ONYX ONE GLOBAL STUDY

- DES vs. DES
- 1-month DAPT
- ~ 2,000 High Bleeding Risk Patients

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Medtronic

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EDITORIAL

WILEY

The hypothesis of an increased mortality following paclitaxel coated device use in peripheral vascular interventions (and the emerging era of meta-analysis based evidence)

Over the last several months, a tsunami of information covered the headlines of all medical media shaking the world of vascular specialists. The controversy, based on the publication of a single meta-analysis[1] showing an increase in long-term mortality following the use of paclitaxel-coated devices (including both drug-coated balloons [DCB] and drug-eluting stents [DES]) for the treatment of femoropopliteal disease continues to challenge the academic, clinical, and regulatory world.

The authors reported a similar mortality rate between both the treatment and control groups at 1-year (2.3%), but a higher mortality at 2 (7.3 vs. 3.8% for paclitaxel-eluting devices vs. uncoated balloons, risk ratio = 1.68, number-needed-to-harm 29) and 5-years (14.7 vs. 8.1%, risk ratio = 1.93, number-needed-to-harm 14). The results were surprising, especially for DCB, a technology application that has always praised itself by either avoiding the use of permanent implants or reducing the amount of systemic drug exposure over time.

Although these results were received with mixed emotions by the clinical community, nobody predicted the rapid consequences this publication had on the field. First, the principal investigators of the largest ongoing trials in the field, the BASIL-3 (BMS vs. PCB vs. paclitaxel-eluting stent for superficial femoral artery disease), and SWEDEPAD 1 and 2 (PCB for the treatment of intermittent claudication and chronic limb ischemia, respectively) trials announced the interruption of patient enrollment, until further investigations shed light on this critical finding. Additionally, at the beginning of the year, the American Food and Drug Administration (FDA) published a warning note on paclitaxel-eluting devices, stating that it would evaluate available long-term data, to assess their potential long-term risks (U.S. FDA-Letter to Health Care Providers, January 2019. http://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm629589.htm). On March 15, following its own internal analysis, the FDA released a communication confirming the nature of these findings and suggested that alternative therapeutic options be sought to treat these patients. As a consequence, a significant decrease in Paclitaxel-coated device use has occurred worldwide. A more recent FDA report summarizes the current status of the field (dated June 20th and August seventh 2019) and included the following points: (a) future trials in peripheral vascular medicine should be better performed with greater attention to patient loss and measure of outcome, including 12-month efficacy and at least 5-year safety endpoints; (b) the results of the studies will have to be always reported in their complete version; (c) physicians should always discuss with patients on the risks and benefits of devices, and explore potential alternative treatments, and finally that (d) the short-term benefits of these devices outweigh the putative increased death risk (https://www.fda.gov/media/128246/download). To make this situation even more complex, most recent publications including individual patient-level data and real-world patients from the Medicare database showed no evidence of increased mortality using Paclitaxel.

Before starting any discussions regarding these findings is important to highlight that that the original meta-analysis at the center of the controversy contains serious methodological flaws. First, all studies included in the analysis involved different devices, dosages and patient population and never were designed nor intended to be pooled. Second, there is a wide variability in the mortality risk as the amount of long-term data available is limited. Three, there was a lack of patient-level data analysis resulting in some major statistical flaws, including no clear definition of baseline characteristics of the different groups studied (differences in baseline comorbidities were not adjusted) and no clear description of specific causes of death, then mechanistic conclusions cannot be drawn. This is noteworthy, especially when considering that all major trials had an event adjudicating committee. For example, in IN.PACT SFA (the trial having the highest all-cause mortality) all events were adjudicated as independent from the index treatment (moreover, such a difference was no more significant at 4 years).[2] Four, all the trials involved in this analysis included different lesion profiles (i.e., in-stent restenosis, native vessel disease), methods of delivery (DCB and DES), drug exposures, and procedural approaches. Finally, the number of patients lost at follow up was significant and long-term follow up rates were not consistent throughout all trials analyzed. All 28 trials included in the analysis had a 1-year follow-up, but the follow up rate dropped to 43% at 2-years, and only 10% of the studies had a follow-up of 4–5 years.

The numerical differences in all-cause mortality are clear and the statistical trends appear to be consistent across different independent analysis, however the trend continues to become weaker as long-term follow up data is added and a convincing, clinically derived mechanistic explanation is still lacking. The authors support their hypothesis in the fact that coating embolization universally occurs at the time of balloon inflation and that the systemic distribution and retention of paclitaxel occurs up to 8-weeks following initial delivery (compared to only a few hours following intravenous administration) (Katsanos,

LINC 2019 presentation). However, the authors fail to explain the lack of differences in mortality during the first year, a period in which paclitaxel tissue levels appear to be the highest, and do not justify the supposed increase in mortality afterwards.

