The paclitaxel files – reasonable doubt or acquittal?

Comment on Böhme et al., pp. 132–138

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Currently, we are all living in dire straits not only because a global pandemic threw the world into turmoil. There is evidence for collateral damage particularly affecting patients with cardiovascular and cerebrovascular conditions [1]. Certainly, another major health problem affected the same target population, and most of us might have forgotten that two sensational meta-analyses recently initiated a heated discussion among physicians treating patients with peripheral artery disease [2, 3].

In 2018 and 2020, Katsanos et al. used summary-level data from randomized controlled trials (RCT) and revealed worse overall survival and amputation-free survival in patients exposed to paclitaxel-coated devices in femoropopliteal and crural arteries, respectively [4, 5]. Since then, although hidden behind the Covid-19 pandemic, the paclitaxel controversy is still ongoing and the end is not yet in sight. Interestingly, in a follow-up meta-analysis using patient-level data on 2,185 patients, the authors confirmed the safety signal, which was not the case in other recent studies [6–8]. Adding to the notably conflicting knowledge base, Böhme et al. now presented new evidence on the matter using data from a large consecutive cohort from a renowned high-volume centre in Germany [9]. Among 8,377 patients that have been treated at the study centre between 2010 and 2016, 624 patients with femoropopliteal lesions were included in the study and subsequently followed for 36 months. In their analyses, the authors found no evidence for a survival disadvantage of patients exposed to paclitaxel-coated balloons when compared to uncoated balloons neither in the full sample nor when taking cumulative paclitaxel dose into account [9]. Within the study period, a staggering 66% of all patients died with carcinoma as most common cause confirming the relevance of cancer in these patients [10]. These findings represent crucial new information for a particularly interesting and high-risk population. While RCTs typically included patients with milder disease severity, younger age and predominantly male sex, the current study focussed on older patients with critical limb ischaemia (Rutherford 5) and exhibited a well-balanced sex ratio. It appears also of great benefit to use data from a single center whereas

meta-analyses often draw their conclusions from heterogeneous cohorts. Having that said, the central question is how cohorts in RCTs vs. real-world cohorts differ. Yet, in this study patients exposed to paclitaxel were younger and potentially suffered more often from chronic comorbidities compared to unexposed patients. The slightly higher rates of relevant post-discharge medication, especially regarding lipid-lowering drugs, may also point at general differentials in treatment among the study groups. In light of the various cautions from regulators worldwide, these results and conclusions appear heartening. Remarkably enough, to date, no single real-world study using a registry or administrative data was able to confirm the association of paclitaxel usage and increased overall mortality. If anything, there are large-scale observational studies using weighting methods and propensity score matching to adjust for confounding that revealed no mortality differences or even improved overall survival in patients exposed to paclitaxel-coated devices [11–14]. Against that backdrop, it has to be emphasized that data from unselected registries are commonly-accepted to be the first choice for quality assurance, most importantly for rare and late (safety) outcomes, while RCTs remain the gold standard in causal research and clinical efficacy.

However, even the strongest proponent of real-world evidence must admit that the challenge of residual confounding remains unsolved to date. The patient populations likely differ across RCT and real-world data. Moreover, patients suffering from peripheral artery disease often exhibit complex comorbidities and numerous succeeding treatments in different vascular beds. Therefore, marginal differences in the inclusion and exclusion criteria, variable selection, and statistical models likely have a significant impact on the results. However, even RCTs are not beyond reproach, and secondary analysis of data from a RCT might be potentially less valid if it was not sufficiently powered from the beginning [15].

Having that said, is the current study by Böhme et al. just another brick in the great wall of evidence or should the cardiovascular community finally close the case? In May 2021, after a transition phase of three years, the new European Union Medical Device Regulation (MDR) will

come into force. Regulators, notified bodies, and medical device industry will have to find a consensual agreement how they can handle emerging device-related health problems in the future to guide physicians through the best possible care of patients receiving implantable devices. Global public-private partnerships such as the Medical Device Epidemiology Network (MDEpiNet) with international chapters in five countries can help to connect all stakeholders in a certain framework and implement a graduated model of approval.

While focusing intensively on potential benefits or harms of drug coating with still insufficient evidence for either of the two, we learned an important general lesson in this innovative field. In the face of the dramatically impaired life expectancy of vascular patients at an advanced disease stage, research on factors affecting long-term survival should definitively receive a much higher priority.

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