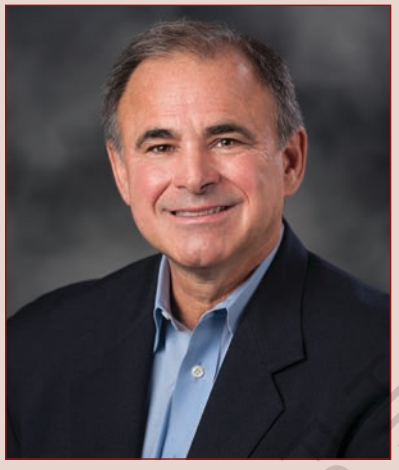
A Potential Danger Signal Associated With Paclitaxel-Eluting Devices



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Hello, and welcome to the January 2019 edition of *Vascular Disease Management*. There are multiple interesting articles in this January issue of great clinical significance. Each of these articles is deserving of attention. However, I have chosen not to comment on these and will instead comment on a recent publication by Katsanos and colleagues of a meta-analysis of the risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg, published in the *Journal of the American Heart Association*. This article concludes that there is an increased risk of death following application of paclitaxel-coated balloons and stents utilized in treating femoropopliteal arterial obstructive disease. I have chosen to comment on this article and its implications as it is hotly disputed amongst peripheral interventionists at this time, and it has the potential to have an impact on clinical decisions because of both clinical and medical-legal implications.

Katsanos and colleagues pooled data from 28 randomized controlled trials with 4663 patients treated with drug-coated balloons (DCBs) and drug-eluting stents (DESs) and then utilized statistical methods to analyze all-cause mortality at 1-year, 2-year, and 5-year time frames. Data were pooled among devices and then weighted according to standard statistical methods. At 1 year, all-cause death was the same at 2.3% in the paclitaxel device and percutaneous transluminal angioplasty (PTA) control groups. At 2 years, death rates in the paclitaxel device group was 7.2% versus 3.8% in the PTA control group. At 5 years, the difference was even greater, with 14.7% death rates in the paclitaxel group and 8.1% in the PTA control arms. The exact cause of death was not routinely documented. The authors concluded that there was 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, $P<0.001$). The authors stated that further investigations are urgently warranted. The authors clearly point out that many of the paclitaxel-eluting devices are different than the paclitaxel infusions used to treat cancer, as crystalline forms of paclitaxel are utilized with many of these devices, which has a longer half-life and may therefore have greater long-term complications.

Conclusions such as those made in this article are of great concern among peripheral interventionists who have adopted paclitaxel-coated balloons and stents as a means to lessen restenosis and the subsequent need for reintervention. Every physician recognizes that the philosophy of "first do no harm (*primum non nocere*)" is an inherent guiding principle of medicine. While the authors recognize that the cause of death was not always documented or known to have a causal relationship, they cite Sir Bradford Hill: "knowledge of the mechanism may be limited by current knowledge." Conclusions such as these must be scrutinized.

While I applaud the intentions of these authors, I am critical of what I think are overreaching assumptions in their conclusions. Are we to believe that all these devices are the same and therefore all data can be pooled? DCBs vary in the dose and form of paclitaxel, the excipient utilized, the cross-sectional profile of the balloon, and the type of balloon material utilized. DESs vary based on the type of stent, the drug form and dosage, and the use of drug-eluting polymers. In the authors' own tables demonstrating hazards ratios, some paclitaxel-eluting devices actually showed lower risk ratios than the control arms. Because of the types of statistical methods utilized, those studies where results were better than the control arm were underweighted in the final analysis. I would be more apt to accept the conclusions made if the conclusions were device specific rather than condemn all paclitaxel devices. There may be increased risks with some devices, but it is also plausible that some

devices are substantially different and may not share the same risks or even be safer than the PTA arm.

Katsanos and colleagues have now identified a potential danger signal associated with paclitaxel-eluting devices via a meta-analysis of reported studies. In my opinion, the conclusions may be overreaching but can't be ignored. Further statistical analysis of reported data will be needed, and I think it will have to be device specific. Conclusions from meta-analyses with poor causal understanding can be misleading and possibly harmful. A colleague in my cath lab commonly says that "Boudin (a very high fat pork and rice sausage made in Louisiana) must be a healthier food than lettuce as there has never been a Boudin recall yet there are frequent lettuce recalls." While I happen to like Boudin, it is obviously not "health food," and this is a flawed conclusion. I have frequently advocated that companies utilize "olimus" drugs in DCBs and DESs intended for use in femoropopliteal disease as these drugs seem to have great efficacy in other vascular beds and "olimus" analogs have a more favorable safety profile than paclitaxel. Despite the fact that I have had longstanding concerns about paclitaxel-eluting devices, I am not convinced by this meta-analysis using pooled weighted data that all paclitaxel-eluting devices pose the same risk, and I suspect that some may actually be shown to have decreased risk. However, we cannot ignore the danger signal.

REFERENCE

Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc.* 2018 Dec 18;7(24):e011245.