Is There a Real Association Between Paclitaxel Devices and Mortality? Time to Pause and Re-Evaluate What We Know About This Statistical Finding

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Drug-eluting stents (DES) and drug-coated balloons (DCB) were approved in the United States on November 2012 and February 2015, respectively. Before this, the majority of patients with lower extremity femoropopliteal peripheral artery disease were treated with PTA (percutaneous transluminal angioplasty) or nitinol, self-expanding stents. However, these devices had significant rates of restenosis, which frequently led to repeat revascularization and were associated with increased healthcare costs. Therefore, the approval of DES and DCB had a profound impact on the management of lower extremity peripheral artery disease and led to the transitional pass-through code approval by Center for Medicare and Medicaid Services, which has rarely been designated for vascular devices.[1,2] Since then, numerous analyses have consistently shown the clinical superiority of DCB over balloon angioplasty with long-term (5-year) data.[3,4] Moreover, both DES and DCB have been shown to be cost-effective therapies, with improved quality of life.[5] Indeed, given the strength of evidence, many experts have encouraged better reimbursement for DES and DCB to encourage wider utilization of these proven technologies. In addition, professional societies have graded this therapy as a class I recommendation with highest evidence.[1,2,6]

However, on December 6, 2018, the *Journal of the American Heart Association* (*JAHA*) published a meta-analysis by Katsanos et al that revealed an increase in long-term mortality with DES and DCB.[7] Briefly, the study evaluated 28 randomized control trials across 12 devices for the treatment of femoropopliteal disease. At 1 year, the analysis included 4432 patients and showed no difference between the paclitaxel-eluting arm and the control arm for all-cause mortality (2.3% versus 2.3%, relative risk 1.06, 95% CI 0.72–1.61). However, at 2 years with 2316 patients (n=12 studies), there was an increase in all-cause mortality with paclitaxel devices compared with control (7.2% versus 3.8%, relative risk 1.68, 95% CI 1.15–2.47). Similarly, at 4–5 years with 863 patients (n=3 studies), there was a persistently higher risk of all-cause mortality for paclitaxel devices compared with control (14.7% versus 8.1%, relative risk 1.93, 95% CI 1.27–2.93). That increased risk was demonstrated as stable in various sensitivity analyses, including DES versus DCB. Moreover, the authors used a dose calculation formula to demonstrate that trials with a higher dose of paclitaxel had a higher risk ratio (highest with a 3.5-mg dose). This dose response was confirmed on meta-regression with 0.4% increased risk for every paclitaxel mg-year.

Overall, the Katsanos et al meta-analysis was well conducted, given the available data; however, it also had many limitations. Most importantly, it did not provide an explanation for or proof of a causal relationship, but rather a hypothesis-generating statistical association. It was a summary level meta-analysis which did not include patient-level data to adjust for clinical and angiographic differences between those who died and those who did not. Less than 50% of the included trials reported data beyond 1 year, 1 had 4-year results, and only 2 reached the 5-year time point. There were a significant number of patients lost to follow-up who were not accounted for in this meta-analysis. Furthermore, the study was conducted as an intention-to-treat analysis; while this is the most valid approach to assess efficacy in randomized clinical trials, it does not represent the "true paclitaxel exposure" when assessing a safety signal, particularly because many of these trials had substantial crossover to the experimental treatment arm. Additionally, the dose-dependent relationship is likely to be flawed, because the equation used to assess the paclitaxel dose/time relationship

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is thought to have overestimated drug exposure and its effect over time. Ultimately, the study findings could be by chance, a type-1 error because of multiple testing, or hidden biases because of incomplete and unstructured follow-up in these trials.

