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Re-analysis of Old Data and New Outcomes Data Do Not Support a Link Between Paclitaxel Coated Balloons and Paclitaxel Eluting Stents and Mortality: These Devices Should be Used in PAD (Peripheral Arterial Disease) Treatment in Femoropopliteal Disease on the Basis of Their Published Efficacy

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Introduction

The efficacy of Paclitaxel DCB (drug-coated balloons) and DES (drug-eluting stents) has been proven in several well-regarded landmark trials [1–3]. DCBs achieved up to 82.2% primary patency and 2.4% freedom from TLR (target lesion revascularization) at 1 year, sustained over 3 years with 69.5 and 15.2% [4] compared to PTA alone (52.4 and 20.6% at one year; 45.1 and 31.1% at 3 years). The efficacy of DES has been proven for two DES – the ZilverPTX (Cook Medical, Bloomington IN) and the Eluvia DES (Boston Scientific Corp., Marlborough MA). For the ZilverPTX trial, 5 years of data are available with primary patency and freedom from TLR of 66.4 and 83.1% respectively, compared to optimized treatment with PTA and/or bare metal stents reaching 43.4 and 67.6% [5]. Data for the Eluvia DES are available in the MAJESTIC trial and the IMPERIAL trial indicating primary patency and freedom from TLR at 2 years in 83 and 87.3%, respectively. [6–9].

These encouraging data were responsible for an increasingly widespread use of drug-based therapies in PAD treatment in femoropopliteal disease. With regards to the below-the-knee (BTK) segment, the available data are not yet sufficient to prove efficacy of DCBs. Conversely, short balloon-expandable DES adapted from cardiology product portfolios have proven efficacy for BTK lesions, mainly as a bailout option in case of failed PTA [10].

In 2018, Katsanos et al. published a meta-analysis on randomized controlled trial data using drug-based therapies with Paclitaxel coated DCBs and DES in claudicants in the femoropopliteal segment. They reported a mortality signal indicating an increased death from all causes of 14.7% at 5 years using Paclitaxel, whereas the all cause of death after PTA was 8.1% at 5 years [11]. This resulted in a metaphorical Tsunami destroying confidence worldwide in Paclitaxel as a safe drug to use for the inhibition of restenosis. The aim of this article is to focus on the mortality risk of Paclitaxel in femoropopliteal DCB and DES usage, and to discuss recent evidence which calls into question such a risk.

Following publication of the Katsanos meta-analysis, major efforts were immediately initiated by endovascular practitioners and industry leaders to review the datasets that were used by Katsanos et al. for their analysis. An FDA expert panel was instituted and produced several

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outputs including sequential updated FDA statements to health care providers and an FDA editorial in Circulation. There were also several national recommendations produced by national expert panels such as the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) in Germany and the UK MHRA (Medicines and Healthcare products Regulatory Agency). There were also statements from international specialist societies such as CIRSE.

In general, all of these publications advocated caution in the use of Paclitaxel and a more detailed informed consent process explaining to the patient a potential mortality risk of Paclitaxel in the intermediate and long-term post procedure. In some cases (e.g. MHRA), practitioners were instructed to limit the use of Paclitaxel-containing devices (PCDs) to a narrow subset of patients e.g. critical limb-threatening ischaemia.

These restrictions on the use of DCB and DES had the effect of reducing substantially the use of Paclitaxel DES and DCB worldwide. This had several effects including the loss of the proven benefits of drug-based device therapies to patients in terms of reduced patency of femoropopliteal angioplasty and stenting using non-PCDs, and probably an associated increase in the need for hospital readmission rates for repeat revascularization procedures.

In addition to the assessment of patient-level data of the existing datasets used for the Katsanos paper mentioned above, new (meta-)analyses from similar patient pools (existing and new patients included) that included assessment for mortality were conducted and published [12–19]. Other studies on randomized industry data, independent randomized data and observational data that also assessed specifically for a link to mortality as well as patency and TLR were initiated and their outcomes are also now in the public domain.

