patients treated in the United States, the difference in long-term mortality between PCD and uncoated devices was greater (16% PCD vs 11% uncoated) than among RCT patients treated with the same devices outside the United States (11.3% PCD vs 9.9% uncoated; Fig 2). This finding was driven primarily by mortality differences in the U.S. cohorts of two trials (IN.PACT SFA and LEVANT-2), whereas cohorts outside the United States of those same trials and same devices did not show a major difference in mortality.[36,49,50] One possible reason for this was that there was a divergence in follow-up visit compliance by geographic region. In an analysis of patient visit compliance in the IN.PACT clinical program, there was no significant difference in late patient follow-up by treatment group in Europe or Japan, but in the United States, PTA patients were significantly more likely to attend follow-up visits (87% DCB vs 96% PTA; $P = .003$).[51] It is not clear whether this variation in follow-up visit attendance between groups resulted in medical treatment differences, such as improved compliance with risk factor management regimens, that could have influenced mortality. Another aspect of consistency is the assumption that patients would receive the same level of care regardless of treatment. Schneider et al evaluated antiplatelet therapy (APT) regimens after treatment in four IN.PACT trials. At all time-points (discharge, 30 days, and 6, 12, 24, and 36 months), PTA patients were more likely to be compliant with pre-scribed dual APT regimens. At 6 months, fewer than one-half the DCB patients were on dual APT regimens (49.4% vs 72.9%; $P < .001$), suggesting that a treatment bias or other factors were present.[37]

The presence of a biologic gradient or dose response is required to support a causal relationship between paclitaxel and long-term mortality. Katsanos et al[15] used a calculated paclitaxel dose-time product expressed in milligram-years based on the device used in each

individual study. They found that there was a highly significant ($P < .001$) association between Dose × Time product and mortality.[15] A criticism of this analysis was that it was based on study-level data and was unable to account for the use of multiple devices or devices of different length on a per-patient basis. Another criticism is the inclusion of time as a multiplier of dose. There is no biological rationale for including time, which would suggest an ever-increasing dose of paclitaxel for as long as the patient lives. Time is also disproportionately available among patients with longer term follow-up and age was a prominent factor associated with mortality risk in several of the RCTs.

Dose is readily ascertained from patient-level data and several analyses of a potential dose relationship have found none. The FDA conducted a dose-response analysis of five RCTs (LEVANT 2, ZILVER PTX, IN.PACT SFA I, SFA II, and ILLUMENATE) and determined that there was not a consistent relationship between dose and mortality across the studies. The FDA noted that there was a small sample size for many of the dose range groups, which limited their conclusions.[24] The VIVA-NAMSA study performed a dose response analysis using patient level data from eight RCTs based on milligrams per square milliliter of paclitaxel received at the index procedure. The analysis was adjusted for covariates through propensity scores and stratified by study. Dose ranges were grouped into terciles of low, medium, and high, and the HRs across these dose levels in a fixed effects model were 1.30 (95% CI, 0.92–1.82), 1.23 (95% CI, 0.87–1.73), and 1.50 (95% CI, 1.08–2.08), respectively. Similar HRs were seen in the random effect model. Both the random and fixed effects models showed there was no mortality effect seen with increasing doses.[32] The Albrecht analysis of four RCTs showed there was no significant difference in paclitaxel dose per patient in patients who died and those who survived during the 2-year follow-up period (5.300 ± 4.224 μg vs 6.248 ± 4.629 μg; $P = .433$).[33] Schneider et al[37] conducted an analysis of paclitaxel exposure on mortality from two single-arm and two randomized trials of the IN.PACT DCB that included 1837 DCB patients, respectively. Survival time by paclitaxel dose was analyzed with adjustment using inverse probability weighting to correct for baseline imbalances and study as random effect. The survival analysis was stratified by terciles of paclitaxel dose. The mean doses for the lower, mid, and upper terciles were 5.0, 10.0, and 20.0 mg, respectively. Freedom from all-cause mortality was not significantly different at five years with rates of 85.8%, 84.2%, and 88.2% for lower, mid, and higher dose ranges, respectively ($P = .731$).[37]

Finally, specificity would indicate that there is a clustering of a specific type(s) of death associated with the increased mortality. Per the analysis conducted by the FDA, there was no discernable pattern and no primary cause of death could be related to PCD use. The FDA also cautioned that the data were insufficient for conclusions to be made.[24] Individual device trial programs have similarly replicated this finding, with no emergence of a specific cause of death linked to paclitaxel exposures.[52]

