

## Is Paclitaxel Causing Mortality During Lower-Extremity Revascularization?

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Drug-coated devices for treatment of lower-extremity peripheral artery disease have been used worldwide for nearly a decade. Before their debut, endovascular treatment options for peripheral artery disease revascularization were limited to conventional balloon angioplasty and bare-metal stenting, both associated with high rates of restenosis, recoil, and vessel closure, yielding primary patency rates of only 30% to 70% by 1 year.<sup>1,2</sup> Vascular specialists quickly embraced drug-coated devices when early trial data revealed 1-year primary patency rates in the range of 70% to 90%.<sup>3–6</sup> In addition, the use of drug-coated balloons (DCBs) avoided the need for a permanent metal scaffold in lower-extremity vessels, where high degrees of shear stress, torsion, and flexion exist. Experts considered the technology to be a significant breakthrough in the field, not only for potentially improving patient outcomes, but also for being cost-effective.<sup>7</sup>

Hence, the surprising results presented in the recent systematic review and meta-analysis by Katsanos et al, published in the *Journal of the American Heart Association (JAHA)*,<sup>8</sup> have led some to have a clinical pause. The analysis was performed with a primary safety measure of all-cause mortality across 28 randomized controlled trials (RCTs), including 4432 cases of drug-coated device use in the femoropopliteal artery of the lower limbs. The increased risk of late death after application of paclitaxel in these vessels was found to be alarmingly high, and the number needed to harm at 5 years was only 14 patients.

In the current Viewpoint, we explore the scientific data behind paclitaxel-coated devices in the context of recent mortality concerns. We also discuss newly generated patient-level analyses and preclinical animal data on potential mechanisms of paclitaxel toxicity to address whether there

is true causation or simply a correlation. Finally, we provide a perspective on use of drug-coated devices and how to apply the results to clinical practice and patient-centered decision making.

### Efficacy and Safety in Early Drug-Coated Device Trials

The Zilver PTX drug-eluting stent (DES) (Cook Medical, Bloomington, IN) was the first paclitaxel-coated device to gain US Food and Drug Administration (FDA) approval in 2012. The stent is directly coated with crystalline paclitaxel at a concentration of 3  $\mu\text{g}/\text{mm}^2$  without any polymer, binder, or excipient. The 12-month Zilver PTX study<sup>3</sup> randomized 474 patients with predominantly claudication and femoropopliteal disease to the DES (n=236) or standard percutaneous transluminal angioplasty (PTA) (n=238). Nearly half of the patients in the PTA group underwent a second randomization because of PTA failure to provisional DES (n=61) or bare-metal stenting (n=59). The primary end points included a safety and efficacy measure, defined as the rate of event-free survival and patency. Twelve-month event-free survival and primary patency were significantly higher in the primary DES group compared with the PTA group (90.4% versus 82.6% [ $P<0.001$ ] and 83.1% versus 32.8% [ $P<0.001$ ], respectively).<sup>3</sup> Five-year follow-up of the Zilver PTX randomized trial was published in 2016 and concluded that the initial results were sustained through this extended follow-up period.<sup>9</sup> The authors maintain this position despite recently correcting an article error that inadvertently reversed the all-cause mortality rates between the 2 groups. The accurate all-cause mortality rates at 5 years were significantly higher at 16.9% in the primary DES group compared with 10.2% in the PTA group ( $P=0.03$ ).<sup>9</sup> Exact causes of death were not discussed at that time, although none was adjudicated to be device or procedure related.

