Meta-Analysis Observes Increased Mortality Trend in Trials of Paclitaxel–Coated SFA Devices, But No Definitive Cause

December 6, 2018—A systematic review and meta–analysis of randomized controlled trials (RCTs) evaluating paclitaxel–coated balloons and stents in the femoral and/or popliteal arteries concluded that there is an increased risk of death after application of these devices in this anatomy. Konstantinos Katsanos, MD, et al published the study online in *Journal of the American Heart Association* (*JAHA*). Although the authors postulated that late paclitaxel toxicity may be the reason for the observed increased death rate, a specific cause or plausible mechanism between paclitaxel and patient death could not be established. Further investigations are urgently warranted, advised the authors.

The study is registered with PROSPERO, the international prospective register of systematic reviews.

The investigators analyzed 28 RCTs composed of 4,663 patients (89% with intermittent claudication). The primary safety measure was all–cause patient death. Risk ratios (RRs) and risk differences were pooled with a random effects model.

As summarized in *JAHA*:

- With 4,432 patients available at 1-year follow-up in the 28 RCTs, the incidence of all–cause patient death was similar between paclitaxel–coated devices and the control arms (2.3% vs 2.3%, crude risk of death; RR, 1.08; 95% confidence interval [CI], 0.72–1.61).
- At 2 years, in 12 RCTs with 2,316 patients, the incidence of all–cause death was significantly increased with paclitaxel versus control (7.2%

vs 3.8% crude risk of death; RR, 1.68; 95% CI, 1.15–2.47; number needed to harm, 29 patients [95% CI, 19–59]).

- In the three RCTs composed of 863 patients with longer-term follow-up of 4 years (IN.PACT SFA, presented but not yet published) and 5 years (Zilver PTX, THUNDER), the all-cause death increased further with paclitaxel (14.7% vs 8.1%, crude risk of death; RR, 1.93; 95% CI, 1.27–2.93; number needed to harm, 14 patients [95% CI, 9–32]). The absolute risk difference was 7.2% (95% CI, 3.1–11.3%). There was no statistically significant heterogeneity between studies (*P* = .92).

A meta-regression analysis showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4% ± 0.1% excess risk of death per paclitaxel mg-year; P < .001), and a trial sequential analysis excluded false-positive findings with 99% certainty (two-sided α, 1.0%), reported the investigators in *JAHA*.

As stated in the article, "The authors consider the herein reported findings of particular concern because most of the interrogated devices have already received clearance by regulatory authorities and are currently under routine clinical use. The potential causes of this alarming late increased incidence of death remain unknown."

The authors noted that experience with coronary paclitaxel-coated devices has shown a significant increase of long-term death and myocardial infarction, as well as issues of vessel wall tissue inflammation, aneurysm formation, and late stent thrombosis. They stated that these factors have caused the coronary field to gradually move away from paclitaxel DES. Additionally, most paclitaxel-coated balloons and stents for the femoropopliteal artery contain at least an order of magnitude higher payload of paclitaxel in comparison with paclitaxel-eluting coronary stents.

As discussed in *JAHA*, "The authors postulate that late paclitaxel toxicity may be the reason for the observed increased death rate." They noted, "Preclinical follow-up studies have shown that in the case of paclitaxel-coated balloons, approximately 1% to 10% of the paclitaxel dose gets

transferred into the target vessel wall, and as much as 90% [...] gets lost into the systemic circulation with unknown consequences."

The investigators advised that limitations of the present meta-analysis include:

- Some study protocols did not include an independent blinded clinical events committee for event adjudication. A single-blind or open-label study design was and nearly universally applied that may have introduced detection or performance bias, respectively.
- Most studies did not report the actual causes of deaths to help infer potential causal links with paclitaxel use.
- Undetected sources of heterogeneity could not be explored in depth in the absence of individual patient data.
- It could not establish a plausible mechanism between paclitaxel and deaths.

The investigators stated, "Within the modern epidemiologic framework of structural causal modeling developed by Judea Pearl, the present work shows strong signals of biomedical causality between paclitaxel and mortality within multiple controlled randomized trials. According to the more traditional Bradford Hill criteria for establishing a causal relationship between a presumed cause and an observed health effect, the present work has shown evidence of strength, consistency, temporality, and biological gradient."