Although the focus of this review has been the use of paclitaxel for femoropopliteal lesions and the vast majority of data is in patients with claudication, the clinical management of patients with CLTI is also in question and much less data have accumulated because there are no FDA approved DES or DCB for below-the-knee (BTK) use. A meta-analysis has suggested decreased short-term amputation-free survival, but not short- or long-term

mortality, after the use of paclitaxel DCBs for BTK arteries.[53] It is not clear whether the conclusions of this meta-analysis are valid because 38% of the studies have not been published, and because the longest term follow-up of two largest trials (Lutonix BTK Trial at 1 year and IN.PACT Deep Trial at 5 years) were inexplicably omitted from the analysis. When the 5-year mortality from the IN.PACT Deep Trial was included in the meta-analysis, for example, the supposed increase in amputation-free survival disappears ($P = .45$).[54]

NEXT STEPS AND PERSPECTIVE

With new trial data that have accumulated since the original meta-analysis, including vital status ascertainment of previously unaccounted patients and inclusion of RCTs performed outside the United States of devices approved by the FDA, the observed association between PCDs and mortality has attenuated substantially (VIVA, 1.27; 95% CI, 1.03–1.58).[32] The safety signal has not been demonstrated in real-world data, including tens of thousands of patients treated for claudication with endovascular procedures. Based on the results that have been presented and published in the ensuing 15 months, we have a more in-depth understanding of the mortality signal associated with PCDs, and the lack of any demonstrated causal relationship but the final story has not been written. As the FDA noted in the postpanel summary in August 2019, there is uncertainty regarding the mortality signal associated with these devices and they recommended that clinical studies of PCDs continue with collection of longer term data on their safety and effectiveness.[25] To that end, 29 RCTs —both independent and industry sponsored—are currently enrolling or in follow-up (Table IV). The accumulated data from these trials are projected to total more than 10,000 patients, including 17 studies in the femoropopliteal vessels. Additional long-term follow-up data will be available on the ILLUMENATE trial, which is critical because it is the investigation device exemption trial for an approved U.S. device that has yet to reach 5-year follow-up. Other vessels being evaluated in RCTs include infrapopliteal and arteriovenous access PCDs. In addition, real-world data from various insurance databases will continue to increase in both numbers of patients and duration of follow-up. Taken together, these data will provide a much larger sample size and robust dataset to make more definitive conclusions regarding the effect of PCDs on long-term mortality.

As additional clarifying data accumulate, most practices have reserved PCD use for a subset of patients at high risk for repeat intervention, based on FDA guidance. The FDA suggested in their August 7, 2020, letter to physicians that paclitaxel be considered in treating patients who are “judged to be at particularly high risk for restenosis and repeat femoropopliteal intervention.”[25] In this situation, “clinicians may determine that the benefits of using a PCD outweigh the risk of late mortality.” Understanding which patients should be designated as high risk for restenosis is not defined and it remains a matter of clinical judgment, practice patterns, collaboration with colleagues, and discussion with the patient.

Katsanos et al are to be acknowledged for identifying a mortality signal that went unrecognized by the broader vascular community. However, the presence of a dose response, and hence the implication of a causal relationship between paclitaxel and mortality on that basis, has since been refuted. Nevertheless, the entire exercise and the broader concern of the potential that we are causing harm to our patients has served as a test case of the resilience

of the vascular community. Because paclitaxel delivery has proven to be an advance in providing more efficacious treatment and because the potential of an increase in mortality is abhorrent, this issue posed a major obstacle to clinicians, patients, researchers, and institutions. The entire community has mobilized to sort through the pertinent issues and build toward a resolution, but there is more work to follow. Over these months, collaboration, responsiveness and collegiality have been exhibited by the FDA, specialty societies, clinical researchers, clinicians, and device manufacturers in an effort to resolve the issue. Trial design improvements will be required going forward. These improvements may include but are not limited to increased cohort size, improved quality and duration of follow-up, veracity of medical management, and vital status ascertainment. This challenge and our efforts to overcome it will likely lead to the development of a more mature, sophisticated, and resilient vascular field.

