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EDITORIAL

# Paclitaxel-Coated Devices: Safety and Efficacy Are in the PVI of the Beholder

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Since Charles Dotter and Melvin Judkins performed the first angioplasty in the superficial femoral artery >55 years ago, endovascular techniques have advanced dramatically, but remain plagued by associated vascular injury and consequent restenosis. Breakthroughs in balloon- or stent-based drug delivery now permit the application of antirestenotic therapy, most often with the antiproliferative drug paclitaxel, directly to the treated arterial segment at the time of percutaneous vascular intervention (PVI). This technology was initially embraced in clinical practice given that the use of paclitaxel-coated devices (PCDs) resulted in marked reduction of restenosis: paclitaxel drug-eluting stents (DESs) have been shown to reduce the relative risk of restenosis or target lesion revascularization by 40% at 5 years; and paclitaxel drug-coated balloon (DCB) therapies may improve primary patency rates to 69.5% at 3 years, compared with 45.1% with conventional, non–drug-coated treatment.[1,2] Along with the widespread clinical application of PCDs to achieve durable outcomes in PVI, societal guidelines recommend PCDs for the treatment of femoropopliteal stenosis.[3,4]

See Article by Gutierrez et al.

## CANARY IN THE COAL MINE AND META-ANALYSIS DATA

In December 2018, however, the safety of PCDs was called to question when a meta-analysis identified excess late mortality associated with PCDs in 28 randomized controlled trials (RCTs) involving 4663 patients. At 1 year, all-cause mortality was indistinguishable between the 2 groups (2.3% with PCDs versus 2.3% with control). At 2 years, however, all-cause mortality was significantly higher (7.2% versus 3.8%) in PCD-treated patients (hazard ratio [HR] 1.68; 95% CI, 1.15–2.47); and at 5 years, excess all-cause mortality was even greater in the PCD cohort (14.7% versus 8.1%; HR, 1.93; 95% CI, 1.27–2.93), with a number needed to harm of 14 patients. Although the precise mechanism of device toxicity was not elucidated by the meta-analysis, a proposed dose-response between paclitaxel exposure and mortality was identified, with 0.4±0.1% excess mortality per paclitaxel mg/y exposure ($P<0.001$).[5]

The alarm raised by this single meta-analysis has had dramatic and lasting repercussions in the clinical arena, although there has also been significant skepticism among interventional thought leaders about the validity of the study's findings. At its core, the lingering unanswered question is: are PCDs truly causal for the increased late mortality reported by Katsanos et al,[5] or is this merely an association brought about by statistical, confounding, or other factors? On the basis of heterogeneous, aggregate (not patient-level) data from 28 RCTs, the meta-analysis could not provide a plausible mechanism to explain the late mortality signal, particularly because paclitaxel has been used for decades as a highly efficacious chemotherapeutic agent at orders of magnitude higher doses, without a previously recognized mortality signal. In addition, methodologic concerns challenge the validity of the study's findings. The RCTs were designed to assess efficacy end points, but not mortality end points, and

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aggregate data were therefore represented in an intention-to-treat, not as-treated, manner. Significant subject crossover within the many included studies obscures the potential for any firm conclusions about causality between PCD use and mortality. Likewise, many patients in the RCTs were lost to follow-up: at 1 year, data from 28 RCTs and 4663 patients were available; at 2 years, there were 12 RCTs and 2316 patients; at 5 years, only 3 RCTs and 863 patients remained, and the excess mortality of PCDs was only identified at 2 and 5 years, with winnowing, and perhaps confounded, patient populations for evaluation.

The concern for PCD-associated late mortality prompted the Food and Drug Administration to act swiftly, convening an emergency advisory panel and halting ongoing clinical investigations of PCD therapies, including the BASIL-3 (Balloon Versus Stenting in Severe Ischaemia of the Leg-3) and the SWEDEPAD (Swedish Drug-Elution Trial in Peripheral Arterial Disease) clinical trials. Much attention has been given to the potential inadequacies of trial-level versus patient-level data, a relevant critique of the meta-analysis by Katsanos et al.[5] As a result, the Vascular InterVentional Advances Physicians research group obtained patient-level data from device manufacturers for 8 RCTs involving 2185 subjects, and conducted a meta-analysis of as-treated rather than intention-to-treat outcomes, further enhancing the fidelity of the findings compared with the meta-analysis by Katsanos et al.[5] The Vascular InterVentional Advances Physicians meta-analysis corroborated the presence of a 38% increase in relative risk for all-cause mortality associated with PCDs at 5 years.[6] As a result, in 2019, the Food and Drug Administration published a Letter to Health Care Providers recommending, in essence, that physicians reserve the use of PCDs for procedures at highest risk of restenosis, and that they discuss with their patients the potential risk of increased mortality associated with PCDs when considering treatment options.[7]

Since the initial publication of the meta-analysis by Katsanos et al,[5] there has remained considerable uncertainty about the safety of PCDs, and an unmet need for clinician guidance. Virtually all subsequent evaluations of industry-sponsored clinical programs and real-world outcomes from nationwide data sets have not demonstrated excess mortality with PCDs. Reviewing these data provides context for the current state of knowledge, and informs perspective on the importance of the article by Gutierrez et al in this issue of the *Journal of the American Heart Association* (*JAHA*).[8]

## PCD MORTALITY IN INDUSTRY-SPONSORED PROGRAMS

In 4 separate clinical programs with intermediate to long-term follow-up, akin to that seen in the meta-analysis by Katsanos et al,[5] independent evaluation of patient-level data did not demonstrate excess mortality with PCDs.