Initial DCBs gained FDA approval in 2014 (Lutonix; C.R. Bard, Tempe, AZ) and 2015 (IN.PACT Admiral; Medtronic, Santa Rosa, CA). The Lutonix DCB is semicompliant, is coated with paclitaxel at 2  $\mu\text{g}/\text{mm}^2$ , and contains excipients (polysorbate and sorbitol) to control drug release and tissue deposition. The IN.PACT DCB is coated with paclitaxel at 3.5  $\mu\text{g}/\text{mm}^2$  and has an excipient that allows for the

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antiproliferative drug to remain in the vessel at the treatment site for up to 180 days.<sup>10</sup>

LEVANT (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) 2 randomized 476 patients with claudication or rest leg pain with femoropopliteal disease in a 2:1 manner to the Lutonix DCB versus plain balloon angioplasty.<sup>4</sup> The primary efficacy end point was primary patency of the target lesion at 12 months (defined as freedom from binary restenosis or from the need for target-lesion revascularization). Safety end points were secondary and included freedom from perioperative all-cause death and 12-month freedom from limb-related death, amputation, and reintervention. Primary patency was superior in the Lutonix DCB group compared with the conventional angioplasty group (65.2% versus 52.6%;  $P=0.02$ ), and for the safety end points measured, there were no significant differences between devices. Continued benefits of patency and similar safety were reported with longer-term follow-up within the LEVANT 2 randomized trial and the Lutonix Global SFA (Superficial Femoral Artery) Registry.<sup>11</sup>

The initial IN.PACT SFA trial<sup>5</sup> randomized 331 patients with similar clinical presentations as in LEVANT 2. The randomization was also 2:1, yielding a final sample size analyzed of 207 patients in the DCB group and 107 patients in the PTA group. The primary end point was primary patency, defined as freedom from restenosis or clinically driven target lesion revascularization at 12 months. The IN.PACT DCB had significantly higher 12-month primary patency at 82.2% versus 52.4% for the standard PTA ( $P<0.001$ ). Safety events were reported and numerically low at 12 months. There were 4 deaths in the DCB group attributed to cerebral infarction, biliary sepsis, sudden death, and a perforated colon. The Clinical Events Committee did not determine that any safety issues were device or procedure related. Longer-term outcomes of the IN.PACT SFA trial to 2 years showed durable patency results of the DCB compared with the PTA.<sup>12</sup> All-cause mortality increased to 16 deaths in the DCB group and 1 death in the PTA group. The DCB deaths were again broad, affecting various organ systems, and were delayed in onset (median time, 565 days) relative to PTA (397 days). When followed out to 3 years, relative efficacy of the DCB was maintained; however, the mortality signal increased further, with 21 deaths in the DCB group and only 2 deaths in the PTA group.<sup>13</sup>

A more recent low-dose paclitaxel DCB (Stellarex DCB; Spectranetics Corp, Colorado Springs, CO) gained FDA approval in 2017. The Stellarex DCB is coated with paclitaxel at 2  $\mu\text{g}/\text{mm}^2$  and has a novel excipient, polyethylene glycol. The ILLUMENATE (Prospective, Randomized, Single-Blind, U.S. Multi-Center Study to Evaluate Treatment of Obstructive Superficial Femoral Artery or Popliteal Lesions With A Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon) pivotal trial<sup>6</sup> randomized 300 symptomatic patients

with femoropopliteal disease to DCB ( $n=200$ ) or conventional angioplasty ( $n=100$ ). Approximately half the patients enrolled were diabetics, were women, and had calcified disease. At 1 year, the primary patency by Kaplan-Meier estimates was 82.3% (DCB) versus 70.9% (PTA) ( $P=0.002$ ). The primary safety end point included freedom from device- or procedure-related death through 30 days, target limb major amputation, and clinically driven target lesion revascularization through 12 months and was superior for DCB versus PTA (92.1% versus 83.2%;  $P=0.025$ ). A pharmacokinetics evaluation within this study showed that detectable levels of circulating paclitaxel declined to low levels within the first hour of DCB deployment, from 54.4 to 1.4 ng/mL.<sup>6</sup> All-cause deaths were no different between groups: 5 of 192 patients (2.6%) in the DCB group and 2 of 96 patients (2.1%) in the PTA group. The 2-year data from the ILLUMENATE European RCT<sup>14</sup> likewise showed a sustained treatment effect and no statistical difference between all-cause mortality: 13 of 199 patients (6.5%) in the DCB group and 3 of 59 patients (5.1%) in the PTA group. No deaths were adjudicated as being device or procedure related.

