Patient-Level Data Presentations at LINC Aim to Disprove Causality Between Paclitaxel and Increased Mortality

Attendees packed a special session to open LINC 2019 in Leipzig, Germany, to hear discussion of the recent meta-analysis published by Konstantinos Katsanos, MD, et al that suggested a link between the use of paclitaxel delivery devices and increased long-term mortality, as well as new data gathered by trialists and device manufacturers aiming to address these concerns. The session was held on January 22, 2019.

Katsanos et al published their meta-analysis in *Journal of the American Heart Association* (*JAHA*) in early December 2018. Since the publication, several trials involving the use of paclitaxel delivery devices have paused enrollment pending review of further data, and the FDA recently posted a letter notifying operators of the meta-analysis findings and that the agency itself is reviewing long-term data from the associated clinical trials. Meanwhile, investigators and sponsors from some of the major drug-coated balloon (DCB) and drug-eluting stent (DES) clinical trials have worked to gather patient-level data and conduct additional statistical analyses to determine whether there truly was a link between the use of these devices and increased mortality.

The meta-analysis postulated that late paclitaxel toxicity contributed to the increased mortality rates seen in the study arms and suggested a significant relationship between exposure to paclitaxel and absolute risk of death. Among the criticisms raised upon publication of the meta-analysis was that it lacked patient-level data, specifically regarding the causes of death and the amount of paclitaxel delivered in each case.

At LINC, trialists representing the paclitaxel delivery programs of Medtronic, BD Interventional, Philips, Cook Medical, and Boston Scientific Corporation each presented new data regarding the safety of their platforms, including patient-level data. Additionally, insights into paclitaxel formulation and toxicology and the responsibilities of clinical events adjudication and safety monitoring were shared, as well as the merits and limitations of meta-analyses.

MORE ON THE META-ANALYSIS

The session began with Dr. Katsanos summarizing the design and findings of his group’s meta-analysis, which reviewed 28 randomized controlled trials (RCTs) including 4,432 patients (89% claudication). The risk of death was analyzed at 1 year (28 RCTs) and 2 years (12 RCTs; 2,316 cases), as well as longer-term follow-up at 4 to 5 years (three RCTs; 863 cases). To address questions raised after publication, Dr. Katsanos shared additional statistical analyses at the 2-year time point, including evaluation by Bayesian methods and trial sequential analysis, each supporting the significant increase shown in the *JAHA* article.

Dr. Katsanos then addressed the findings related to paclitaxel dose and evidence of a biological gradient—the theory that greater amounts of the drug pose more significant risks. He summarized the pharmacology of paclitaxel, with specific attention to the differences in plasma and tissue half-life.

QUICK LINKS

CONTINUING COVERAGE: PACLITAXEL IN PAD

durations and its nonlinear pharmacokinetics. A 0.4% ± 0.1% excess risk of death per paclitaxel mg-year beyond 1 year was shown, and at 2 years, the meta-analysis determined that devices with higher concentrations of paclitaxel were associated with improved reduction in target lesion revascularization but higher risk of death. Dr. Katsanos did reiterate, however, that this evaluation is a study-level analysis without patient-level data. Possible mechanisms driving the association of adverse events with the potential for systemic toxicity of paclitaxel were explored, and a comparison of causes of death between the study and control groups from IN.PACT SFA was shown. Dr. Katsanos concluded that there remains much to learn about the ideal uses of paclitaxel in the lower extremities, specifically the need to identify the ideal effective yet safe dosage for these patients.

IN.PACT DCB PROGRAM

Peter A. Schneider, MD, presented a patient-level data analysis of 1,837 patients enrolled in five studies from Medtronic’s IN.PACT clinical program, which evaluates the safety and efficacy of the In.Pact Admiral DCB. The Baim Institute for Clinical Research performed the independent analysis. Data sources included 5-year IN.PACT SFA and 3-year IN.PACT Japan RCT data (the Katsanos study used unpublished data from 4 and 2 years, respectively); IN.PACT Global and IN.PACT China single-arm registries were also included. The data collection included access to narratives/comorbidities, times to events, and paclitaxel dose calculations per patient rather than per study.

Although it was stated that the total DCB- and control-treated arms are not directly comparable (in part due to the pooling of populations and disparate sample sizes), the evaluation found no statistically significant difference in all-cause mortality between the two arms (9.3% for DCB vs 11.2% for PTA; \( P = .399 \)). Presenting the multivariable Cox analysis, Dr. Schneider said, “There were a lot of things that predicted death, but paclitaxel wasn’t one of them.”

Dr. Schneider called attention to the low (0.9%) mortality rate seen in the control arm of the IN.PACT SFA trial at 2 years and its potential impact on the Katsanos et al meta-analysis. “If you have a small control group, and you get a world-class and most-amazingly low mortality [rate], it’s going to have an outsized effect on a summary-level meta-analysis,” he said.