Given the significant concern about a potential association between paclitaxel devices and mortality, the scientific community, the US Food and Drug Administration (FDA), and professional societies have all responded. Collectively, the consensus has been that the benefit of these devices outweighs any potential risk. The scientific community has also responded with multiple studies using patient-level trial data and real-world data sets to provide further evaluation of the long-term safety of DES and DCB. The first set of studies was presented at the 2019 Leipzig Interventional Course (LINC) on January 22, 2019. During that conference, unpublished data from major clinical trial programs that involved drug-eluting devices were presented to the public, providing greater understanding of the safety of these devices through a deep-dive analysis of patient-level data. The most descriptive data came from Medtronic's Total IN.PACT DCB program,[8] which were simultaneously published in *Journal of the American College of Cardiology.*[9] This huge data set provided supportive evidence for the safety of the IN.PACT DCB in comparison to balloon angioplasty. Two-year mortality rates were shown from major trials of both drug-coated and non-drug-coated devices, and demonstrated similar death rates across different device types. For instance, the IN.PACT Global DCB trial had a 2-year mortality rate of 7.0%,[10] which was comparable to mortality rates associated with the Zilver PTX DES (Zilver PTX RCT; 7.6%),[11] EverFlex Self-Expanding Peripheral BMS (DURABILITY II trial; 7.7%),[12] and uncoated balloons (LEVANT I trial; 12.2%).[13] Furthermore, data from a patient-level meta-analysis of both randomized clinical trials and registry data involving the IN.PACT DCB were presented. This analysis, which involved 1837 patients treated with the IN.PACT DCB and 143 control patients treated with uncoated balloons, demonstrated a similar cumulative incidence of mortality at 5 years between groups (15.1% versus 11.2%, respectively; P=0.092). There was also no difference in mean paclitaxel dose between patients who died or survived, and when stratified by tercile of DCB-delivered paclitaxel dose, those who received the highest tercile dose were at no greater risk and had numerically fewer deaths compared with those treated with the mid- and lowest-tercile doses.[9] Importantly, the authors also evaluated differences in compliance with the study protocol's follow-up schedule among those treated with DCB and uncoated balloons. Patients treated with DCB were found to be less compliant with scheduled follow-up, and study compliance correlated with better survival. This raised the question as to whether the relationship between drug-coated devices and survival was biased by lower rates of compliance compared with those in the control arm, who then received more frequent medical contact and possibly better medical care.

Data from other peripheral DCB programs were also presented at LINC, further supporting the safety of this class of device. Results from the Lutonix DCB program demonstrated a similar cumulative incidence of survival at 60 months between the Lutonix DCB (N=1029) and uncoated balloons (N=160) (82.7% versus 87.8%, respectively; P=0.264).[14] An analysis of the Stellarex DCB program also showed comparable cumulative incidences of 3-year mortality between the Stellarex DCB (N=419) and uncoated balloons (N=170) (9.3% versus 9.9%, respectively; P=0.93).[15] Finally, from the Ranger DCB program, 3-year mortality rates between the Ranger DCB (N=65) and uncoated balloons (N=28) were numerically similar (13.8% versus 10.7%, respectively).[16]

Data supporting the safety of peripheral DES were also presented at LINC. Re-analyzed 5-year data from the ZILVER PTX RCT program, which used survival analysis methodology to account for patient withdrawal and loss to follow-up, demonstrated a cumulative incidence of death associated with the ZILVER PTX (N=336) that was comparable to that following treatment with uncoated balloons and/or bare metal stents (N=143) (18.7% versus 17.6%, respectively; P=0.53). In addition, shorter-term safety data from the Eluvia DES program demonstrated similar 1-year mortality rates between the Eluvia DES (N=301) and the Zilver PTX DES (N=152) (2.0% versus 3.9%, respectively).[16]