## The Katsanos Meta-Analysis

Given clustering of late mortality in several of the RCTs with long-term follow-up, Katsanos et al performed an important systematic review and meta-analysis of the major paclitaxel-coated trials with a focus on all-cause mortality.<sup>8</sup> The number of RCTs evaluating paclitaxel-coated devices since the early FDA approval studies has grown steadily and involves use of the devices in various locations (above and below the knee) and in a range of clinical presentations, from intermittent claudication to critical limb ischemia. Several studies included in the meta-analysis by Katsanos et al<sup>8</sup> are multicenter, are global, and use PTA as the control arm. In total, 28 RCTs with 4663 patients were analyzed.

A careful examination of the demographics of the total patient population included in the meta-analysis is pertinent to review in the context of all-cause mortality. The average age ranged from 67 to 76 years, two thirds of patients were men, and the prevalence of diabetes mellitus ranged from 21% to 77%. In addition, there was a high incidence of smoking, hypertension, and hyperlipidemia across all studies.

All-cause death was no different between paclitaxel-coated devices and control at 1 year (2.3% versus 2.3% crude risk of death; risk ratio, 1.08; 95% CI, 0.72–1.61). At 2 years, the all-cause risk of death became significant, with higher risk in the paclitaxel group (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47). Finally, at 5 years, the all-cause risk of death in paclitaxel-treated patients was nearly doubled (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93). This resulted in a number needed to harm of only 14 patients.<sup>8</sup>

## Paclitaxel Biological Effects

There are no obvious biological mechanisms that explain a direct link between paclitaxel and mortality. Paclitaxel is a known cytotoxic agent that inhibits smooth muscle cell proliferation and neointimal hyperplasia through binding of microtubules and prevention of tubulin disassembly. The arrest of mitosis reduces vascular restenosis when applied locally, an effect well demonstrated historically in the coronary vasculature.

Paclitaxel doses on peripheral devices are an order of magnitude higher than what was used in relatively smaller coronary stents. Furthermore, when long lesions are involved in the femoropopliteal region, it is common for multiple paclitaxel-coated devices to be used, increasing patient exposure and dose. Interestingly, Katsanos et al performed a meta-regression of all-cause death against paclitaxel exposure and found a  $0.4 \pm 0.1\%$  excess risk of death for every paclitaxel milligram-year (95% CI, 0.1%–0.6%;  $P < 0.001$ ).<sup>8</sup>

Peripheral paclitaxel-coated devices vary in terms of paclitaxel dose per surface area, and some use proprietary excipients to allow for effective drug transfer. The excipients themselves can be involved in hypersensitivity reactions, although the mortality signal was also seen in studies of devices without excipients. Peripheral paclitaxel devices use the crystalline form of the cytotoxic drug, which aids in tissue uptake and retention. Despite these features, drug transfer remains inefficient and  $\approx 80\%$  to  $90\%$  of paclitaxel is lost in the systemic circulation. Animal studies have shown evidence of distal embolization to downstream vessels. Histopathological analysis has confirmed crystalline paclitaxel remnants and fibrinoid necrosis, particularly with DCBs over DES.<sup>15,16</sup> Paclitaxel transferred to the vessel wall may cause positive remodeling, arterial wall dilation, and medial wall necrosis.

The half-life of paclitaxel is generally in the range of months. The peak plasma concentration occurs soon after the procedure and is thought to be below the level known to cause systemic adverse effects.<sup>17</sup> For these reasons, one would hypothesize that any mortality linked directly to paclitaxel would occur sooner than the divergence in event rates seen at 2 years and beyond. The causes of deaths in the RCTs were also broad and included cardiovascular causes, infectious causes, pulmonary causes, and malignancy, among others. Establishing biological plausibility is difficult without a clear signal of one type of adverse event. Further mechanisms and markers of systemic inflammation should be considered.

