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COMMENTARY

The Truth on Paclitaxel and the Mysterious Ways of Data Interpretation?

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Recently, the endovascular community was alarmed by a paper regarding a meta-analysis of drug-eluting therapies for steno-occlusive disease of the superficial femoral and popliteal artery (generally considered to be clinically beneficial), suggesting an increase in mortality when using these devices [1]. The same paper also found indications of a dose relationship of paclitaxel and mortality. In this issue of CVIR, a paper by Albrecht et al. [2] evaluates the midterm outcomes of four German studies using paclitaxel-coated balloons. The authors should be congratulated on their timely and expedite re-evaluation of these four studies that were already published in CVIR last year [3]. While the 2018 paper focused mainly on outcome in relation to lesion characteristics, 2-year mortality rates were also (briefly) reported. The most recent paper by Albrecht re-evaluated patient-level data for mortality and looked at the relation between paclitaxel dose and mortality. As in the 2018 paper, no statistically significant difference in mortality was seen: it is, however, important to note that the mortality rates in the 2018 paper were given as 5.5% for the uncoated group and 7.9% for the drug-coated balloon group ($p = 0.317$), while in the 2019 paper mortality rates were calculated to be 7.0% and 8.7%, respectively ($p = 0.55$). The higher mortality rates seen when using patient-level data (that take into account those patients that withdrew consent or that were lost to follow-up) emphasize the importance of using patient-level data. In fact, the Katsanos paper has been criticized for the fact that no patient-level data but only trial-level were used [4].

Further support for an absence of an increased mortality came from a recent paper from Schneider et al. [5] that included patient-level data from some of the trials that were also included in the evaluation by Katsanos et al., as well as one additional randomized control trial and a global registry with the same device. Although a correction of this paper was necessary because of a source code programming error, the new calculation that resulted also showed an absence of a statistically significant difference in an all-cause mortality [13.16% in the drug-coated balloon group and 10.98% in the angioplasty group ($p = 0.188$)] [6].

All papers mentioned in the Katsanos paper reported on outcomes in trials including mainly claudicants and may therefore not reflect a 'real-world' scenario. The safety of drug-eluting devices in daily clinical practice that includes both patients with intermittent claudication and critical limb ischemia has been demonstrated in two recent studies that evaluated two large cohorts of Medicare patients (16.560 and 51.456 patients, respectively) [7, 8]. No difference between drug-eluting therapy and 'standard' (non-drug based) therapy was seen. The analysis that included drug-eluting stents only [8] had a median follow-up of 2 years, while the other study (that included both drug-eluting stents and drug-coated balloons) had a mean follow-up of 389 days [7]. The follow-up of the latter study may still be too short in order to be able to exclude a safety hazard, keeping in mind that the difference in mortality as demonstrated by Katsanos became only obvious after 2 years of follow-up, became more pronounced at 3 years of follow-up, and then diminished for some drug-eluting

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devices at 5-year follow-up. Given the differences in paclitaxel dose, presence of polymers, and pharmacokinetics [4], a separate analysis of drug-eluting stents and drug-coated balloons also seems to be warranted.

One of the other issues that was raised in the Katsanos meta-analysis was the relationship between paclitaxel dose and mortality. Dose estimation was based on the lesion length as described in the original papers. The paper by Schneider et al. [5] estimated the total dose of paclitaxel on the basis of the number and length of the balloons used as estimated from patient-level data (without correcting for the residual paclitaxel that always remains on the balloon). In the overall population, there was no statistically significant difference in the nominal paclitaxel dose between those patients that died and those that survived (12.20206 ± 7.72166 µg vs. 11.36872 ± 7.37119 µg; $p = 0.186$; data from updated version [6]). Also a survival analysis that stratified the study population in three terciles based on nominal paclitaxel dose (low, mid, and high dose) could not demonstrate an statistically significant difference in all-cause mortality [5]. In the study by Albrecht et al. presented here, all angioplasty balloons were returned to the various sponsors, and by quantifying the residual amount of paclitaxel on the balloon, the actual dose delivered to the patient could be determined (which is probably the most reliable method). A dose relationship could not be confirmed, and the mean delivered paclitaxel dose in the patients that died was actually numerically lower than those surviving (although this difference was not statistically significant).

Other similar studies re-evaluating patient-level data for various devices from different manufacturers are on their way. It is of utmost importance to get these studies performed, and the ultimate goal should be to pool all data and perform a new meta-analysis using patient-level data (since controversy exists over the validity of systematic reviews and meta-analyses using trial-level data [4, 9]). This can be done using the same statistical method as Katsanos et al. have used (in order to eliminate any influence of methodology), or any other validated statistical method.

While awaiting further analysis, on March 15, 2019, the FDA issued a letter to healthcare providers stating 'our preliminary review of this data has identified a potentially concerning signal of increased long-term mortality in study subjects treated with paclitaxel-coated products compared to patients treated with uncoated devices,' followed by several recommendations and a statement that the data should be interpreted with caution and further evaluation of the data is necessary (https://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm633614.htm; accessed March 17, 2019).

All randomized controlled trials involving drug-eluting therapy have been performed on patients that presented in the majority of cases with intermittent claudication. It is well known that the 5-year mortality in this patient population is different from those patients that present with critical limb ischemia. Therefore, it is important to rule out any relationship of therapy with increased mortality in a patient group that is treated for a lifestyle-limiting disease. It should, however, also be kept in mind that also in patients with claudication that are treated with non-drug-eluting therapy their survival varies with the comorbidities they present with. A recent Japanese study that evaluated 5-year prognosis after non-drug-eluting endovascular therapy in patients with intermittent claudication caused by iliofemoral disease stratified patients into low-, moderate-, and high-risk categories, based on their comorbidities [10]. The overall survival rates at 5 years was 83.4%, while the risk stratification analysis showed a significantly lower survival rate in high-risk patients (53.5%) as compared to the medium- and low-risk groups (78.6% and 90.1%, respectively; $p = 0.0001$), and therefore, the natural course of patients with intermittent claudication may not be as benign as always thought. This is also reflected by mortality rates as seen in trials evaluating bare metal stents, where mortality at 3 years ranged from 9 to 14% [5].

All the above underscores the fact that all data need to be interpreted with caution and that thorough knowledge of statistical methods is necessary in order to reach a final conclusion. The issue raised by Katsanos et al. is extremely important and needs to be taken seriously. Thus far their findings have not been confirmed in published analyses of patient-level data with extended follow-up. It is probably too early to rigorously stop the use of paclitaxel-eluting devices, but we should reflect and re-analyze the currently available new data. There is still a lot of information lacking, and until this gap in knowledge is filled in, the jury on the topic is still out.

Compliance with Ethical Standards

Conflict of interest The author states he has no conflict of interest.

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