The total systemic paclitaxel exposure resulting from single DCB use is several orders of magnitude lower compared to the intravenous use of the drug. Although drug delivery profile differs amongst different balloon coating technologies, a significant fraction of the coating remains attached either to the balloon surface or delivery catheters following use. Then, not all paclitaxel coating is finally introduced to the systemic circulation. Even in the worst-case scenario, this total systemic exposure is a very small fraction compared to the total exposure found in chemotherapy patients. Also, it has been suggested that coating particle crystallinity may play a role. However, experimental systemic toxicity studies suggest that paclitaxel tissue levels fall below therapeutic levels rapidly after 30-days and these levels fall below quantification after 90-days. Also, one of the DES included in the analysis is a polymer-free platform and follows a similar pharmacokinetic profile and systemic exposure. Finally, the other DES included (Eluvia) is polymer-based and presents one of the lowest paclitaxel concentrations ever used in any local drug delivery device for this particular application. Then, the main question is why there is a clear disconnection between the science and the clinical data?

It is also puzzling why no mortality differences have been described in the Oncology literature with the chronic use of high-dose Taxane derivates in cancer patients. Paclitaxel used in chemotherapy is solvent-based and has a shorter half-life, but is usually administered at higher dosages (reaching also 260 mg/m^2, while the one delivered by DCB is usually below 20 mg), and longer treatment cycles provide significantly higher tissue exposure over time.

Complications derived from mechanical occlusions of microvessels leading to ischemic complications could be another explanation. However, higher amputation rates were not reported in any of the randomized controlled trials. Finally, even considering a random drug distribution to the entire body, expected side effects would be related to tissues displaying high cellular turnover (bone marrow, muscle, and mucosa) or peripheral nerve toxicity. In all published studies, there is no mention of long-term adverse effects in patients treated with Paclitaxel-eluting devices, then a causality link is even more elusive.

As a response to the results of this meta-analysis, all the companies presented their individual patient-level data at different follow-up periods. A new patient-level meta-analysis including 1980 patients from two randomized controlled trials and two prospective single-arm studies (1,837 treated with the IN.PACT Admiral DCB, 143 with POBA) the 4-year mortality rates were similar between patients treated with PCB and those treated with uncoated balloons (9.3% vs. 11.2%, respectively, p = .399), and no deaths were considered as device-related by an independent event adjudicating committee.[3] Furthermore, the investigators did not find any association between different dose exposures and adverse events and found no difference in mean nominal dose of paclitaxel between patients treated with DCB and those who died.

Recently, two large registries reported on the late occurrence of mortality: Secemsky obtained data from 16,560 Medicare and Medicaid patients treated for femoropoliteal disease through a median follow up of 389 days, and found a reduction in all-cause mortality with paclitaxel-devices,[4] and Jones reported the outcome of 82,906 Medicare patients, where the final matched-analysis showed a significant reduction in overall mortality, need for hospitalization and amputation in patients treated with paclitaxel-DCB (TCT 2018 presentation).

If interventional cardiology has always benefited from adequately powered studies, development of clinical evidence in the peripheral field has not counted with the same degree of research quality compared to other interventional fields. Now, comparative head-to-head studies are critically needed in this field, taking into consideration some important lessons derived from this current situation. First, clinical trial planning and execution are now more critical than ever before. Second, the standardization of safety/efficacy clinical endpoints seems mandatory, also in the view of pooling together studies in case each single data seems confounding. Finally, a more open access to clinical data is warranted, allowing investigators to perform independent analysis and reporting of data in this field. In this regard, we applaud the recent editorial initiative launched by the International Committee of Medical Journals Editors (ICMJE) on data sharing.[5]

The possibility of avoiding prosthesis or stent implantation in the periphery is still highly advisable in many clinical and lesion settings, and although a long road is still to be asphalted, the introduction of local drug delivery consistently changed the therapeutic scenario for our patients, which often suffer of many comorbidities including high bleeding risk. If the echoes of this meta-analysis will not be properly and wisely driven, the risk of avoiding the right treatment for our patients could become somewhat unethical. An ongoing effort towards the independent collection, analysis and reporting of the clinical data is already under development (https://www.prnewswire.com/news-releases/viva-physicians-to-lead-pan-industry-collaboration-to-further-evaluate-the-use-of-paclitaxel-drug-eluting-technologies-in-pad-300781264.html). As part of this initiative, companies with commercially available paclitaxel-coated devices have agreed to provide this independent working group with deidentified, patient-level data from each of their clinical programs. This access to patient-level data will hopefully provide the highest level of scientific rigor necessary to evaluate this important clinical issue and provide some answers to this crucial clinical question.

If this hypothesis is proven to be right, the interventional treatment of peripheral vascular disease is at risk to be limited to the use of non-drug eluting technologies proven to be safe but not necessarily effective at long-term. If this hypothesis is proven to be wrong, the publication of this data has created a reputational dent that will be difficult to recover from. Then, regardless of the outcome of other independent investigations there will be likely no winners coming out of this controversy. Opportunities arise from challenges and a new wave of innovation will likely be ignited as a consequence of these findings. However, it will take a long while before we have convincing performance data comparable to what it is already available for paclitaxel-based devices. In the absence of a credible mechanistic explanation,

negating access to an effective technology may be harmful for patients. Patient level data supports the safety profile and continuous use of these devices; however, the judicious use of paclitaxel-based devices taking into consideration the patient's and lesion's risk–benefit profile is warranted now more than ever. Due to the statistical challenges presented by pooling studies not powered to study mortality differences we may be forced to face the uncertainty of an inconclusive outcome. This is the right time to take an action, and follow an evidence-based-built new reputation for the peripheral field.

CONFLICT OF INTEREST

The authors have nothing to disclose.

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SUPPORTING INFORMATION

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