A Safety Update on Paclitaxel-Coated Devices for Peripheral Vascular Intervention

An overview of the controversy surrounding a late mortality signal associated with paclitaxel-coated devices and an exploration of new data regarding their safety.

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In December 2018, a meta-analysis by Katsanos et al revealed surprising findings: patients with femoropopliteal peripheral artery disease (PAD) treated with paclitaxel-coated devices (PCDs) had a higher mortality rate than those treated with non-PCDs at long-term follow-up.[1] This was unexpected, as PCDs promised to be a breakthrough intervention for patients with medication-refractory claudication and chronic limb-threatening ischemia (CLTI), with clinical trials demonstrating significantly lower rates of restenosis, target lesion revascularization (TLR), and late lumen loss in patients treated with PCDs compared to those treated with non-PCDs.[2-4] However, there are several major methodologic shortcomings of the Katsanos meta-analysis that rendered its findings controversial. In response, the FDA investigated the late mortality signal, including reanalyzing a portion of the data from the meta-analysis. The FDA was unable to reach a conclusion about the safety of PCDs due to significant missing data from the studies included in the meta-analysis, among other issues. Thus, the FDA emphasized the need for additional data to assess the safety of PCDs. Subsequently, patient-level meta-analyses, randomized controlled trials (RCTs), and large observational studies have been published that largely contradict the findings of the Katsanos meta-analysis. This article summarizes the controversy surrounding the late mortality signal associated with PCDs and the evidence to date regarding their safety.

A MORTALITY SIGNAL ASSOCIATED WITH PCDs

Revascularization is central to the management of medication-refractory claudication and CLTI. Endovascular revascularization is now considered the first-line modality of revascularization for patients with femoropopliteal lesions[5] as it offers patency rates comparable to those of surgical revascularization, with reduced rates of morbidity and mortality.[6] Unfortunately, high rates of restenosis (up to 40%-60% within 1 year) limit the impact of endovascular revascularization.[7]

The use of paclitaxel to produce PCDs was a significant innovation in endovascular therapy. Paclitaxel's properties, including its ability to inhibit the proliferation of vascular smooth muscle cells and its lipophilicity, produce a significant and durable reduction in restenosis.[8] PCDs are a breakthrough in the therapeutic options for patients with PAD. Multiple clinical trials have demonstrated the benefit of PCDs over non-PCDs in terms of rates of restenosis, TLR, and late lumen loss.[2-4] After introduction of PCDs into the market, their use skyrocketed relative to that of non-PCDs.[9]

Then, in 2018, Katsanos et al published a meta-analysis of summary-level data of 28 RCTs, which revealed a mortality signal associated with PCDs compared with non-PCDs at 2 and 5 years of patient follow-up.[1] Specifically, there was no increase in mortality associated with PCDs at 1 year but a 68% increase at 2 years and a 93% increase at 5 years. Katsanos et al also reported a dose-response relationship between paclitaxel and mortality. This publication had a tremendous impact on patients with PAD because, as a consequence, the FDA recommended limiting PCD use to high-risk patients most prone to restenosis.[10] The use of PCDs abruptly fell, and RCTs designed to evaluate PCDs were halted.

These far-reaching effects occurred despite several major defects in the design of the meta-analysis. First,

the individual RCTs studied in the meta-analysis were designed to study short-term, limb-related outcomes. Many patients were lost to follow-up after the designated short-term outcomes were reached, resulting in large amounts of missing data. Specifically, the analysis began by assessing 28 trials and 4,432 patients at 1 year. At 2 years, there were 12 trials and 2,316 patients remaining, and at 5 years, there were only three trials and 863 patients analyzed. Compounding this issue, the use of summary-level data did not allow the researchers to censor patients who were lost to follow-up. Second, many of the deaths in the trials were not properly adjudicated. Third, the use of summary-level data did not allow for adjustment for comorbidities, and the patient populations in the PCD and non-PCD cohorts may have been significantly different. In addition to the meta-analysis design defects, no mechanism linking paclitaxel to mortality has been reported.

FDA INVESTIGATION

In response to the Katsanos meta-analysis, the FDA conducted its own investigation into a possible late mortality signal associated with paclitaxel, the findings of which were presented at a Safety Advisory Panel in June 2019.[11] The panel included stakeholders from the FDA, academia, and industry. The FDA conducted several analyses of data from PCDs approved in the United States. Specifically, they gathered individual-level data from a subset of RCTs included in the Katsanos meta-analysis (Zilver PTX, LEVANT 2, IN.PACT SFA I and II, ILLUMENATE). In addition, they analyzed data from large registries of PCDs with > 200 patients and also repeated the analysis conducted by Katsanos et al. The FDA concluded that, although a mortality signal was present in these data, the quality of the data was insufficient to make conclusions about the safety of PCDs due to the significant amount of data missing from the individual RCTs. In addition, they found no dose-response relationship between paclitaxel and mortality.

The FDA panel also included presentations of observational analyses from real-world data, such as analyses of Medicare and Optum claims data and findings from the Peripheral Vascular Intervention registry within the Society for Vascular Surgery Vascular Quality Initiative. These analyses did not show an increase in mortality associated with PCDs.

Overall, the FDA concluded that they did not have the ability to give clear guidance on the safety of PCDs based on the available evidence and that higher-quality, longitudinal data were needed. They recommended that PCDs be reserved for high-risk patients in clinical practice, advised risk-benefit discussions between providers and patients, and noted that device labels for PCDs should be updated to reflect a possible increase in mortality associated with paclitaxel.[12]

Since the FDA panel, data have been published in the form of RCTs, large observational studies, and meta-analyses, which are reviewed herein.