Shortly after the presentation of these data, the first of 2 analyses from Medicare claims data were published in *JAMA Cardiology.*[17] In this analysis, the authors used *International Classification of Diseases, Tenth Revision-PCS* (*ICD-10-PCS*) codes to examine 16 560 Medicare beneficiaries who underwent inpatient revascularization with either a drug-coated device (DCB±DES) or an uncoated device (PTA± bare metal stent) in the year 2016. During a median follow-up of 389 days and longest follow-up of 600 days, there was a crude mortality signal favoring drug-coated devices (32.5% versus 34.3%, respectively; P=0.007), which was no longer statistically significant following adjustment for patient, procedural, and hospital characteristics (adjusted hazard ratio 0.97; P=0.43). No relationship was observed between device type (DCB or DES) and all-cause mortality, as well as among patients with or without critical limb ischemia. Notably, although median follow-up was only ≈1 year, among those patients with longer-term follow-up, there was no evidence of accumulating death in the drug-coated device arm between days 365 and 600, which would be expected if the 2-year mortality signal seen in the Katsanos et al meta-analysis[7] was reproducible.

In addition to this study, a second analysis of Medicare claims data involving a separate population of Medicare

beneficiaries who underwent DES implantation was published in *JACC*,[18] providing a longer period of follow-up after paclitaxel exposure. Using *ICD-9-PCS* claims codes, the authors examined 51 456 Medicare beneficiaries who underwent in-hospital peripheral artery stenting with either a DES or a bare metal stent from December 1, 2012 (which corresponded with the approval of the first peripheral DES, the Zilver PTX) through September 30, 2015. Over a median follow-up of 2 years and longest follow-up of 4.1 years, the study found similar crude survival between DES and bare metal stent implantation (51.7% versus 50.1%, respectively; P=0.16). This relationship remained statistically nonsignificant after multivariable adjustment (adjusted hazard ratio 0.98, P=0.53), and persisted among the subgroup of patients with and without critical limb ischemia.

Appraising these apparently conflicting data has been challenging for the vascular community. Faced with an association between the use of paclitaxel-eluting technology and mortality, there is an ongoing attempt to identify a plausible biological mechanism for paclitaxel-related death. Wide consultation with toxicologists, oncologists, and scientific researchers has so far failed to identify any such mechanism. This is surprising for a drug that has been used extensively in oncology for many years (first FDA approval 1992), at doses that far exceed that received from DES and DCB (≈200–400-fold), in a patient population that has shown no increased long-term mortality risk and is considered so safe it is used in pregnant women.[19] Without a plausible explanation of how low doses of paclitaxel, liberated locally in the femoropopliteal artery, could lead to death 3 to 5 years after treatment, experts have begun to consider whether the meta-analysis findings are simply a statistical association, and started a search for alternative explanations.

Randomized controlled trials were designed to compare pharmaceutical drugs with one another or placebo. One of the fundamental principles of a well-conducted randomized trial is that of blinding the participants, healthcare team, and outcome assessors. However, it is extremely difficult to blind the healthcare team (study coordinator, interventionalist, and investigators) to the subjects' treatment arm in an interventional trial. It is well established that this failure to blind may result in performance and determination bias that significantly influences end points.[20–24] Although mortality is an end point that appears difficult to bias, it is in the proper classification of subjects from "lost-to-follow-up" or "withdrawn" to "mortality" where bias may creep in. Unlike Core lab adjudication used to assess outcomes such as restenosis and target lesion revascularization (TLR), mortality is generally adjudicated by the healthcare team themselves. In the 28 studies included in the Katsanos et al meta-analysis, all healthcare teams were unblinded and considered by those authors to have introduced a high risk of bias to the individual studies.[7] This is known to lead to conscious and unconscious bias in the ascertainment of whether subjects no-longer-contactable were simply that or had actually perished. The determination of such outcomes is dependent on the tenacity by which a healthcare worker pursues the answer through contact with the local doctor, family, hospital medical records, or Medicare documentation and is thought to be influenced by factors such as the study arm (experimental or control) and whether the subject had already failed their primary end point of patency or TLR. The proportion of subjects withdrawn or lost-to-follow-up in the 3 studies included at the 5-year meta-analysis time point was significant (THUNDER,[4] 22.9% and 46.3%; IN.PACT SFA,[25] 18.6% and 14.4%; ZILVER-PTX,[3] 30.3% and 26.1%; drug-coated versus control groups, respectively), leaving us to speculate how many of those lost were in fact mortalities, left unidentified. This is a failure of clinical trial design where the secondary end point of mortality has historically been given little consideration during the planning phase, and particularly relevant in a meta-analysis of mortality, given how influential a few misclassified episodes can be to outcomes of such low frequency. The unblinding and significant proportion of subjects lost-to-follow-up raises significant concerns around the accuracy of the pooled estimate in the Katsanos et al study, and in our view raises doubt over the legitimacy of the entire meta-analysis.

