Real-World Data Collection Regarding Paclitaxel Treatment

An overview of why real-world data are pertinent to the safety assessment of paclitaxel-coated devices, with separate summaries of the projects investigating the late mortality signal via real-world data analyses.

BY ANNA KRAWISZ, MD, AND ERIC A. SECEMSKY, MD

The recent controversy regarding the late mortality signal associated with paclitaxel-coated devices (PCDs) has highlighted the application of real-world data to inform on the safety and efficacy of medical devices. Real-world data, which are taken from clinical care settings such as electronic health records (EHRs), claims and billing records, and quality improvement registries, offer the advantage of relatively rapid access to information from a large number of patients. In addition, real-world data provide insights into practice patterns and adherence and can assess the generalizability of therapies in broad patient populations.[1] This article summarizes the use of real-world data for evaluating paclitaxel-based therapies.

Pertinent to this discussion, Katsanos et al recently published a summary-level meta-analysis in *Journal of the American Heart Association (JAHA)* describing an increase in all-cause mortality associated with drug-coated balloons (DCBs) and drug-eluting stents (DESs) relative to percutaneous transluminal angioplasty (PTA) and bare-metal stents (BMSs), as well as a positive association between paclitaxel dose and risk of death.[2] The investigators pooled summary-level data from 28 randomized controlled trials (RCTs) and found that at 1 year (4,432 patients), there was no mortality difference between the DCB/DES and PTA/BMS cohorts; however, at 2 years (12 trials, 2,316 patients) and at 4 to 5 years (three trials, 863 patients), there were significant increases in the relative risks of mortality (68% and 93% increased risk, respectively) associated with DCBs/DESs compared with PTA/BMSs.

FDA SAFETY ADVISORY PANEL MEETING

The findings by Katsanos et al prompted an FDA investigation into the safety of PCDs, which culminated in an FDA safety advisory panel meeting in June 2019. The panel involved representatives from the FDA, academia, industry, and the public. As part of this meeting, the FDA conducted an independent analysis of updated clinical trial data and reaffirmed the presence of a late mortality signal.[3] However, the FDA stated that the quality of data from which its conclusion was derived was poor. For example, the original RCTs were designed to examine limb-rated outcomes, not mortality. Thus, there was significant loss to follow-up after primary endpoints were reached, the majority of which occurred at 1 year. This resulted in a significant proportion of missing data, even after industry stakeholders reobtained some of these data. In addition, the FDA found no firm dose-response relationship between paclitaxel and mortality and no clear mechanism linking paclitaxel to death. Finally, they found that many of the deaths in the trials were not properly adjudicated, and among the causes of death that were available, there was no clear relationship with paclitaxel exposure. Therefore, the FDA concluded that the quality of the data was insufficient to draw conclusions directly linking paclitaxel to the observed increase in mortality.

The FDA meeting also provided the opportunity for researchers to present real-world data examining the safety of PCDs. These presentations included analyses of data from the Medicare claims database, the Optum claims database, and individual device programs run by industry stakeholders, which are summarized later in more detail. Overall, after considering the totality of evidence, the FDA concluded that a late mortality signal exists in the incomplete data available for analysis; however, there was insufficient evidence to establish a causal relationship between paclitaxel and this increase in mortality. Moreover, paclitaxel-based therapies offer a clear therapeutic advantage for patients, because they decrease rates of restenosis, target lesion revascularization, and symptoms of claudication compared with use of standard PTA and BMS.[4] This creates a dilemma for the vascular community between protecting patients

from interventions that may cause unintended harm and ensuring that beneficial interventions are not unnecessarily restricted. Data to better guide our use of these devices are desperately needed.

WHAT'S NEXT?

Although the best way to confirm the safety of PCDs is to perform an RCT powered to detect a difference in mortality, the FDA concluded that this is not feasible due to the large number of patients and the lengthy time of follow-up that would be required. More specifically, the study would require at least 40,000 patients and a follow-up period of at least 5 years to be certain whether a mortality risk exists. In addition, this study would need a patient population with peripheral artery disease (PAD) that has never been exposed to paclitaxel.