References

1. Rooke T, Hirsch A, Misra S, Sidawy A, Beckman J, Findeiss L, et al. Management of patients with PAD (Compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Asscociation Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:1555–70. [PubMed: 23473760]
2. Aboyans V, Ricco J, Bartelink M, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763–816. [PubMed: 28886620]
3. Hunink MGM, Donaldson MC, Meyerovitz MF, Polak JF, Whittemore AD, Kandarpa K, et al. Risks and benefits of femoropopliteal percutaneous balloon angioplasty. J Vasc Surg 1993;17:183–94. [PubMed: 8421335]
4. Vardi M, Novack V, Pencina MJ, Doros G, Burke DA, Elmariah S, et al. Safety and efficacy metrics for primary nitinol stenting in femoropopliteal occlusive disease: a meta-analysis and critical examination of current methodologies. Catheter Cardiovasc Interv 2014;83:975–83. [PubMed: 23996913]
5. Spencer C, Faulds D. Paclitexal: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of cancer. Drugs 1994;48:794–847. [PubMed: 7530632]
6. Waugh J, Wagstaff AJ. The paclitaxel (TAXUS™)-eluting stent: a review of its use in the management of de novo coronary artery lesions. Am J Cardiovasc Drugs 2004;4: 257–68. [PubMed: 15285700]
7. Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, Micari A, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease. Circulation 2015;131:495–502. [PubMed: 25472980]
8. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in twelve-month Zilver PTX randomized study results. Circ Cardiovasc Interv 2011;4: 495–504. [PubMed: 21953370]
9. Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med 2015;373:145–53. [PubMed: 26106946]
10. Krishnan P, Faries P, Niazi K, Jain A, Sachar R, Bachinsky WB, et al. Stellarex drug-coated balloon for treatment of femoropopliteal disease: twelve-month outcomes from the randomized ILLUMENATE pivotal and pharmacokinetic studies. Circulation 2017;136:1102–13. [PubMed: 28729250]

11. Mohapatra A, Saadeddin Z, Bertges DJ, Madigan MC, Al-Khoury GE, Makaroun MS, et al. Nationwide trends in drug-coated balloon and drug-eluting stent utilization in the femoropopliteal arteries. J Vasc Surg 2020;71:560–6. [PubMed: 31405761]
12. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, et al. Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. Circulation 2016;133:1472–83. [PubMed: 26969758]
13. Schneider PA, Laird JR, Tepe G, Brodmann M, Zeller T, Scheinert D, et al. Treatment effect of drug-coated balloons is durable to 3 years in the femoropopliteal arteries: long-term results of the IN.PACT SFA randomized trial. Circ Cardiovasc Interv 2018;11:1–8.
14. Laird JR, Schneider PA, Tepe G, Brodmann M, Zeller T, Metzger C, et al. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN.PACT SFA. J Am Coll Cardiol 2015;66:2329–38. [PubMed: 26476467]
15. 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. [PubMed: 30561254]
16. Monteleone PP, Banerjee S, Kothapalli P, Stern AD, Fehder D, Ginor R, et al. The market reacts quickly: changes in paclitaxel vascuar device purchasing within the Ascension Healthcare System. J Invasive Cardiol 2020;32:18–24.
17. BASIL-3 and SWEDEPAD trials paused for review of paclitaxel meta-analysis data - Vascular News. Available at: https://vascularnews.com/basil-3-swedepad-trials-paused-paclitaxel/. Accessed January 12, 2020.
18. Treatment of peripheral arterial disease with paclitaxel-coated balloons and paclitaxel-eluting stents potentially associated with increased mortality - letter to health care providers | FDA. Available at: https://www.fda.gov/medical-devices/letters-health-care-providers/treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel-eluting-stents. Accessed January 12, 2020.
19. UPDATE. Treatment of peripheral arterial disease with paclitaxel-coated balloons and paclitaxel-eluting stents potentially associated with increased mortality - letter to health care providers | FDA. Available at: https://www.fda.gov/medical-devices/letters-health-care-providers/update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel-eluting. Accessed January 12, 2020.
20. PCR STATEMENT on clinical outcomes after interventions with paclitaxel drug-coated balloons. Available at: https://www.pcronline.com/News/PCR-Press-Releases/PCR-STATEMENT-on-clinical-outcomes-after-interventions-with-paclitaxel-drug-coated-balloons. Accessed January 12, 2020.
21. Recommendations from the independent Expert Advisory Group on the use of paclitaxel drug-coated balloons (DCBs) and drug-eluting stents (DESs) to the MHRA - GOV.UK. Availableat: https://www.gov.uk/government/publications/recommendations-from-the-independent-expert-advisory-group-on-the-use-of-paclitaxel-drug-coated-balloons-dcbs-and-drug-eluting-stents-dess-to-the. Accessed January 12, 2020.
22. Start - SWEDEPAD. Available at: https://www.ucr.uu.se/swedepad. Accessed January 12, 2020.
23. Pause Recruitment - University of Birmingham. Available at: https://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/portfolio-v/Basil-3/Recruitment-Pause.aspx. Accessed January 12, 2020.
24. FDA Executive summary circulatory system devices panel meeting June 19 and 20, 2019. Available at: https://www.fda.gov/media/127698/download. Accessed January 12, 2020.
25. August 7, 2019 UPDATE: Treatment of peripheral arterial disease with paclitaxel-coated balloons and paclitaxel-eluting stents potentially associated with increased mortality | FDA. Available at: https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel. Accessed January 12, 2020.
26. Ng VG, Mena C, Pietras C, Lansky AJ. Local delivery of paclitaxel in the treatment of peripheral arterial disease. Eur J Clin Invest 2015;45:333–45. [PubMed: 25615282]