RCT DATA

Following publication of the Katsanos meta-analysis, patient enrollment in clinical trials of PCDs was stopped. SWEDEPAD is a multicenter RCT comparing amputation rates of patients with CLTI who received PCDs versus non-PCDs.[13] An unplanned interim analysis of the patients enrolled prior to publication of the Katsanos meta-analysis was performed with all-cause mortality as the primary outcome. There were a total of 2,289 patients assigned to either PCD or non-PCD and followed over a mean of 2.49 years. No difference in mortality was found between patients treated with PCDs compared with those treated with non-PCDs (25.5% vs 24.6%, respectively; hazard ratio [HR], 1.06; 95% CI, 0.92-1.22). When stratified by indication, there was no difference in mortality among patients with intermittent claudication treated with PCDs versus those treated with non-PCDs (10.9% vs 9.4%, respectively; HR, 1.18; 95% CI, 0.72-1.93).

A number of industry-sponsored RCTs now have longer follow-up times. First, a combined analysis of long-term follow-up from IN.PACT SFA and IN.PACT Japan found no significant difference in mortality in those treated with paclitaxel-coated balloons (PCBs) versus percutaneous transluminal angioplasty (PTA) at 5 years of follow-up. Paclitaxel exposure was not an independent predictor of mortality, and there were no differences in major causes of death in the PCB arm relative to the PTA arm.[14] Second, 5-year results from the ILLUMENATE EU and ILLUMENATE pivotal RCTs were presented at the Leipzig Interventional Course in January 2021, reporting no difference in all-cause mortality between drug-coated balloon and PTA.[15] Multiple other industry-sponsored RCTs including LEVANT 1 and 2, LEVANT 2 CAR, LEVANT Japan, and Zilver PTX similarly showed no difference in mortality in patients treated with PCD versus non-PCD.

LARGE OBSERVATIONAL STUDIES

Observational studies have been performed in both clinical trial data sets and real-world data. A subgroup analysis of the VOYAGER PAD trial data compared mortality in patients treated with PCDs to those treated with non-PCDs.[16] In VOYAGER PAD, patients treated with endovascular revascularization were random-

ized to rivaroxaban 2.5 mg twice daily or placebo after revascularization.[17] There was no difference in mortality among patients treated with PCDs compared with non-PCDs (HR, 0.95; 95% CI, 0.83-1.09; *P* = .49).

In terms of real-world data, medical claims data have contributed greatly to these efforts. Using the BARMER claims records in Germany, Freisinger et al evaluated 64,771 patients who underwent endovascular revascularization between 2007 and 2015 and examined outcomes at 5 years.[18] There was no difference in mortality in patients who received PCDs relative to those treated with non-PCDs (paclitaxel-eluting stent [PES]: HR, 1.01; 95% CI, 0.83-1.23; *P* = .91; PCB: HR, 0.97; 95% CI, 0.89-1.06; *P* = .49).

Two key analyses have been performed using the United States Medicare claims database. In one study, 16,560 patients who received either PCDs or non-PCDs were evaluated over a median follow-up of 389 days (interquartile range [IQR], 277-508 days). PCDs were associated with a lower cumulative incidence of all-cause mortality compared with non-PCDs (32% vs 34%; log-rank *P* = .007).[19] After adjustment, there was no difference in all-cause mortality among patients treated with PCDs relative to non-PCDs (adjusted HR, 0.97; 95% CI, 0.91-1.04; *P* = .43). SAFE-PAD is being extended through a median follow-up of 5 years (NCT04496544). Initial findings from SAFE-PAD at a median follow-up of 2.7 years demonstrated that PCDs are noninferior to non-PCDs for mortality (53.8% and 55.1%, respectively; non-inferiority *P* < .001).[20] Another study evaluated PESs relative to bare-metal stents (BMSs), comparing 51,456 patients over a mean follow-up of 2 years (IQR, 1.2-3.0 years).[21] There was no difference in mortality among patients treated with PESs versus BMSs through 4.1 years (51.7% vs 50.1%; log-rank *P* = .16).

PATIENT-LEVEL META-ANALYSES

In addition to the patient-level meta-analyses performed by the FDA, Rocha-Singh et al gathered additional data to analyze some of the RCTs from the Katsanos et al study with reduced loss to follow-up.[22] They redemonstrated the mortality signal associated with paclitaxel that was seen in the Katsanos meta-analysis when analyzed as summary-level data. Interestingly, as they added patient data to reduce the loss to follow-up in the study, the association between paclitaxel and mortality was diminished. Specifically, at loss to follow-up rates of 27% and 25% in the treatment and control arms, respectively, the HR for the association of all-cause mortality with treatment with PCD was 1.38 (95% CI, 1.06-1.80). When loss to follow-up decreased to 10% and 9%, the HR decreased to 1.27 (95% CI, 1.03-1.58).

CONCLUSION

Since publication of the Katsanos meta-analysis in 2018, a multitude of studies have been published supporting the safety of PCDs. The large observational studies using real-world and clinical trial data as well as the RCTs have found no association between PCDs and long-term mortality. The meta-analyses that conclude there is an increase in mortality associated with PCDs are based on the same group of RCTs analyzed in the Katsanos meta-analyses. These RCTs were designed to make conclusions about short-term, limb-related endpoints, not long-term mortality. Overall, a robust body of evidence now exists to refute the existence of a long-term mortality signal associated with PCDs. The vascular community awaits further guidance from the FDA for changes in regulation of PCDs. ■

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