In this vein, real-world data offer a particularly powerful approach to continuing the safety assessment of PCDs. Retrospective data can be readily accessed and allow for the study of patients who preceded the *JAHA* meta-analysis. This is critical because after publication of the manuscript and the fallout that ensued, a different patient population has been treated with PCDs—primarily those at the highest risk and without other therapeutic options. In addition, as a tool for postmarket safety monitoring, real-world data naturally enable us to study factors that may alter the determination of PCD safety, such as comorbid illnesses, treatment with optimal medical therapy, and the burden of health care use in follow-up. In the example of large databases, real-world data also grant access to significantly larger numbers of patients than RCTs can typically enroll. This allows for adequate power to assess subgroups, such as by sex, age strata, or disease severity. The broad representation of patients allows for improved generalizability of conclusions to the patients commonly treated in practice. Finally, data sets such as the Medicare database provide the opportunity to passively account for survival with near-complete ascertainment.

It is also critical to understand the limitations of real-world data for a comparative safety assessment. Although advanced statistical analyses can be performed to strengthen the assessment of such data, biases such as confounding by indication may be introduced and are challenging to account for. As a result, analyses using real-world data are often viewed as being less rigorous than RCTs. Second, there is a possibility of misclassification, such as with inaccurate billing claims codes.

Fortunately, these mistakes are less frequent when claims codes are linked to compensation and may pose fewer problems in registries such as the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI). Lastly, some real-world claims-based data sets lack detailed patient and procedure characteristics. For example, in PAD, this may include lesion characteristics or specific devices used. Although device registries often collect such details, they are often not adjudicated and may be of variable quality.

The tremendous growth in big data sets containing patient information such as EHRs, claims databases, and registries has allowed for significant expansion in research using these tools, which are particularly well-suited for safety analyses. The following sections highlight four projects investigating the late mortality signal in paclitaxel via real-world data analyses: the Medicare database project, the Optum database project, the SVS VQI, and the American College of Cardiology (ACC) National Cardiovascular Data Registry (NCDR).

1. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence — what is it and what can it tell us? N Engl J Med. 2016;375:2293-2297.
2. Katsanos K, Spiliopoulos S, Kitrou P, et al. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2018;7:e011245.
3. US Food and Drug Administration. FDA executive summary: circulatory system devices panel meeting, June 19 and 20, 2019. General issues panel: paclitaxel-coated drug-coated balloon and drug-eluting stent late mortality panel. https://www.fda.gov/media/127698/download. Accessed August 21, 2019.
4. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e726-e779.

Medicare Database Project

BY ANNA KRAWISZ, MD, AND ERIC A. SECEMSKY, MD

The Medicare database project aims to monitor the safety of PCDs in a real-world population to better understand the relationship of paclitaxel with the late mortality signal identified in RCT data. Medicare is the largest single insurer in the United States, covering the majority of patients aged > 65 years. The claims data collected are clinically relevant and include procedural data, admission/discharge dates, sociodemographic data, and institutional characteristics. Furthermore, > 99% of deaths among Medicare beneficiaries are recorded. The inclusion of specific device codes for femoropopliteal artery revascularization, including codes for drug-coated devices, allows clear identification of treatment populations, making it well-suited for this safety assessment. Thus far, the study of Medicare data has resulted in three analyses examining the relationship between PCDs and all-cause mortality.

Secemsky et al evaluated 5,989 patients undergoing treatment with DCBs or DESs versus 10,571 patients who were treated by PTA or BMSs.[1] Patients underwent inpatient femoropopliteal artery revascularization over a median

follow-up of 389 days (interquartile range, 277–508 days). Treatment with DCBs/DESs was associated with lower mortality than treatment with PTA/BMSs through 600 days (32.5% vs 34.3%, respectively; *P* = .007). There was no association between drug-coated devices and all-cause mortality in multivariate analyses (adjusted hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.91–1.04; *P* = .43). In addition, the safety of these devices persisted when stratified by critical limb ischemia (CLI) (HR, 0.93; 95% CI, 0.85–1.01; *P* = .09) and non-CLI (HR, 0.94; 95% CI, 0.85–1.03; *P* = .2), as well as by DCB alone (HR, 0.94; 95% CI, 0.86–1.03; *P* = .17) and DES with or without DCB (HR, 0.97; 95% CI, 0.89–1.06; *P* = .48).

