Peripheral Paclitaxel Update

Lessons on the use of paclitaxel-coated devices in femoropopliteal disease from the long-term RCT and registry data.

By Peter A. Schneider, MD

Endovascular intervention for femoropopliteal occlusive disease is practiced widely in patients who require lower extremity revascularization for chronic limb-threatening ischemia (CLTI) or claudication, the main benefit of which is its less invasive nature compared with that of open surgery. However, the longer-term patency with endovascular mechanical manipulation alone (ie, balloons, atherectomy, stents) has been poor compared with surgical bypass, especially in patients with long lesions (TransAtlantic Inter-Society Consensus C and D). Biologic therapy added to mechanical therapy has been a major step forward in improved patency and has resulted from use of paclitaxel-coated balloons (PCBs) and paclitaxel-eluting stents (PESs).

Multiple trials have been conducted in the femoropopliteal arteries using PCBs or PESs. Trials have included prospective randomized trials of coated versus noncoated devices; prospective randomized trials of different coated devices in a head-to-head fashion; and prospective single-arm trials, registries, observational studies, and database analyses. The most important of these trials are the IN.PACT SFA, LEVANT, ILLUMENATE, RANGER SFA, Zilver PTX, and IMPERIAL trials.[1-11] Although a summary of all these studies is beyond the scope of this article, the dramatic improvement in patency with PCBs and PESs has been routinely evident. As a result, numerous PCBs and two PESs have been cleared by the FDA for use in the femoropopliteal arteries.

THE PACLITAXEL META-ANALYSIS

At the end of 2018, a summary-level meta-analysis was published by Katsanos et al that evaluated international randomized trial results up until that time.[12] The article demonstrated substantial risk of mortality with a hazard ratio (HR) of 1.93 at 5 years in patients who received paclitaxel compared with those treated with uncoated devices. The study also claimed a biologic gradient or dose response. This was calculated with the dose equal to the amount of estimated paclitaxel on the balloon or stent multiplied by time. The authors' conclusion stated, "There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted."[12]

This very definitive conclusion led to a drastic and immediate change in the use of PCBs and PESs. Prior to that time, drug-coated balloons (DCBs) and drug-eluting stents (DESs) had been included in the treatment algorithm in up to half of cases of femoropopliteal interventions performed. As clinicians, researchers, institutions, regulatory bodies, manufacturers, and all associated personnel sought to understand this to ensure patient safety, use of these devices came to a stop.

Key factors in evaluating whether an agent is causing harm include dose response (biologic gradient), clustering of deaths as to cause (suggesting a mechanism), and a consistent danger signal. In the ensuing 3.5 years, a substantial amount of inquiry has been undertaken and additional data have accumulated. Although it is beyond the scope of this article to list these data in line-item fashion, there has not been a single credible subsequent study that showed a late mortality risk anywhere approaching that asserted by the summary-level meta-analysis after paclitaxel usage in the femoropopliteal arteries.

These data have included additional follow-up of preexisting randomized controlled trials (RCTs). A substantial effort was undertaken to ascertain the vital status of patients who had been lost to follow-up or withdrawn. The passage of additional time and the maturation of additional RCTs resulted in a dramatic increase in available 5-year data from three studies (863 patients) to nine studies (2,288 patients).[13] Additional RCTs had been

designed for other purposes but also became available for post hoc analysis of any evidence of a mortality signal. A prospective RCT (VOYAGER PAD), which included drug-coated devices in 31% of 4,316 patients, and a prospective RCT of drug-coated versus plain devices from Sweden (SWEDEPAD, n = 2,289) both demonstrated no difference in mortality between those who received paclitaxel and those who underwent treatment with uncoated devices.[14,15] Data were analyzed from various databases, including the BARMER database from Germany with up to 11 years of follow-up, a study of tens of thousands of Medicare recipients (SAFE-PAD), the Optum database of United States Medicare Advantage patients, a study from the United States Veterans Administration, the Vascular Quality Initiative, and others.[16-20] With added follow-up to the previous RCTs and identification of many of the patients lost to follow-up, the steps of the initial summary-level meta-analysis were retraced with the same operations and the larger cohort of long-term follow-up, and this demonstrated no significant difference between paclitaxel-coated and uncoated devices with respect to mortality.[13]

LESSONS LEARNED

A summary-level meta-analysis showed an increase in mortality[12] that shut down worldwide use of one of our most effective treatments for femoropopliteal occlusive disease, but we subsequently have been unable to detect this initially very dramatic and threatening signal of harm to our patients. In any complex system with multiple fail-safe mechanisms, it is usually multifactorial when there is a malfunction, and this appears to have been the case with the paclitaxel mortality signal. The following are factors related to epidemiology, clinical practice, and trial design that have emerged and lessons that we will carry forward to enhance our development of patient-care algorithms.