The most important findings include the following:

1. A new meta-analysis, which is based on the same group of RCTs analyzed in the Katsanos meta-analysis concluded that there is a minimal or no increase in mortality associated with PCDs. Moreover, when the patient-level data of the trials used for the Katsanos meta-analysis were assessed, the absolute increased mortality risk associated with Paclitaxel use at 5years decreased from 14.7 to 4.6% [12]. Disparate study designs, mixed data sources, and variable ascertainment rates may explain differences in reported mortality outcomes [12]. However, the FDA commented in an editorial in Circulation in 2020 that the data as mentioned above suggest increased mortality similar to the reports by Katsanos and the FDA resulting in a relative risk of 1.93 and 1.57, respectively [13]. This was similarly observed in a subsequent US FDA review of US-approved devices [14]. However, it must be highlighted that these RCTs were designed to make conclusions about short-term, limb-related endpoints, and not long-term mortality.
2. Recent pooled randomized trial data with updated vital status (vital status serves as an indicator of whether a patient is alive or deceased.) ascertainment (re-analysis of the trials used for Katsanos) showed that paclitaxel was associated with improved efficacy but was not associated with increased mortality [15]. Evaluation of the long-term 5-year all-cause mortality of Paclitaxel-Coated Zilver PTX Drug-Eluting Stents used in the ZilverPTX trial showed a 5-year vital status of 94% of the patients and no mortality signal related to Paclitaxel [16]. Data evaluation from other patient cohorts even reported advantages in survival with drug-based therapies [17–19]. Treatment with drug-coated devices was associated with a lower cumulative incidence of all-cause mortality compared with non-drug-coated devices through 600 days post procedure (32.5% vs 34.3%, respectively; log-rank P = 0.007). No evidence of increased all-cause mortality following femoropopliteal artery revascularization with drug-coated devices compared with non-drug-coated devices was found in this retrospective cohort study that included 16 560 patients and drug-coated devices were used in 5989 participants (36.2%) [17]. In assessment of real-world data from 64,771 patients in Germany who received 200,681 devices, no evidence for increased mortality associated with paclitaxel-based drug-eluting devices was found for over 11 years of follow-up [18]. Even for BTK lesions, 10-Year Paclitaxel Dose-Related Outcomes of Drug-Eluting Stents Treated Below the Knee in Patients with CLTI Ischemia (The PADI Trial) showed no difference in the 10-year mortality between the paclitaxel-coated DES and PTA ± BMS in patients with CLI treated below the knee. Additionally, no dose-related adverse effects of paclitaxel-coated DES were observed in CLI patients treated below the knee [19].

Various types of bias that may have led to the Katsanos mortality effect exist. An in-depth discussion of these are outside the scope of this article. However, a major flaw in the Katsanos conclusions was that all trials used in the 2018 meta-analysis were formulated to specifically evaluate primary endpoints such as primary patency and TLR. None of those trials were designed to assess for a difference in mortality between the patient groups treated by the Paclitaxel eluting devices or the controls.

Overall, a robust body of evidence now exists to refute the existence of a long-term mortality signal associated with PCDs i.e. any mortality risk is negligible or absent. Finally, all efforts to find a link and a causal explanation

for the perceived mortality risk between Paclitaxel dose and mortality have failed. None of the studies found a single cause or group of similar causes that might explain mortality following PCDs.

Clearly, having raised the potential issue of a link between mortality of drug-based therapy, further investigation for such an effect must continue. Future endovascular device trial designs must incorporate strategies and methods to maximize patient retention and facilitate long-term assessment and reporting of vital statistics including mortality. There is also a need for further research into the determinants of coating transfer. One of the major challenges in drug therapy is how to achieve the selective delivery of small-molecule drugs and proteins to the intended therapeutic target [20] from PCDs and similar technologies using Sirolimus.

We await with interest data on the efficacy of Sirolimus-eluting devices (SED) and also data regarding comparative efficacy PCDs compared with SEDs.

In summary, since the publication of the 2018 article by Katsanos, analysis of the patient level data from the trials used for that meta-analysis and all subsequent studies and trials have failed to find a significant risk of mortality for patients who have been treated by Paclitaxel DCB or DES.

In the absence of a proven risk of mortality of PCDs, we advocate that the benefits of Paclitaxel coated device use in the femoropopliteal segment in terms of increased primary patency and reduced TLR warrant their use in the routine treatment of patients with femoropopliteal disease.

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Declarations

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