27. Package insert: TAXOL (paclitaxel) injection. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf. Accessed January 12, 2020.
28. Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med 2015;373:145–53. [PubMed: 26106946]
29. Gray WA, Keirse K, Soga Y, Benko A, Babaev A, Yokoi Y, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. Lancet 2018;392:1541–51. [PubMed: 30262332]
30. Laird JA, Schneider PA, Jaff MR, Brodmann M, Zeller T, Metzger DC, et al. Long-term clinical effectiveness of a drug-coated balloon for the treatment of femoropopliteal lesions: five-year outcomes from the IN.PACT SFA randomized trial. Circ Cardiovasc Interv 2019;12:1–10.
31. Katsanos K New insights from our meta-analysis of oaclitaxel-coated device randomized trials for SFA disease (and the response it has generated). In: Transcatheter Therapeutics. San Francisco, CA; 2019. Available at: https://www.tctmd.com/slide/new-insights-our-meta-analysis-paclitaxel-coated-device-randomized-trials-sfa-disease-and32. Accessed January 12, 2020.
32. Rocha-Singh KJ, Duval S, Jaff MR, Schneider PA, Ansel GM, Lyden SP, et al. Mortality and Paclitaxel-Coated Devices: An Individual Patient Data Meta-Analysis. Circulation 2020;141:1859–69. [PubMed: 32370548]
33. Albrecht T, Schnorr B, Kutschera M, Waliszewski MW. Two-year mortality after angioplasty of the femoro-popliteal artery with uncoated balloons and paclitaxel-coated balloons - a pooled analysis of four randomized controlled multi-center trials. Cardiovasc Intervent Radiol 2019;42:949–55. [PubMed: 30843092]
34. Dake MD, Ansel GM, Bosiers M, Holden A, Iida O, Jaff MR, et al. Paclitaxel-coated Zilver PTX drug-eluting stent treatment does not result in increased long-term all-cause mortality compared to uncoated devices. Cardiovasc Intervent Radiol 2020;43:8–19. [PubMed: 31502026]
35. Gray WA, Jaff MR, Parikh SA, Ansel GM, Brodmann M, Krishnan P, et al. Mortality assessment of paclitaxel-coated balloons: patient-level meta-analysis of the ILLUMENATE clinical program at 3 years. Circulation 2019;140:1145–55. [PubMed: 31567024]
36. Ouriel K, Adelman MA, Rosenfield K, Scheinert D, Brodmann M, Peña C, et al. Safety of paclitaxel-coated balloon angioplasty for femoropopliteal peripheral artery disease. JACC Cardiovasc Interv 2019;12:2515–24. [PubMed: 31575518]
37. Schneider PA, Laird JR, Doros G, Gao Q, Ansel G, Brodmann M, et al. Mortality not correlated with paclitaxel exposure: an independent patient-level meta-analysis of a drug-coated balloon. J Am Coll Cardiol 2019;73:2550–63. [PubMed: 30690141]
38. Secemsky EA, Kundi H, Weinberg I, Jaff MR, Krawisz A, Parikh SA, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. JAMA Cardiol 2019;4:332–40. [PubMed: 30747949]
39. Secemsky EA, Kundi H, Weinberg I, Schermerhorn M, Beckman JA, Parikh SA, et al. Drug-eluting stent implantation and long-term survival following peripheral artery revascularization. J Am Coll Cardiol 2019;73:2636–8. [PubMed: 30831175]
40. Secemsky EA. Medicare Beneficiary presentation. In: Circulatory System Devices Panel Meeting. Gaithersburg, MD: United States Food and Drug Administration, Department of Health and Human Services; 2019.
41. Yeh R Optum presentation. In: Circulatory System Devices Panel Meeting. Gaithersburg, MD: United States Food and Drug Administration, Department of Health and Human Services; 2019.
42. Bertges DJ, Sedrakyan A, Schermerhorn ML, Eslami MH, Goodney PP, Beck AW, et al. RS01. Mortality after paclitaxel-coated balloon angioplasty and stenting of superficial femoral and popliteal artery. J Vasc Surg 2019;69:e98–9.
43. Freisinger E, Koeppe J, Gerss J, Goerlich D, Malyar NM, Marschall U, et al. Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis. Eur Heart J 2019;49:1–8.