- **DCBs and DESs were effective, with improved results of the treatment of femoropopliteal lesions at 5 years.** PCBs and PESs were not used for almost 4 years and were not of value to patients because of our mistaken interpretation of the situation. We would like to optimize results and minimize harm for our patients. Restricting the use of efficacious treatments also produces some degree of harm.
- **A summary-level meta-analysis is a hypothesis-generating tool.** It should not be used for dictating practice. Inclusion of the Zilver PTX trial in the meta-analysis is a case in point. In the Zilver PTX trial, because of the dual randomization scheme with a secondary randomization of suboptimal percutaneous transluminal angioplasty (PTA) to bare-metal stents versus PESs and because many patients who had optimal PTA in the original PTA group subsequently crossed over to paclitaxel, about 70% of the study participants received paclitaxel. When analyzed "as treated," the trial actually showed no difference in mortality between coated and noncoated stents.[7] The authors of the meta-analysis could not have known this because these details were not thought to be germane and were not published at the time.[7,21] This is important because the Zilver PTX trial comprised 47.7% of the weight of the 5-year data available in the summary-level meta-analysis and had the largest HR demonstrating a mortality risk (2.09).
- **The summary-level meta-analysis was published with an unsupported equation for dose response, which is an important factor in establishing causation of a harmful agent.** Dose response was the purported "smoking gun" for an offending agent in this case that moved the discussion from association to causation.
- **Mortality is an extremely important patient-related issue for both claudication patients and those with CLTI.** As a field of specialists, we have developed a much better understanding of mortality, its causes, and its impact on our patient population. Mortality will continue to be a more important facet of clinical trials going forward than it has been in the past.
- **Studies designed for regulatory approval have been powered for 1-year efficacy, not long-term mortality.** Sample sizes in some of the studies were small enough that a few events one way or the other could drastically change the result. An example of this was seen in the IN.PACT trial in which the PTA group had the lowest-ever reported mortality measured in a peripheral artery disease trial at 1 and 2 years.[1] Smaller sample sizes can lead to unstable estimates, especially when doing a subsequent analysis of a variable for which the trial was not powered to assess.
- **With respect to trial design, a 1-year follow-up is important for understanding efficacy, but longer-term follow-up with more complete data is required to understand the bigger picture.** Approval trials are typically committed to 5 years of follow-up; however, the number of patients lost to follow-up beyond 1 year in these trials was excessive, and going forward, this must be corrected.
- **Ascertainment bias was present in the paclitaxel RCTs.** In other words, patients were randomized going into the trials but were not randomized in the way in which they were lost to follow-up or withdrawn. Within each study, some patients previously lost to follow-up or withdrawn were identified and their vital status was ascertained, and the difference in mortality between the control group and the paclitaxel group became smaller. Thus, the actual mortality rate for

paclitaxel was lower than thought and/or the actual mortality for PTA was higher than it seemed.[22]

- **An RCT can still have treatment bias.** These studies cannot be double-blinded trials because they involve treatment with a specific device, and as a result, patients in each group may have been treated differently. There was circumstantial evidence to support the presence of treatment bias in some studies.[23] Where the data exist, the veracity of clinical visit follow-up was higher for those in the control group who received the less efficacious treatment than those in the experimental group who received the more efficacious treatment, suggesting that other differences in treatment—such as smoking cessation, statins, antiplatelet agents, and antihypertensives—may also have taken place.
- **No dose response was identified.** This was true with each of the DCBs and DESs that were evaluated in multiple studies.
- **No clustering of deaths was identified that would assist us in hypothesizing a mechanism of action for how paclitaxel could be causing harm.**
- **There was substantial geographic variation of mortality.** Why would an agent that is causing mortality be more harmful in one geography and of no harm in another?
- **In these trials of DCBs and DESs, medications were generally not monitored,** including statins, antiplatelet, antihypertensive, and antiglycemic drugs, all of which likely have a significant effect on mortality, especially in the long term.
- **In most situations, we place the value of real-world data (such as an insurance database or Social Security database) at a lower level of quality than that generated by an RCT.** However, in the case of mortality analysis—because it is a binary and binding variable and an insurance program cannot function without highly accurate data about who has died—real-world data in tens of thousands of patients over many years and broad geographic areas may be more applicable than an RCT with a few hundred or even a few thousand patients.

CONCLUSION

Moving forward, this enhanced understanding of epidemiology, clinical practice, and trial design will help us to develop a more sophisticated and more robust approach in our efforts to offer efficacious and safe treatments to our patients. ■

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