From the Editor: The Paclitaxel Paradox

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As medical editor of Vascular Specialist, it has always been my hope to use our excellent reporters and rapid production schedule to keep readers abreast of the latest news in vascular surgery. While my colleagues at the Journal of Vascular Surgery publish studies that will drive treatment, my goal is to drive discussion.

With topics like burnout, workforce shortages, and electronic medical records, I feel we have been successful. The downside of staying current is we sometimes find ourselves publishing contradictory stories. This has been the case with paclitaxel. Let’s take a break from the fray and review where we are, and where we might go from here.

In 2012, the Zilver PTX became the first drug-eluting stent (DES) to gain Food and Drug Administration approval for the treatment of peripheral vascular disease. Two years later, the FDA approved the Lutonix 035 as the first drug-coated balloon (DCB) for use in the femoral-popliteal arteries. The Lutonix would also gain a second indication for failing dialysis fistulas. Medtronic and Spectranetics received authorizations for their DCBs in 2015 and 2017, respectively.

While the safety of paclitaxel-coated devices in the coronary system had previously been called into question, the drug was generally considered safe and effective in the peripheral arterial system. The controversy began in December 2018, when Katsanos et al. published a meta-analysis of 28 randomized, controlled trials (RCTs) investigating paclitaxel-coated devices in the femoral-popliteal arteries. While allcause patient mortality was similar at 1 year between paclitaxel-coated devices and controls (2.3% in each), at 2 years the risk of death was significantly higher in those treated with paclitaxel (7.2% vs. 3.8%). The 5-year data were available for three trials where there was a continued significantly increased risk of mortality with paclitaxel (14.7% vs. 8.1%).

Opposition to these findings was prompt from both physicians and industry. Weaknesses of the analysis, both perceived and real, were hammered. The meta-analysis did not include individual patient data, and the actual cause of death was unknown in most of the included trials. The study was not adequately powered to eliminate the risk of type 1 error when comparing mortality after 2 years. Individuals assigned to the control group may have received paclitaxel treatment at some point in their follow-up. The DCB and DES treatment groups were combined. The methods employed by the authors, however, stood up reasonably well to scrutiny.

On Jan. 17, 2019, the FDA issued their first response stating, “the FDA 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.”

Later that month, Peter Schneider, MD, and associates published a patient-level meta-analysis in the Journal of the
American College of Cardiology. The study included 1,980 patients and found no statistically significant difference in all-cause mortality between DCB (9.3%) and percutaneous transluminal angioplasty (PTA) (11.2%) through 5 years. Shortly after that, however, a correction was issued.

On Feb. 15, 2019, Medtronic reported an error in the 2- and 3-year follow-up periods for the IN- PACT Global postmarket study. The company stated, “Due to a programming error, mortality data were inadvertently omitted from the summary tables included in the statistical analysis.” The mortality in the DCB cohort was corrected from 9.30% to 15.12%. The authors stated that this new mortality rate was still not significantly higher than the PTA group (P = .09).

Less than 1 week later, another device company issued a correction. And once again, the error had been made in favor of the paclitaxel-treated group. In 2016, the 5-year data from Cook Medical’s Zilver PTX trial were published in Circulation. The study reported a mortality of 10.2% in the DES group and 16.9% in the PTA cohort. Regrettably, these numbers were reversed and significantly higher in the paclitaxel-treated group (16.9% vs. 10.2%, P = .03).

On Feb. 12, 2019, another response to the Katsanos meta-analysis was published in JAMA Cardiology. In this study, Secemsky et al. analyzed patient-level data from a Medicare database. The authors reported finding no evidence of paclitaxel-related deaths in 16,560 patients. Unfortunately, the mean follow-up time was only 389 days, which may have been insufficient to detect the late mortality reported in the Katsanos meta-analysis.

On March 15, 2019, the FDA issued a second statement, this time with a much stronger tone. The agency reported an ongoing analysis of the long-term survival data from the pivotal randomized trials. In the three studies with 5-year data available, each showed a significantly higher mortality in the paclitaxel group (see cover story).

When pooled, there were 975 patients, and the risk of death was 20.1% in the paclitaxel group versus 13.4 % in the controls. The FDA recommended discussing the increased risk of mortality with all patients receiving paclitaxel therapy as part of the informed consent process. They also stated that for most patients alternative options should generally be used until additional analysis of the mortality risk is performed.

Industry bristled at this new, strongly worded statement. Becton Dickinson, makers of the Lutonix balloon, asserted that the FDA recommendation was based on “a limited review of data from less than 1,000 patients.” The company noted that its LEVANT 2 trial did not see a signal of increased mortality at 5 years. Although they did acknowledge that, among the randomized patients, there was a significantly higher mortality at 5 years for those treated with paclitaxel.

How do we make sense of this? Paclitaxel is a cytotoxic drug. Its pharmacokinetics vary significantly based on the preparation and administration. The FDA label for the injectable form (Taxol) warns of anaphylaxis and severe hypersensitivity reactions, but there is no mention of long-term mortality. In the coronary vessels, paclitaxel-coated devices have been associated with myocardial infarction and death. Obviously it is easy to comprehend how local vessel effects in the coronary system can lead to increased mortality. The pathway is less clear with femoral-popliteal interventions. If the association of paclitaxel with death is truly causation there must be some systemic effects. The dose delivered with femoral-popliteal interventions is much higher than that seen with coronary devices.

The mortality may be associated with the platform used or even the formulation (crystalline formulations have a longer half-life). Could it be something more benign? Paclitaxel-treated patients see less recurrence of their femoral-popliteal disease. Are the control group patients with more recurrences seeing their interventionalist more often and therefore receiving more frequent reminders to comply with medical therapy?

At this point, we have few answers. After an all-day town hall at the recent Cardiovascular Research Technologies conference, one moderator said, “I came in with uncertainty and now I’m going away with uncertainty, but we made tremendous progress.” His comoderator added, “I know I don’t know.” Well then, glad we cleared that up!

In any event, changes are coming. The BASIL-3 trial has suspended recruitment. Physicians using paclitaxel-coated devices are now advised by the FDA to inform patients of the increased risk of death and to use alternatives in most cases. Therefore, if you employ these devices routinely in the femoral-popliteal vessels you are seemingly doing so in opposition to the recommendations of the FDA. Legal peril may follow.
The time for nitpicking the Katsanos analysis has ended. Our industry partners must be compelled to supply the data and finances needed to settle this issue. The signal seems real and it is time to find answers. Research initiatives are underway through the SVS, the VIVA group, the UK Medicines and Healthcare Products Regulatory Agency, and the FDA.

Going forward, the SVS has formed a Paclitaxel Safety Task Force under the leadership of President-elect Kim Hodgson. Their mission is to facilitate the performance and interpretation of an Individual Patient Data meta-analysis using patient-level RCT data from industry partners. The task force states: “We remain troubled by the recent reports of reanalysis of existing datasets, pooled analyses of RCTs, and other ‘series’, as we believe that the findings of these statistically inferior analyses bring no additional clarity, cannot be relied upon for guidance, and distract us from the analysis that needs to be performed.”

References