44. Behrendt CA, Sedrakyan A, Peters F, Kreutzburg T, Schermerhorn M, Bertges DJ, et al. Long term survival after femoropopliteal artery revascularisation with paclitaxel coated devices: a propensity score matched cohort analysis. Eur J Vasc Endovasc Surg 2020;59:587–96. [PubMed: 31926836]
45. Katsuki T, Takahara M, Soga Y, Okamoto S, Iida O, Fujihara M, et al. Mortality risk following application of a paclitaxel-coated stent in femoropopliteal lesions. J Endovasc Ther 2019;26:593–9. [PubMed: 31431154]
46. Liistro F 6-year comparison of mortality and its causes in 1500 patients treated with paclitaxel coated DCBs or DESs versus bare metal stents (BMSs) or plain old balloon angioplasty (POBA). Presented at the 2019 VEITHsymposium 2 23–27, 2019. New York, NY.
47. Donas KP, Sohr A, Pitoulias GA, Alfonso F, Torsello G. Long-term mortality of matched patients with intermittent claudication treated by high-dose paclitaxel-coated balloon versus plain balloon angioplasty: a real-world study. Cardiovasc Intervent Radiol 2020;43:2–7.
48. Hill AB. The environment and disease: association or causation? J R Soc Med 1965;58:295–300.
49. Brodmann M, Werner M, Meyer DR, Reimer P, Krüger K, Granada JF, et al. Sustainable antirestenosis effect with a low-dose drug-coated balloon: the ILLUMENATE European randomized clinical trial 2-year results. JACC Cardiovasc Interv 2018;11:2357–64. [PubMed: 30522663]
50. Iida O, Soga Y, Urasawa K, Saito S, Jaff MR, Wang H, et al. Drug-coated balloon versus uncoated percutaneous transluminal angioplasty for the treatment of atherosclerotic lesions in the superficial femoral and proximal popliteal artery: 2-year results of the MDT-2113 SFA Japan randomized trial. Catheter Cardiovasc Interv 2019;93:664–72. [PubMed: 30747489]
51. FDA Day One Presentation. Paclitaxel-Coated Drug-Coated Balloon (DCB) and Drug-Eluting Stent (DES) Late Mortality Panel. Gaithersburg, MD: United States Food and Drug Administration, Department of Health and Human Services; 2019.
52. Mauri L Medtronic Presentation. In: Circulatory System Devices Panel Meeting. Gaithersburg, MD: United States Food and Drug Administration, Department of Health and Human Services; 2019.
53. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Paraskevopoulos I, Karnabatidis D. Risk of death and amputation with use of paclitaxel-coated balloons in the infrapopliteal arteries for treatment of critical limb ischemia: a systematic review and meta-analysis of randomized controlled trials. J Vasc Interv Radiol 2020;31:202–12. [PubMed: 31954604]
54. Schneider PA, Varcoe RL. Re: Risk of death and amputation with use of paclitaxel-coated balloons in the infrapopliteal arteries for treatment of critical limb ischemia: a systematic review and meta-analysis of randomized controlled trials. J Vasc Interv Radiol 2020;31:1030–2. [PubMed: 32376180]