## Considerations and Opportunities

Although the pooled mortality signal is concerning given the statistical power afforded by a meta-analysis, the overall results are subject to limitations of the imputed data from the

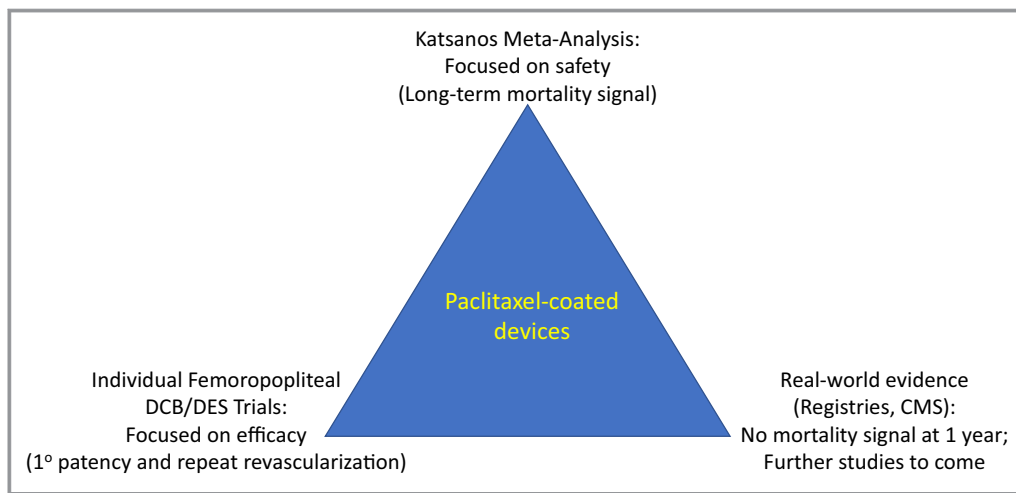
individual trials. The individual trials were not primarily designed to look at safety, but rather efficacy. As a result, analyses were performed on the basis of the intention-to-treat principle. Factoring in crossovers and now focusing on safety (all-cause mortality), it would be prudent to review and analyze the data when reclassified according to as-treated groups.

Another consideration is the number of patients who were lost to follow-up. Even in the setting of RCTs, several studies had a noteworthy number of patients who were lost, impacting the numerator and denominator when recording safety event rates and calculating frequencies. In the 5-year Zilver PTX data,<sup>9</sup> for example,  $\approx 20\%$  and  $17\%$  of the as-treated patients for DES and non-DES therapies, respectively, were lost during the study period. In the 5-year follow-up of THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries),<sup>18</sup>  $15\%$  and  $24\%$  of patients in the paclitaxel-coated balloon and control groups, respectively, were lost to follow-up, yielding a small sample size for final analysis. These 2 studies were the only 5-year follow-up RCTs available for inclusion in the meta-analysis. Although Katsanos and colleagues<sup>8</sup> conducted meticulous and complex statistical models, there can be skewed and biased results within a meta-analysis when the included studies have unbalanced groups, small numbers in the control arms, and low event rates, particularly with zero events or a single event in some groups. For hard end points, such as all-cause mortality, efforts to complete follow-up or use the social security death index database could assist in tracking accurate mortality rates.

Clinical event committees, when established, did not deem any deaths as device or procedure related. Adjudication of death is, of course, limited by not always knowing potential underlying mechanisms of systemic paclitaxel toxicities. Analyzing these data at the patient level would offer additional insights, particularly when trying to draw conclusions about drug dose and mortality.