Ouriel et al examined all-cause mortality in the 3 RCTs involving the Lutonix DCB. Among 1093 patients treated with DCB and 250 treated with uncoated balloon percutaneous transluminal angioplasty (PTA), the 5-year all-cause mortality HR was 1.01 (95% CI, 0.68–1.52).[9]

Data from the IN.PACT Admiral DCB clinical program (2 RCTs and 2 single-arm studies) were pooled, with 1837 patients treated with DCB and 143 treated with PTA. There was no dose-dependent harm associated with low-, mid-, or high-dose terciles of paclitaxel. All-cause adjusted mortality at 5 years was 13.2% for DCB and 11.0% for PTA ($P$=0.188).[10]

Data from the Stellarex low-dose paclitaxel DCB platform included 2 RCTs, with 419 patients treated with DCB and 170 patients treated with PTA. Three-year all-cause mortality was 8.4% in the DCB cohort and 8.8% in the PTA cohort ($P$=0.86).[11]

Patient-level data from the Zilver PTX paclitaxel DES program included 336 patients treated with DESs and 143 patients in control cohorts. The 5-year all-cause mortality with DESs (19.1%) was not statistically different from control (17.1%; $P$=0.60).[12]

## NATIONAL DATA SET ANALYSES OF PCD MORTALITY

Several studies have examined the association of PCDs with all-cause mortality in retrospective cohort studies using real-world outcomes from national data registries.

Using the Centers for Medicare and Medicaid Services nationwide data set, Secemsky and colleagues[13] examined the outcomes of 16 560 patients who underwent femoropopliteal PVI in 2016. At a median follow-up of 389 days, of the 5989 patients (36.2%) treated with PCDs, unadjusted all-cause mortality was lower (32.5%) compared with patients who underwent PVI with non-PCDs (34.3%; $P$=0.007). Following multivariable adjustment, the all-cause mortality was not different between the groups (HR, 0.97; 95% CI, 0.91–1.04; $P$=0.43), a finding that was consistently demonstrated when considering patients treated with DCB alone, patients treated with DES alone or in combination with DCB, and patients in whom critical limb ischemia was present.[13] Concerns with this assessment included that the use of administrative codes to identify patient characteristics and treatment is inevitably heterogeneous and may include unmeasurable confounding variables; the patient population treated in the database was entirely inpatients; there was an exceptionally high burden of critical limb ischemia (51%) in the

Centers for Medicare and Medicaid Services data set, which is associated with such high mortality that any modest impact of PCD-associated mortality may be overwhelmed by other clinical factors; and the Centers for Medicare and Medicaid Services evaluation had median follow-up of 389 days, which was shorter than the 2- and 5-year time points, where excess all-cause mortality was identified in the meta-analysis by Katsanos et al.[14]

Another analysis of the Centers for Medicare and Medicaid Services data set included femoropopliteal PVI in outpatient and inpatient settings from 2015 to 2016. Of the 83 225 patients identified, DCB was used in 29% of PVI, with lower adjusted 1-year all-cause mortality compared with non-DCB PVI (HR, 0.89; 95% CI, 0.84–0.94; $P<0.001$).[15]

An evaluation of the Optum Database of 16 976 Medicare Advantage insured patients treated with femoropopliteal PVI between April 2015 and December 2017 found no significant difference between all-cause mortality of the 26.4% treated with PCDs compared with 73.6% treated with non-PCDs (adjusted HR, 1.03; 95% CI, 0.96–1.10; $P=0.39$) at median follow-up of 2.66 years.[16]

In the German nationwide BARMER health insurance program, 64 771 patients were identified who underwent femoropopliteal PVI from 2007 to 2015, with no statistically significant difference in all-cause mortality between PCD PVI and those treated with non-PCDs at exceptionally long median follow-up of 7.6 years.[17]

## CLINICAL TRIAL INTERIM AND SUBGROUP ANALYSES FOR PCD SAFETY

Immediately following the publication of the concerning meta-analysis by Katsanos et al,[5] the SWEDEPAD and BASIL-3 clinical trials were halted. An unplanned interim analysis of all-cause mortality in the SWEDEPAD clinical trial was conducted, and the findings were recently published. In this multicenter, randomized, open-label registry study, 2289 patients had been enrolled, with 1149 receiving PCDs. At a median follow-up of 2.49 years, all-cause mortality was 25.5% in the PCD cohort and 24.6% in the non-PCD cohort (HR, 1.06; 95% CI, 0.92–1.22). There was also no statistically significant difference between the 2 cohorts when stratified by claudication or critical limb ischemia clinical status.[18]