Another criticism of the Katsanos et al meta-analysis was that it did not explore alternative hypotheses as to why higher mortality rates were seen in paclitaxel study arms beyond late paclitaxel toxicity. The IN.PACT meta-analysis found that patients treated with PTA alone had better follow-up compliance than DCB patients and that patients who died in the DCB group had a lower level of compliance compared to those who survived. Dr. Schneider noted that these preliminary findings suggest that this surrogate for repeat touch points with the health care system are associated with lower mortality risk, although further evaluation is needed in this regard.

These data have been published online ahead of print in Journal of the American College of Cardiology. Please see page 22 to read more.

Key Highlights

- No statistically significant difference in all-cause mortality between In.Pact Admiral DCB (9.3%) and uncoated percutaneous transluminal angioplasty (PTA; 11.2%) at 5-year studies
- No correlation seen between paclitaxel dose and long-term survival; freedom from all-cause mortality across dose-range terciles (upper, 91.7%; mid, 90.6%; lower, 90% by Kaplan-Meier estimate); highest survival rate in patients with the most paclitaxel
- No difference in mean nominal dose between overall survival in patients treated with DCB and those who died
- DCB-treated patients who died were older and had more carotid and coronary disease, diabetes, and renal insufficiency, as well as critical limb and below-the-knee disease
LUTONIX DCB PROGRAM

Key Highlights

▶ No statistically significant difference in all-cause mortality between the Lutonix DCB and PTA groups in any of the four SFA randomized trials.
▶ Five-year LEVANT 2 quartile dose administration analysis of the actual applied doses showed similar all-cause mortality rates across the groups; no statistically significant difference in binary and Kaplan-Meier analyses.
▶ The most frequent causes of death were the same in both groups (cardiovascular and respiratory).
▶ No significant difference in mortality rates between DCB and PTA in randomized trials in other vascular beds (below the knee and AV access).

Dierk Scheinert, MD, provided an overview of data gathered in BD Interventional’s Lutonix DCB program, including four superficial femoral artery (SFA) trials and two registries, as well as the investigational device exemption randomized controlled trial data aimed at arteriovenous (AV) access and below-the-knee indications.

Prof. Scheinert stated that product development included testing of 50,000 balloons, > 250 formulations, and 45 preclinical studies aimed at establishing safety with the lowest possible optimized dose.

Lutonix has also gained an AV access indication in addition to SFA, in-stent restenosis, and long lesions. Data from each trial were discussed in the presentation.

STEellarX DCB PROGRAM

Sean Lyden, MD, shared an analysis of seven clinical trials evaluating above-the-knee intervention with Philips’ Stellarex DCB. In his presentation, Dr. Lyden shared an independent, third-party, patient-level analysis of available mortality data. Data were collected from two pivotal RCTs as well as single-arm studies and a real-world registry.

“The Katsanos paper raised new concerns of safety with the use of drug-coated balloons in the PAD population. Patient-level data are truly required to validate or refute this association found in the meta-analysis,” said Dr. Lyden in comments to *Endovascular Today.*

“The Stellarex platform combining two randomized clinical trials with patient-level data showed no concerns of increased mortality, and similar event rates were found when combining all of the Stellarex trials, comprising almost 2,400 patients with adjudicated outcomes. I look forward to the combined analysis of adjudicated patient-level data for all randomized trials across platforms being led by VIVA Physicians and performed by an independent statistical body.”

Key Highlights

▶ All ILLUMINATE trials met their primary safety endpoints, with significantly lower major adverse event rates versus either performance goals or PTA control arms.
▶ No device- or procedure-related mortality was identified in 2,351 patients treated in these trials to date, with clinical event committee (CEC) adjudication of events.
▶ No significant difference in mortality for patients (whether all-cause, cardiovascular, or noncardiovascular deaths) were seen in the Stellarex DCB and PTA arms by Kaplan-Meier estimate through 1, 2, and 3 years for the pooled RCTs; at 3 years in RCTs: all-cause death ($P = .93$), cardiovascular mortality ($P = .33$), noncardiovascular death ($P = .67$).
▶ Although not directly comparable, there was also no significant difference when including non-RCTs; at 3 years in all included studies: all-cause death ($P = .78$), cardiovascular mortality ($P = .21$), noncardiovascular death ($P = .74$).
Michael D. Dake, MD, presented long-term safety and efficacy data for Cook Medical’s Zilver PTX paclitaxel-eluting peripheral stent. His presentation included DES data from the Zilver PTX randomized trial and the Zilver PTX Japan randomized trial.

Dr. Dake noted that the Katsanos et al meta-analysis did not identify/have data from all of the patients who were ultimately treated with Zilver PTX in the randomized trial. Within the first year after randomization to control, 31 patients who had optimal PTA required a stent. Of these, 30 received a Zilver PTX stent. One patient who had suboptimal PTA and a bare Zilver stent at randomization later received a Zilver PTX stent. All 31 of these patients with later Zilver PTX placement (within 1 year but after randomization) were treated as control patients in the meta-analysis.