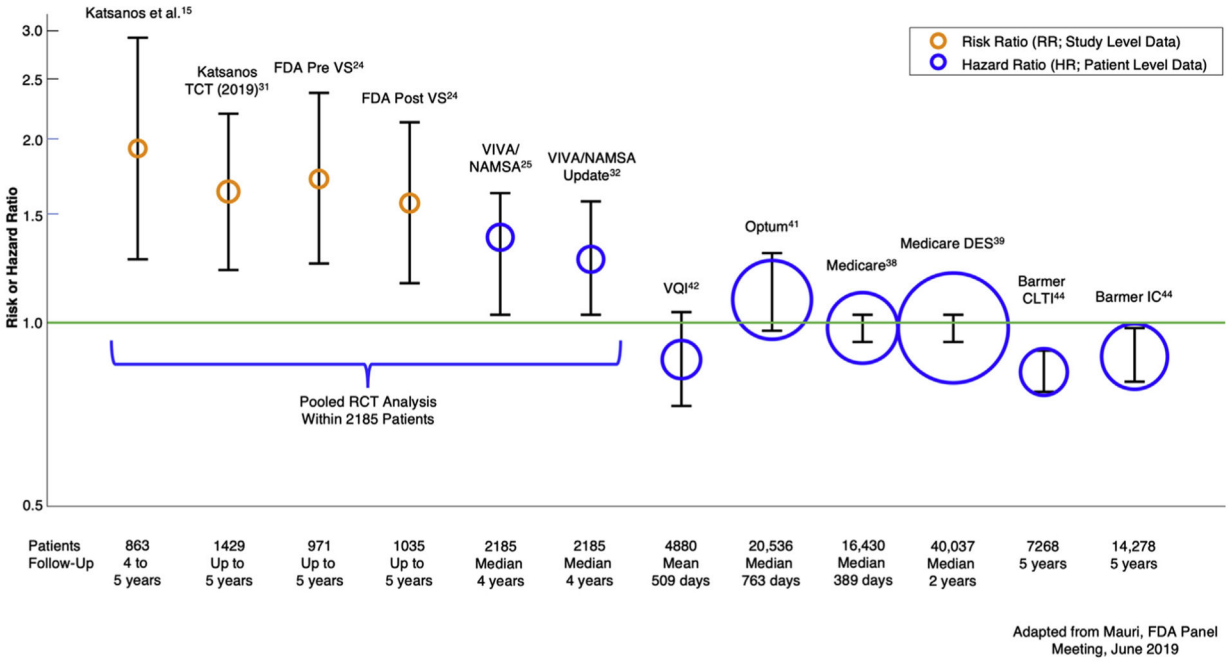

Fig 1.

Risk ratio (*RR*) or hazard ratio (*HR*) from meta-analyses of randomized controlled trial (RCT) meta and insurance databases. Data presented as RR (*orange circles*) or HR (*blue circles*). *Circle diameters* are proportional to the number of patients. *Bars* represent 95% confidence intervals (CIs). *CLTI*, chronic limb-threatening ischemia; *DES*, drug eluting stent; *IC*, intermittent claudication; *FDA*, U.S. Food and Drug Administration; *NAMSA*, North America Science Associates, Inc.; *TCT*, transcatheter therapeutics; *VIVA*, Vascular Interventional Advances; *VQI*, Vascular Quality Initiative; *VS*, vital status.

