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Commentary
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The Below-the-Knee Paclitaxel Angioplasty Meta-Analysis Lacks the Bite of Its Blockbuster Predecessor; Shall We Let Sleeping Dogs Lie for Now?

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Abstract

The recent meta-analysis, published by Katsanos et al. whereby findings of a worse amputation free survival signal, from the use of paclitaxel-coated balloons in the infra-popliteal arteries for treatment of critical limb ischemia, was reported, has once again found itself center-stage in the peripheral endovascular community. However, like all sequels, it does not have the impact of its predecessor. In this article, we examine the limitations of this meta-analysis in comparison to their previous work. For now, the findings of this meta-analysis should not impact anyone's practice until these issues have been adequately addressed.

Keywords: Drug-coated balloon; Amputation free survival; Mortality; Paclitaxel; Knee

Commentary

The sequel to the blockbuster meta-analysis published by Katsanos et al. [1], which dominated the endovascular landscape in 2019 and had shown an increased mortality risk signal in the medium term (two and five years) following the use of paclitaxel-coated devices in claudicants with femoro-popliteal disease, has also found itself centre-stage in the peripheral endovascular community. However, like all sequels except perhaps for Star Wars V: The Empire Strikes Back-it does not have the impact of its predecessor.

In the newly published installment on 15th January 2020 in the Journal of Vascular and Interventional Radiology [2], data from eight Randomized Controlled Trials (RCTs) of Paclitaxel-Coated Balloons (PCBs) showed worse one-year Amputation-Free Survival (AFS) rates (a composite of death and major Lower Extremity limb Amputation (LEA) above the ankle) following treatment of infra-popliteal arteries with PCBs. The analysis included 1,420 patients, of which 1,380 (97.1%) had Critical Limb Ischemia (CLI). The crude risk of major limb loss or mortality was 13.7% in patients who had received treatment with PCBs, compared to a 9.4% risk in subjects treated with uncoated balloons (39 deaths and 17 LEA in 585 patients) [HR 1.25; 95% CI, 1.12 to 2.07, P=0.008]. However, this composite primary endpoint was found to be driven by non-significant individual increases of both all-cause death (OR 1.39; 95% CI, 0.94 to 2.07; P=0.10) and major LEA (OR 1.63; 95% CI, 0.92 to 2.90; P=0.09). Similar to their meta-analysis on PCB application in femoro-popliteal arteries, the authors also suggest a dose-dependent increase risk of LEA and mortality with "high dose" drug coated devices. As a secondary endpoint, the study also demonstrated that the use of PCBs significantly reduced the need for Target Lesion Revascularization (TLR). There was an 11.8% crude risk of TLR in the PCB group (103 TLR events in 875 cases) versus a 25.6% crude risk in the control group (159 TLR events in 620 control cases) (RR 0.53; 95% CI 0.35 to 0.81, P=0.004).

Critics of the original 2018 meta-analysis focused on several limitations, specifically its methodology and conclusions. Notable points were that it was a study-level driven meta-analysis, which lacked patient-level data [4]and, long-term follow-up data of the included trials [3], the combination of outcomes from the use of PCBs and drug-eluting stents [5], the likelihood that some control patients were treated with paclitaxel either contralaterally or for subsequent TLR, flaws in dose calculations [6], and the insufficient power of trials to drive long-term endpoints that were not designed to primarily assess mortality beyond 1 year [7]. Review and subsequent

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investigations by the respective clinical safety committees and each of the industry-sponsored trial teams have also determined that the deaths observed in the trials were not paclitaxel-related.

In this below-the-knee meta-analysis, only PCBs were included and a maximum 12-month time-point was used. Given the previous 2018 finding of a late mortality signal at two and five years post-treatment, this is perhaps too short-term and inconsistent. The meta-analysis included both five published peer-reviewed studies and three presented but unrefereed unpublished trials, along with follow-up data through either 6 (three studies, 46% of patients) or 12 months (five studies, 54% of patients). Results were also dominated by the two larger studies (IN.PACT DEEP and Lutonix BTK), both of which employed a 2:1 randomization, resulting in the notable difference in patient numbers between the PCB and control arms available for one-year follow-up (835 *vs.* 585, respectively). These discrepancies may well introduce potential detection, performance, attrition and selection biases, making it difficult to draw definite conclusions.

The employment of a study-level model, as opposed to obtaining patient-level data, also did not allow for more meaningful subset analysis of confounding factors such as co-morbidities and clinical severity of tissue loss. As evident from the IN.PACT DEEP study, multi-center RCTs involving CLI are difficult to execute due to the influence of varying confounders, such as wound care standards, practices, and outcomes on LEA rates [8]. Thus, cohorts should be analyzed at patient-as opposed at study-level in order to avoid Simpson's paradox - whereby trends from pooled data are reversed or non-significant when analyzed with non-aggregated data.

Another concern is the use of a composite AFS primary endpoint. When observed separately, all cause mortality and major LEA rates showed no significant differences between the two groups. But combined, they appeared to have found better AFS in the uncoated balloon group. This may simply imply the presence of publication bias in some of the individual studies included. The use of a composite endpoint is always weaker and dilutes a hard outcome measure such as mortality. AFS should be the relevant safety and efficacy endpoint in any CLI study. Clinically, the main issue presented is how many patients are alive and have not undergone a major LEA. From a wider perspective, we need to know exactly the reasons behind the amputations and mortalities, and these parameters ought to be analyzed separately.