Accounting for all patients treated with Zilver PTX, the 5-year mortality rates were 18.7% for Zilver PTX patients and 17.6% for PTA/BMS patients (P = .53). A comparable 5-year mortality rate was seen in a separate 110-patient trial of the bare Zilver stent (16.9%).

Dr. Dake also stated that the Zilver PTX stent carries approximately 10% to 20% the amount of paclitaxel compared to a DCB of same size and dose density.

Key Highlights
- Patient-level analysis shows no difference in mortality for Zilver PTX compared to PTA and/or bare-metal stent (BMS)
- No significant differences in causes of death were observed between Zilver PTX and PTA/BMS cohorts (P = .56)
- Paclitaxel dose had no observed impact on mortality rate at 5 years; quintile analysis showed that the highest quintile had the second lowest mortality rate (first quintile had the lowest)
- Covariate analysis of possible comorbidities leading to mortality showed no significant differences between Zilver PTX and PTA/BMS as a variable; the only factor with statistical significance was age
- The Japanese RCT showed comparable 3-year mortality rates between Zilver PTX and BMS (15.6% and 15.4%, respectively; P = .96); no exclusion criteria, critical limb ischemia was present in 21% of patients
William A. Gray, MD, reviewed data from two of Boston Scientific Corporation’s drug delivery devices: the Eluvia DES and Ranger DCB. Mortality rates with Eluvia were presented from the IMPERIAL multicenter RCT (N = 465 patients; Eluvia, 309 patients vs Zilver PTX, 156 patients) and the MAJESTIC single-arm study (N = 57 patients). Because the IMPERIAL trial was a head-to-head trial comparing Eluvia to Zilver PTX, no comparative PTA or BMS arm data were presented for Eluvia. Presented mortality rates for the Ranger DCB were from the RANGER-SFA trial (N = 105).

In comments to *Endovascular Today*, Dr. Gray noted that no safety signals have been identified for the patient-level data for the IMPERIAL, MAJESTIC, or RANGER studies. No change to the 5-year follow-up plans for the IMPERIAL trial, which led to the FDA approval of Eluvia, are expected.

**DISCUSSION**

After the presentations, the time left for a panel discussion was short, and there was unfortunately little room for additional questions, rebuttal of criticisms, debate, or work toward consensus points. Dr. Katsanos presented additional statistical points for consideration and stood by the findings of the meta-analysis, while acknowledging the limitations of conclusions from study-level data.

“This is a very strong signal,” said Dr. Katsanos, referring to the findings of his group’s meta-analysis. “We can discuss technicalities, but this signal can’t be dismissed.”

When asked if he is still using paclitaxel in his practice, he said that he is, but that he aims to use as little as necessary. He expressed that there remains a continued role of the drug in peripheral intervention, which he believes must still be closely monitored and further studied. “We are not dismissing paclitaxel,” he said, which he believes is effective but may have a narrow therapeutic index.

Dr. Schneider presented the goals of an upcoming VIVA Physicians Vascular Leadership Forum, which include collaborating with all five United States companies that have commercially available DCBs and DESs to gather and independently evaluate deidentified patient-level data from the respective clinical programs and publish the findings. However, even this data collection will come with uncertainties. For example, the comparative state of the various databases is not yet known nor is there a timeline for this process at this time. Furthermore, other trends or issues could still be identified, he cautioned.

Despite the data presented by the respective investigators and companies at LINC, the panelists agreed with the need for further transparent, independent analysis and ongoing review of data.

A full video of the session is available on the LINC website.

**FDA Issues Letter on Potential Increased Mortality With Paclitaxel-Coated Devices in SFA**

January 17, 2019—On its website, the FDA posted an advisory to peripheral interventionalists and vascular medicine physicians to inform them that the agency is evaluating recent information regarding the potential for increased long-term mortality after use of paclitaxel-coated balloons and paclitaxel-eluting stents to treat peripheral artery disease (PAD) in the femoropopliteal artery. There are a number of these devices approved or under study for peripheral vascular use in the United States.

As noted by the FDA, the recent meta-analysis of randomized trials suggests a possible increased mortality rate after 2 years in PAD patients treated with paclitaxel-coated balloons and paclitaxel-eluting stents compared with patients treated with control devices (noncoated balloons or bare-metal stents). The specific cause for this observation is yet to be determined. The study was published by Konstantinos Katsanos, MD, et al online in *Journal of the American Heart Association* (JAHA).

The agency concluded that it believes that the benefits continue to outweigh the risks for approved paclitaxel-coated balloons and paclitaxel-eluting stents when used in accordance with their indications for use. The FDA recommends that health care providers: