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EDITORIAL COMMENT

Mortality Increase and Paclitaxel-Coated Device Use

A Plausible But Inconclusive Hypothesis*

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"If you use the right tone, you can say anything. With the wrong tone, nothing. The only trouble is finding the right tone."
—George Bernard Shaw (1)

Over the past year, the publication of a meta-analysis (2) showing an increase in long-term mortality following the use of paclitaxel-coated devices (PCDs) (both drug-coated balloons and drug-eluting stents) for the treatment of femoropopliteal disease shook the clinical and regulatory world. This meta-analysis reported no differences in mortality at 1 year (~2.3%) but a higher mortality risk at 2 years (RR: 1.68) and 5 years (RR: 1.93). The results were rapidly challenged by the academic community due to the controversial statistical methodology used and lack of a mechanistic explanation of the findings. Following this publication, a preliminary U.S. Food and Drug Administration communication confirmed a potentially concerning increased mortality signal. A recently presented individual patient data analysis (Vascular InterVentional Advances/North American Science Associates) including only randomized controlled trial (RCT) data of devices used in the United States confirmed the mortality risk; however, the risk was lower and declined as the number of patients lost at follow-up were added (from 25% loss [hazard ratio: 1.72; 95% confidence interval: 1.22 to 2.38] to 9% loss [hazard ratio: 1.27; 95% confidence interval: 1.03 to 1.58]) (personal communication, Krishna J. Rocha-Singh, MD, 2019). Other publications including individual patient data from device-specific RCTs and real-world Medicare patients showed contradicting results (3-5).

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In this issue of *JACC: Cardiovascular Interventions*, Bittl et al. (6) aimed to shed some light on the current paclitaxel controversy using Bayes factor meta-analysis, which measures the strength of the evidence without being influenced by a priori selections. This model requires distinct and independent datasets at each time point of the follow-up, avoiding the duplication of information inevitably occurring in studies reporting cumulative mortality rates at different time points as it happened in the Katsanos et al. (2) analysis. This new analysis showed insufficient support for increased mortality at 2 years but plausible support at 3 to 5 years; therefore, inconclusive support for increased mortality with the use of PCDs was established. Given the importance of mortality as a clinical endpoint and our responsibility to inform patients, how should the current clinical evidence guide the decision-making process?

The result of this controversy has led to a significant decrease in peripheral PCD use worldwide, limiting the therapeutic options to patients suffering from peripheral artery disease (PAD). One thing we all seem to agree on is that a consistent mortality signal must not be ignored and deserves to be further investigated. However, one of the biggest challenges at the center of this controversy is whether the

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science and clinical evidence support the concept of "causality." Although the lack of a specific biological mechanism must not overlook these mortality findings, neglecting properly generated scientific data may be equally misleading.

The scientific evidence gathered to date do not seem to support the reported mortality risk. In general, paclitaxel systemic exposure following PCD use is small and self-limited in time. A random drug distribution to the entire body occurs; however, no immediate toxic effects have been reported in RCTs in the immediate phase. Also, systemic toxicity studies suggest that paclitaxel tissue levels fall below therapeutic levels weeks after delivery and are practically undetectable at 1 year. It is difficult to scientifically reconcile how a mortality difference may exist during the period in which the drug may not be present anymore. Finally, distal particle shedding is known to occur following PCD use. Complications derived from mechanical occlusions of downstream microvessels could be another explanation. In all clinical evidence presented to date, no statistical increase in vascular-related complications has been reported.

The direction of our field has always been guided by thoughtful analysis of evidence-based data derived from prospective RCTs. That is why it is somewhat perplexing that results of a single meta-analysis have been able to overshadow all the clinical evidence accumulated over the last decade. All the studies pooled in these analyses are diverse and methodologically limited. Despite all devices used being paclitaxel based, they display different input doses and pharmacological behavior. All studies were small, not powered to show mortality differences, and not designed to follow-up patients for a long period of time. The amount of patients lost at follow-up was significant, resulting in a wide variability in mortality risk as the amount of long-term data became limited over time.

The development of clinical evidence in the peripheral field has not followed the same degree of academic rigor compared with the interventional coronary field. That is why, it is a shame this level of academic confusion is occurring at a time in which RCTs had started to be performed properly in this field. However, important lessons can be drawn from this controversy. First, careful clinical trial design and execution are now more critical than ever before. Although none of the studies included in these analyses were powered to detect mortality differences, a more disciplined execution of these studies would have minimized some of the statistical challenges we are now facing. Also, standardization of clinical trial design allowing proper pooling of the data in the peripheral field is also warranted. The significant variability in trial design, collection, and reporting of device success and failure has made the interpretation of the data dangerously confusing.

The introduction of local drug delivery opened a new frontier in the treatment of patients suffering from PAD. Although still there is room for improvement, the introduction of PCDs improved clinical outcomes and expanded therapeutic options for these patients. That is why unveiling the potential explanations for this mortality differences are critically needed. The uncertainty created by the Katsanos et al. (2) meta-analysis has not only the potential to stall innovation in this field, but also neglect an effective treatment to patients that critically need it. The conclusion of the Bittl et al. (6) paper precisely summarizes the present status of the mortality increase hypothesis: insufficient data, plausible but still inconclusive. Unfortunately, on the one hand, it is unlikely that pooled clinical trial data will provide a definitive answer to this question. In the other hand, there is a risk that interventional treatment of PAD could regress more than 20 years. This controversy has already created a reputational dent to the field, leaving physicians with the difficult responsibility of "properly judging" the best clinical scenarios in which to use these devices.

Opportunities arise from challenges, and a new wave of innovation will likely be ignited as a result of this controversy. However, it will take a long while before we have convincing performance data with new devices comparable to that available for PCDs. In the interim, limiting access to an effective technology may be also deleterious for patients. Physicians are now challenged to make clinical decisions based on this controversial data. Then, we will have to decide whether we want to continue on this path or base our decisions in clinical-based experience supported by randomized controlled clinical data.

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