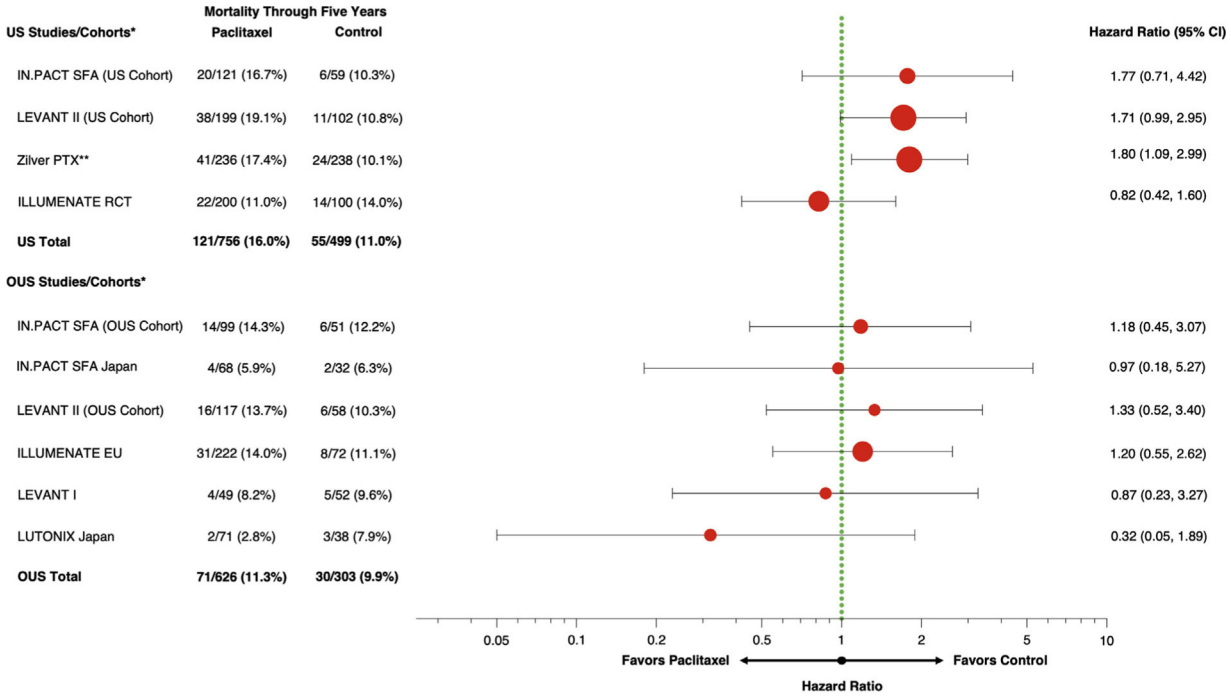

Fig 2.

All-cause mortality and hazard ratios (HRs) in patients by geographic region in patients treated with paclitaxel-coated devices (PCDs) and uncoated (control) devices. *Data for each randomized controlled trial (RCT) is updated to the extent that it is publicly available. Sources include: Rocha-Singh[32]; U.S. Food and Drug Administration (FDA) panel presentation[24]; Ouriel et al[36] (published combined results; in the United States [US] vs outside the United States [OUS] cohort provided to authors as a separate analysis). **The Zilver PTX HR of 1.80 as presented at the FDA panel in June 2019 is substantially higher than a recent published correction of “modified as-treated” patients whose mortality was calculated after the patients were categorized as to whether or not they received paclitaxel in the Zilver PTA Trial.[34] *CI*, Confidence interval.

Table I.

Paclitaxel-containing devices approved by the U.S. Food and Drug Administration (FDA) for treating femoropopliteal lesions[24]

Device name	Platform	Nominal dose, μg/mm^2	Potential dose range, mg	Lengths, mm	Diameters, mm
Zilver PTX	Stent	3	0.2–1.3	40–140	5–8
LUTONIX 035	Balloon	2	1.0–9.7	40–220	4–7
IN.PACT Admiral	Balloon	3.5	1.1–17.0	20–250	4–7
Stellarex	Balloon	2	1.1–4.7	40–120	4–6
Eluvia	Stent	0.167	0.1–0.4	40–120	6–7

Table II.

Pivotal randomized controlled trials (RCTs) of paclitaxel-coated devices (PCDs) for the treatment of femoropopliteal lesions

Device	Study name reference	Patient allocation in study arms	Primary effectiveness end point	Results
Zilver PTX DES	ZILVER PTX Dake et al (2011)[8]	DES (n = 241) BMS (n = 238)	Primary patency at 1 year	DES: 83.1% vs BMS: 32.8%; $P < .001$
IN.PACT Admiral DCB	IN.PACT SFA Tepe et al (2015)[7]	DCB (n = 220) PTA (n = 111)	Primary patency at 1 year	DCB 82.2% vs PTA 52.4%; $P < .001$
Lutonix DCB	LEVANT II Rosenfield et al (2015)[9]	DES (n = 316) BMS (n = 160)	Primary patency at 1 year	DCB 65.2% vs PTA 52.6%; $P = .02$
Stellarex DCB	ILLUMENATE Pivotal Krishnan et al (2017)[10]	DES (n = 200) BMS (n = 100)	Primary patency at 1 year	DCB 76.3% vs PTA 57.6%; $P = .02$
ELUVIA DES	IMPERIAL Gray et al (2018)[29]	ELUVIA DES (n = 309) Zilver PTX DES (n = 156)	Primary patency at 1 year (noninferiority design)	ELUVIA 86.8% vs Zilver PTX 81.5%; $P < .0001$

BMS, Bare metal stent; *DCB*, drug-coated balloon; *DES*, drug-eluting stent; *PTA*, percutaneous transluminal angioplasty.

Table III.

Summary of cumulative data analysis of long-term all-cause mortality of individual randomized, controlled trials (*RCTs*)