Another consideration is the difference in medication compliance and medical therapy regimen in each of the study arms. The efficacy in reducing rates of TLR by drug-coated balloons and stents is well established and not under debate. With the higher rates of TLR in the uncoated control arm come more presentations to the healthcare team. This was clearly demonstrated in the independent, patient-level analysis of the IN.PACT DCB clinical program. That analysis showed that over the 5-year study period, patients who had PTA treatment were more likely to be compliant with follow-up than those who received DCB (94.2% versus 87.9%; P<0.001), and those patients who survived at 5 years were more likely to have been compliant with follow-up than those who had died (88.3% versus 82.9%; P<0.001).[8] It is thought that those increased presentations provided an opportunity for the healthcare team to ensure compliance with best medical therapy. Furthermore, it is likely that with more frequent TLR events there was an escalation of medical therapy as is common practice, to improve risk factor control for dyslipidemia, hypertension, hyperglycemia, lifestyle modifications, and smoking cessation, or to commence additional antiplatelet and/or anticoagulation agents. Controlling for each of those risk factors and adding such additional agents is known to reduce mortality.[26]

These proposed mechanisms for both the underreporting and reduction of mortality in the control arms of each RCT in the Katsanos et al study provide a scientifically plausible, alternative explanation for the observed "association with paclitaxel." Such a mechanistic theory becomes all the more

compelling in the absence of a rational biological mechanism for paclitaxel-related mortality.

Collectively, we believe Katsanos's article represents nothing more than a statistical association with multiple explanations for the findings, as we have detailed above. We applaud the efforts of the FDA and other third parties for commencing independent, patient-level meta-analyses aimed toward a higher level of understanding and hope that they give further insight towards determining the truth. However, if this statistical association is because of bias from clinical trial design, it is likely that any repeat analysis of the same data will find a similar association between paclitaxel use and mortality. Indeed, the recent FDA announcement revealed a preliminary association between paclitaxel devices and mortality. It is our view that safety end points such as mortality need to be prioritized in current and future clinical trials designed to evaluate paclitaxel-coated devices. It is of utmost importance that we understand the outcomes of subjects who withdraw from studies or are lost to follow-up, utilizing tools such as electronic communication, fastidious, systematic follow-up protocols, and death registry data-linkage. We also believe that real-world analyses like those from Medicare data are at least as relevant as randomized control trials, because although they may be at risk of confounding, they provide us with the largest experience of the very patient population we are treating. It is certainly true that any drug or device association with mortality requires serious evaluation and consideration; however, an overreaction at this juncture could lead to dire public health consequences at a time when we are still uncertain of the truth. Collectively, given the current state of our knowledge about this association, we found the recent FDA announcement on March 15, 2019 surprising. The current FDA communication will likely result in significant reduction in DCB use and will potentially have negative consequences on public health. We look forward to learning more from those analyses; however, at the present time we believe that the undisputed benefit of DES and DCB outweigh their theoretical and uncertain risk.

Disclosures

Shishehbor is a global advisor for Medtronic, Abbott Vascular, Boston Scientific, Phillips, and Terumo. Varcoe is a consultant for Abbott Vascular, Medtronic, Intervene, and Shockwave. Secemsky has no disclosures to report.

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