A subgroup analysis of the efficacy and safety of rivaroxaban in reducing the risk of major thrombotic vascular events in subjects with symptomatic peripheral artery disease undergoing peripheral revascularization procedures of the lower extremities (VOYAGER PAD) clinical trial, evaluating PCD all-cause mortality, was recently presented at the Transcatheter Cardiovascular Therapeutics Connect 2020 conference. VOYAGER PAD was an RCT examining the impact of rivaroxaban (2.5 mg twice daily) versus placebo in 6564 patients undergoing peripheral revascularization.[19] In the subgroup analysis, Hess and colleagues examined the impact of PCDs on all-cause mortality in the 4379 patients in the study who were treated with PVI, of whom 1358 (31%) were treated with PCDs. The weighted all-cause mortality at 42 months was 12.1% in the PCD-treated cohort and 12.6% in the non-PCD cohort (HR, 0.95; 95% CI, 0.83–1.09; $P=0.49$). In a rigorous, adjudicated RCT with 99.6% ascertainment of vital status, there was no indication of excess mortality with PCD use compared with non-PCD treatment of PVI.[20]

## VETERANS' HEALTH ADMINISTRATION DATA REVIEWED FOR PCD MORTALITY

In this issue of *JAHA*, Gutierrez et al[8] present an observational retrospective cohort study from the Veterans Administration Corporate Data Warehouse, adding to the growing body of support from real-world assessment of large data sets that do not disclose an increase in mortality associated with PCDs. Using *International Classification of Diseases, Tenth Revision* (*ICD-10*), coding and Current Procedural Terminology and Healthcare Common Procedure Coding systems, 10 505 Veterans Administration–based patients were identified who underwent femoropopliteal PVI from October 1, 2015, to June 30, 2019. Of this cohort, 2265 patients (21.6%) underwent PCD-based PVI, whereas 8240 patients (78.4%) were treated with a non-PCD PVI. Atherectomy was performed more often in PCD (26.8%) versus non-PCD (20.4%) procedures, raising the question whether within this nonrandomized population, patients treated with PCDs may have had more complex, severe, diffuse underlying PAD. Moreover, patients treated with PCDs had a higher rate of current tobacco use, valvular heart disease, and a critical limb ischemia presentation, suggesting a higher clinical risk substrate in the PCD cohort. Despite this specter, the study found no significant difference in survival rates of PCD and non-PCD cohorts at 2 years (77.4% versus 79.7%) or at 3 years (70.7% versus 71.8%) with all-cause mortality (HR, 1.06; 95% CI, 0.95–1.18; $P=0.3013$). Access to patient-level data identified no difference in cause of death between PCD and non-PCD cohorts: cardiovascular (34.0% PCD versus 39.7% non-PCD; $P=0.28$); diabetes mellitus complications (13.0% PCD versus 13.5% non-PCD; $P>0.999$); malignancy

(11.8% PCD versus 11.0% non-PCD; *P*=0.78); infection (9.5% PCD versus 8.5% non-PCD; *P* = 0.78); as well as pulmonary, genitourinary, cerebrovascular, and gastrointestinal causes. The use of this Veterans Administration data set, which had no missing patient outcomes, and clearly characterized patient cause of death, adds considerable understanding to the debate about mortality associated with PCD-based PVI.

Notable limitations to this report include the fact that the study population was predominantly men (98.1%) and White individuals (73.5%), which may reduce the generalizability of the results. In addition, the primary results of this nonrandomized retrospective cohort analysis may be confounded by unknown variations in baseline patient characteristics, but many measured factors, if anything, may have predisposed to worse outcomes in the PCD cohort.[8]

## CONCLUSIONS AND FUTURE DIRECTIONS

An extensive body of literature supports the use of PCD therapy for improved patency in femoropopliteal PVI. The findings of excess 2- and 5-year all-cause mortality associated with PCD use in the meta-analysis by Katsanos et al[5] have raised significant and appropriate concern in the interventional community, and have prompted a rapid and diligent call-to-arms evaluation of the findings. Such investigation must clarify the veracity of a truly causal relationship versus simple association, and provide guidance for PVI operators and patients alike. Since that time, the preponderance of data collected from patient-level evaluation of industry clinical studies, retrospective analysis of administrative databases, subgroup analyses of clinical trials, and interim analysis of an ongoing randomized controlled open-label trial of PCDs have all demonstrated no excess death associated with PCD use in femoropopliteal lower-extremity intervention. The study by Gutierez and colleagues in this issue of *JAHA* advances our understanding by including a rigorous data set with complete and long-term follow-up, and specific details about cause of death, with no clear indication of causality or of a probable mechanism of PCD-associated mortality.

For now, the guidance from the Food and Drug Administration remains clear: reserve use of PCDs for anatomic and clinical situations where their efficacy may be most advantageous and where their risk is lowest, while participating in shared, individualized consideration of risk and benefit with our patients. With a growing body of data, including randomized controlled assessments on the horizon, our understanding of the safety and efficacy of PCDs continues to evolve, as will our optimal interventional strategies for the care of patients with symptomatic lower-extremity peripheral artery disease.

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### Disclosures

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