Authors, data source	Devices compared	No. of patients	Time of follow-up	Mortality difference
Dake (2020)[34] Zilver PTX RCT and Japan post-market registry	Zilver PTX DES PTA and/or BMS	336 (RCT) 904 (Japan) 143 (RCT) 190 (Japan)	5 years (RCT) 3 years (Japan)	No difference RCT (19.1% DES vs 17.1% PTA/BMS; *P* = .60) Japan (15.8% DES vs 15.3% BMS; *P* = .89).
Gray et al (2019)[35] Combined Stellerex trial data	Stellerex DCB PTA	419 170	3 years	No difference Unadjusted cumulative incidence: 8.4% DCB vs 8.8% PTA; HR, 1.18; 95% CI, 0.75–1.87; *P* = .47
Ouriel et al (2019)[36] Combined Lutonix trial data	Lutonix DCB PTA	1078 212	5 years	No difference Cumulative incidence 14.0% DCB vs 10.4% PTA; *P* = .186 HR, 1.01; 95% CI, 0.68–1.52; *P* = .95
Schneider et al (2019)[37] Combined IN.PACT trial data	IN.PACT DCB PTA	1837 143	5 years	No difference Unadjusted K-M cumulative incidence 15.1% DCB vs 11.2% PTA; *P* = .092 Adjusted K-M cumulative standard cohort (patients with who met pivotal trial enrollment criteria; DCB = 712 and PTA = 143) 13.2% DCB vs 11.0% PTA; *P* = .188.

BMS, Bare metal stent; *CI*, confidence interval; *DCB*, drug-coated balloon; *DES*, drug-eluting stent; *HR*, hazard ratio; *PTA*, percutaneous transluminal angioplasty.

Table IV.

Randomized trials of paclitaxel-coated devices (PCDs) that have not yet been published

Study	No.	Status	Estimated completion	Clinical Trial Identifier
Independent (n = 7350)				
Femoropopliteal				
ZILVERPASS	220	Enrollment complete	December 2019: 2-year follow-up	NCT01952457
HEROES-DCB	250	Currently enrolling	April 2019:1-year follow-up	NCT02812966
DCB-SFA	1080	Currently enrolling	June 2021: 2-year follow-up	NCT02648334
BEST-SFA	120	Currently enrolling	September 2021: 2-year follow-up	NCT03776799
Pittsburgh CLI DCB	50	Currently enrolling	December 2020:1-year follow-up	NCT02758847
Compare I	414	Enrollment complete	October 2020: 2-year follow-up	NCT02701543
TRANSCEND	446	Currently enrolling	April 2024: 5-year follow-up	NCT03241459
BASIL-3	861	Currently enrolling	December 2024: 5-year follow-up	ISRCTN14469736
Infrainguinal				
SWEDEPAD	3800	Currently enrolling	June 2021: 5-year follow-up	NCT02051088
BEST-CLI	2100	Currently enrolling	December 2019: 5-year follow-up	NCT02060630
Below the knee				
DCB vs PTA in CLI and Crural arteries	70	Currently enrolling	June 2019:1-year follow-up	NCT02750605
Arteriovenous access				
DEB in AVG	33	Enrollment complete	December 2018:1-year follow-up	NCT03388892
DCB for AVG restenosis	40	Currently enrolling	December 2019: 3-month follow-up	NCT03360279
Industry sponsored (n = 2768)				
Femoropopliteal				
RANGER II SFA	388	Enrollment complete	August 2023: 5-year follow-up	NCT03064126
IMPERIAL	524	Enrollment complete	March 2022: 5-year follow-up	NCT02574481
The Chocolate Touch Study	585	Currently enrolling	December 2026: 2-year follow-up	NCT02924857
EMINENT	750	Currently enrolling	December 2022: 3-year follow-up	NCT02921230
BIOPACT-RCT	302	Not yet enrolling	June 2021:1-year follow-up	NCT03884257
Italy DEB vs Nitinol stents	84	Enrollment complete	December 2018:1-year follow-up	NCT02212470
ILLUMENATE US	300	Enrollment complete	July 2020: 5-year follow-up	NCT01858428
ILLUMENATE EU	501	Enrollment complete	November 2018: 3-year follow-up	NCT01927068

Study	No.	Status	Estimated completion	Clinical Trial Identifier
DISRUPT PAD III	400	Currently enrolling	December 2021: 2-year follow-up	NCT02923193
Below the knee				
DES BTK SAVAL	201	Currently enrolling	May 2024: 3-year follow-up	NCT03551496
RANGER-BTK	30	Enrollment complete	November 2018:1-year follow-up	NCT02856230
Lutonix BTK	442	Enrollment complete	June 2020: 3-year follow-up	NCT01870401
ILLUMENATE BTK	354	Currently enrolling	April 2024: 3-year follow-up	NCT03175744
IN.PACT BTK	60	Enrollment complete	December 2020: 3-year follow-up	NCT02963649
Arteriovenous access				
ABISS AV DCB	150	Currently enrolling	December 2019:1.5 year follow-up	NCT02753998
IN.PACT AV Access	330	Enrollment complete	June 2023: 5-year follow-up	NCT03041467