However, they cautioned, "The present meta-analysis is underpowered to discern outcome differences between the different paclitaxel devices as some devices are supported by a single trial and follow-up beyond 2 years is missing in most cases. The authors would therefore encourage collection of longer-term follow-up (beyond 1 year) in case of all studies to help confirm or refute the present findings."

In comments to *Endovascular Today* regarding the publication, Gary M. Ansel, MD, said that the authors raise important questions regarding safety and any potential link between mortality rates and drug toxicity.

However, Dr. Ansel was surprised that the authors and journal published a meta-analysis with a conclusion of this magnitude that lacks discussion of patient-level data, considering that such data were independently evaluated in several of the cited trials.

"This paclitaxel meta-analysis is significantly handicapped by its lack of patient-level data," said Dr. Ansel, the System Medical Chief for Vascular Services for OhioHealth and Associate Medical Director for OhioHealth Research Institute in Columbus, Ohio. He also served as Principal Investigator of the Zilver PTX trial involving Cook Medical's Zilver PTX drug-eluting stent (DES) and as an investigator in the IN.PACT SFA trial of Medtronic's In.Pact Admiral drug-coated balloon (DCB); these represent two of the three data sources used by the authors to generate the longer-term findings of the *JAHA* paper.

These trials involved independent core lab adjudication and clinical events committees examining patient-level outcomes—including death—at predetermined follow-up points and found that although there were differences in mortality, no links between the studied technologies and mortality were observed in enrolled patients, said Dr. Ansel.

"An independent clinical events committee reviewed all of the deaths in IN.PACT SFA at the 2-year follow-up point and found no link to the use of the paclitaxel-coated balloon. And, as Co-National Principal Investigator for the Zilver PTX DES trial, I am aware that a similar process was employed for all patient deaths at 5 years," said Dr. Ansel. "I take mortality and morbidity very seriously. The current authors call for 'urgent' closer scrutiny of the devices included in the meta-analysis. Having presented on these devices to the Centers for Medicare & Medicaid Services and the US Food and Drug Administration, I know that these agencies and the sponsors who develop these technologies (Cook Medical, Medtronic, etc) also take patient safety very seriously."

Dr. Ansel also commented that the mortality trend would be more alarming if the rates associated with paclitaxel-delivering devices greatly exceeded the rates seen across the body of literature regarding bare-metal

stents and uncoated balloons. "Having been an investigator on many non–drug-based device trials as well as drug-based trials, it is curious that this association is being made with mortality rates that are very similar to those of the trials for non–drug-based technologies," he said.

He further contends that it would be still more concerning if the deaths in these trials were clustered around only a few etiologies, instead of a wide array of causes. For example, the meta-analysis shows that deaths at 3 years in the study arm of the IN.PACT SFA trial were attributed to cardiovascular (9), cancer (2), infectious (5), pulmonary (3), and other (3) causes. A further limitation was the meta-analysis' grouping together of DES and DCB technologies and platforms, which have very different mechanisms of drug bonding and release. "The DES is associated with very little distal embolization and specifically does not utilize an excipient," Dr. Ansel said. "The paclitaxel on the Zilver PTX has a very quick release and little long term in distinction to DCBs."

"The authors also do not offer any plausible mechanism for a possible link between the drug and mortality remote from the procedure," he continued, wondering if other factors might play a role in the observed trend. "Even if we were to superficially look for alternative mechanisms, we would ask the simple question of why repeat procedures appear to have a 'mortality benefit.' Also, might there be an association with improved survival between being seen more often by a vascular physician who also underscores the importance of medication compliance? Was the compliance for follow-up lower in the patient population with less symptoms [ie, fewer follow-up office visits due to reduced symptoms]? All of these mechanisms will need to be evaluated."

"This meta-analysis highlights our need to better understand these outcomes, and it underscores the importance of sponsors publishing the entirety of their data, at all follow-up periods, and making patient-level data available for independent analyses," concluded Dr. Ansel. "Certainly, there is a difference, but assigning this difference to paclitaxel may be premature. These efforts should continue to have us look at long-term

patient-level results for our procedures, and I hope that the close evaluation will be the rule and not the exception."

Further discussion on the findings of the *JAHA* article, the value of patient-level data releases, and considerations for contemporary applications of drug-delivery therapies will follow in future *Endovascular Today* coverage.