It should also be noted that the distribution of CLI severity may not have been the same amongst the various studies and this was not accounted for. The authors simply noted that tissue loss and foot ulcers were reported in approximately three-quarters of the population. At the time of study design, these trials would also not have benefited from the improved wound staging systems in current use, such as the WiFi Classification system [9], to allow for better trial arm allocation by using a balanced randomization process based on wound severity. CLI encompasses a broad clinical spectrum. As we know, outcomes for Rutherford class 4 (rest pain) patients are very different from those with Rutherford 6 wounds, who represent the extreme end of CLI with poorer prognosis. Thus, the lack of heterogeneity in the distribution of CLI severity amongst the various studies can introduce bias.

The use of trial data that have yet to be published is also concerning. Three of the eight trials, which represent approximately a quarter of the patients included, reflect only podium presentations at the major CIRSE and LINC congresses (SINGA-PACLI, ACOART BTK, ACOART II) [10-12]. Suffice to say, data analysis cannot be considered optimal when taking the numbers from single slides presented during a conference proceeding. Such studies have not undergone peer-review and evaluation for statistical rigor. It is also common for event rates to change between a presentation and final publication, which may alter the findings of a meta-analysis. This is particularly pertinent for low-frequency endpoints such as at 6 to 12 months AFS. One of the trials in particular, SINGA-PACLI [2], showed one of the highest odds-ratio for increased risk of major LEA at one year. Despite being a RCT, it is a local study and known to the authorship of this editorial, with multiple limitations such as a strict cut-off of patients with poor cardiac ejection fractions and the recruitment of patients with End-Stage Renal Failure (ESRF) on dialysis, resulting in the inclusion of patients that did not reflect real-world outcomes. Given that ESRF is an independent prognostic indicator of wound outcome [13], the results of the SINGA-PACLI trial were of no surprise. Furthermore, the study enrolled patients over a four-year period with varying wound practices that were not standardized or unified amongst the attending physicians and hospitals.

Although the inclusion of unpublished data is not unheard of, particularly when there are relatively few published studies, what is of concern is the exclusion of the five-year data follow-up of the most significant study of PCB use in BTK-CLI arteries to date. IN.PACT DEEP's five-year data were recently presented at the AMP Symposium in Chicago, US in August 2019 [14]. Like the other three studies, it was unpublished in September 2019 and remains so when the systematic review was conducted. However, if you include some unpublished studies, you must include all for consistency and validity. This seminal trial was instead represented by its one-year published data [8], which were less favorable with regard to safety, ultimately resulting in the withdrawal of the device from the worldwide market. In the five-year follow-up, AFS was numerically better in the PCB group (PCB, 135/239 (56.5%) *vs.* uncoated balloon angioplasty, 65/119 (54.6%)). If these contemporary data had been included, the conclusions regarding AFS and safety would have been different.

Another criticism of the original 2018 meta-analysis was how the total dose of paclitaxel administered to each patient was calculated. In this BTK PCB meta-analysis, without patient-level data, the authors have further simplified their dose-response analysis and have simply assigned balloon dosing, not taking into account total lesion length treated and number of PCBs used. It includes only one study with a 'low-dose' device (2.0 μg/mm^2) and compares that to the other seven studies with 'high-dose' (3.0 μg/mm^2 to 3.5 μg/mm^2) devices, which does not allow for a meaningful quantitative meta-regression analysis.

This new meta-analysis of use of PCB in the peripheral vasculature brings more controversy and questions than answers. How do you reconcile the outcomes reached to the differing conclusions attained by two recently published cohort series with many more patient numbers [15,16]? Both studies found no worsening difference in mortality with use of PCBs in CLI patients. The Behrendt et al. [16] study even showed a benefit in favor of PCB. This meta-analysis moves us backwards in our understanding of the risk-benefit ratio of PCBs for peripheral artery disease because we are now seeing a lower AFS at an earlier time interval (6 and 12 months), when a higher mortality signal at two and five years was seen in the femoral-popliteal data. We know from the events of the past year that data quality is essential, even for summary-level meta-analyses. When

data is incomplete or extrapolated, an overwrought reaction can be generated. This has been well demonstrated by the curtailed use of PCB and drug eluting stents, despite shrinking hazard ratio for use of paclitaxel devices and the inability to demonstrate any mortality signal from massive amounts of real-world data, subsequent to the 2018 meta-analysis publication.

Taken together, the conclusions derived from this meta-analysis could simply be a coincidental statistic and would require higher analysis with patient-level outcomes to better substantiate its findings. We applaud the authors for their transparency and in acknowledging the limitations that have been imposed on them with the lack of available patient-level data. Nevertheless, every meta-analysis is only as good as the data that it pools. Data from the three unpublished studies should be re-run when the final publications for these studies are available, along with the 5-year data from IN.PACT DEEP and 1-year data from the Lutonix BTK trial, which has just been presented at a major meeting [17]. Patient level data should be made available from these RCTs to determine whether there is a true poorer AFS signal with PCBs. For now, the findings of this meta-analysis should not impact anyone's practice until these issues have been adequately addressed. Given the reduced restenosis and TLR rates of PCB, as demonstrated in the secondary endpoint, we must clarify the AFS signal. Similar to the aftermath of the 2018 femoro-popliteal meta-analysis, paclitaxel-based technology may be seen to have turned to the Dark Side but balance can be brought to the Fforce with more data and adequately powered multi-center studies with longer follow-up. We owe it to our CLI universe of frail patients.

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