## Emerging Data

New patient-level data are emerging rapidly and will take time to completely synthesize and review in an unbiased manner. Secemsky et al evaluated 16 560 Centers for Medicare and Medicaid Services beneficiaries admitted for femoropopliteal interventions and reported no differences in all-cause mortality between patients treated with drug-coated versus non-drug-coated devices.<sup>19</sup> However, there were important differences between this data set and the meta-analysis of Katsanos et al.<sup>8</sup> The former were inpatients, with most having critical limb ischemia, and the median follow-up time period was just over a year at 389 days (a time point at which even the meta-analysis of Katsanos et al<sup>8</sup> did not find a signal for mortality difference). Another Medicare analysis, by Long et al, with  $>83\,000$  all-treated patients (inpatients, outpatients, patients with critical



**Figure.** Paclitaxel-coated devices as the focus of various types of clinical outcome data. Initial randomized controlled trials of these devices were focused on efficacy end points and not powered for safety events. A safety alert signal from a recent systematic review and meta-analysis has led to analyses of larger registries and Centers for Medicare and Medicaid Services (CMS) data. Further studies at the patient level and with longer-term follow-up are pending. This highlights the future importance of capturing longitudinal clinical outcome data via a pragmatic approach. DCB indicates drug-coated balloon; DES, drug-eluting stent.

limb ischemia, and patients with claudication), showed that patients treated with drug-coated devices had lower mortality and amputation risk compared with those treated with non-coated devices.<sup>20</sup>

Schneider et al performed an independent patient-level meta-analysis of 1980 patients treated with DCB (n=1837) and standard PTA (n=143) from 4 independently adjudicated prospective studies, with most patients coming from IN.PACT Global (n=1230), a real-world, prospective, multicenter, single-arm study in which patients were more likely to have long lesions, chronic total occlusions, and in-stent restenosis.<sup>21</sup> There was no difference in all-cause mortality through 5 years (9.3% versus 11.2%;  $P=0.40$ ). In addition, time to survival by paclitaxel dose tercile was performed and showed no statistically significant difference in all-cause mortality between the 3 groups. This analysis is limited by the small number of control patients and variations in the setting and baseline characteristics of included patients.

## Summary and Future Investigations

The FDA has released a “Letter to Health Care Providers”<sup>22</sup> that recommends that providers use these devices only in the highest-risk patients and ensure close postprocedure follow-up. The recommendations also emphasize discussing risks and benefits with patients during the consent process. The concerns have already impacted clinical care and ongoing trials; the BASIL-3 (Balloon Versus Stenting in Severe Ischemia of the Leg-3) and SWEDEPAD (Swedish Drug-elution Trial in

Peripheral Arterial Disease) studies were immediately paused after the meta-analysis publication of Katsanos et al.<sup>8</sup> As confusion remains about the current safety of paclitaxel devices during lower-extremity revascularization procedures, it is important to convene stakeholders for open discussions as new data emerge. The Vascular Leaders Forum and the DCB Safety Town Hall meetings are important steps.

In the meantime, a reasonable approach toward patient care is to use caution and have straightforward conversations with patients. Perhaps the same as low as reasonably achievable concept used for radiation protection should be applied herein (essentially, to use the lowest dose of paclitaxel necessary to get an effective result). Simultaneously, research and development of nonpaclitaxel treatment strategies should continue. Sirolimus-eluting balloons, for example, are under development. When currently faced with patients who we think will benefit from the technology (long lesions, chronic total occlusions, or in-stent restenosis), we should use our best clinical judgement and be as transparent as possible with our patients, assessing each individual case’s risk and benefit.

Finally, the current example of drug-coated devices highlights the shortcoming of the vascular medicine field, specifically on the lack of consistent longitudinal clinical outcome data (Figure). Many patients with vascular disease get numerous touchpoints by multiple providers without ongoing clinical data capture. We must learn how to study devices in peripheral arterial disease effectively, pragmatically, and with adequate follow-up. This is the only path to ultimately making a safe decision for our patients.

## Disclosures

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