Secemsky et al also published an analysis of peripheral DESs versus BMSs in the Medicare population.[2] In this study, the authors analyzed 51,456 patients who underwent inpatient peripheral artery stenting over a median follow-up of 2 years (longest, 4.1 years) and found no difference in mortality (51.7% for DESs vs 50.1% for BMSs; log-rank *P* = .16). Similarly, there was no association between DESs and mortality after multivariable adjustment (adjusted HR for DES vs BMS, 0.98; 95% CI, 0.93–1.03; *P* = .53). In addition, there was no increase in mortality when stratified by CLI (HR, 0.97; 95% CI, 0.92–1.03; *P* = .32) or acute limb ischemia (HR, 0.99; 95% CI, 0.81–1.21; *P* = .95).

Dr. Secemsky and colleagues presented an extension of these data for the FDA panel that included both inpatient and outpatient procedures and longer follow-up times. The analysis included procedural data from more than 150,000 Medicare beneficiary patients who underwent femoropopliteal artery revascularization from 2015 through 2017. Patients were followed for a median of 799 days and as long as 1,573 days. No increase in mortality was identified with DCBs/DESs (adjusted HR, 0.94; 95% CI, 0.93–0.96). In addition, the authors found no increase in mortality when data were stratified by DES and DCB, CLI and non-CLI, or inpatient and outpatient procedures. Although the same limitations of real-world data apply, in particular to the nonrandomized treatment assignment, the authors increased the rigor of their conclusions by performing a sensitivity analysis examining mortality at the institutional level. In this analysis, the investigators found no difference in mortality among patients treated at high-volume PCD centers as compared with low-volume PCD centers.

These investigators are continuing the evaluation of PCD safety among Medicare beneficiaries as part of the SAFE-PAD study. In this prespecified analysis reviewed by the FDA, the investigators will examine extended follow-up of all patients so that the median follow-up time of the group surpasses 5 years. They will perform sensitivity analyses to confirm the safety signal previously observed with PCDs as well as subgroup analyses including a "low-risk" Medicare population. The intent of this project is to provide an ongoing, rigorous safety assessment using the largest data set available on PCDs.

OPTUM DATABASE PROJECT

BY ROBERT YEH, MD, AND ERIC A. SECEMSKY, MD

Similar to the Medicare analysis, the objective of the Optum database analysis is to evaluate the safety of PCDs using claims-based data. However, this analysis (which we are leading in conjunction with Medtronic) aims to examine a lower-risk, younger population who are primarily enrolled in private insurance or Medicare Advantage, Medicare's private plan option. By diversifying the populations studied, the project hopes to augment the ability of the ongoing real-world data analyses to detect a safety signal for PCDs.

Initial data from the Optum database project were presented at the FDA panel in June 2019. This analysis included 20,536 patients who underwent femoropopliteal artery revascularization procedures between April 2015 and December 2018. Median follow-up was 763 days (interquartile range, 522–1,028 days). There was no difference in adjusted mortality when comparing all drug-coated devices to uncoated devices (HR, 1.09; 95% CI, 0.98–1.22; *P* = .11), DCBs to noncoated balloons (HR, 1.07; 95% CI, 0.95–1.21; *P* = .27), or DESs to BMSs (HR, 1.09; 95% CI, 0.91–1.32; *P* = .35). The analysis is currently ongoing, with plans to update survival data to ensure no late mortality signal is found among these patients with more follow-up.

1. Secemsky EA, Kundi H, Weinberg I, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. JAMA Cardiol. 2019;4:332-340.
2. Secemsky EA, Kundi H, Weinberg I, et al. Drug-eluting stent implantation and long-term survival following peripheral artery revascularization. J Am Coll Cardiol. 2019;73:2636-2638.

Society for Vascular Surgery Vascular Quality Initiative

BY DANIEL BERTGES, MD

In response to the meta-analysis by Katsanos et al, which reported increased 2- and 5-year mortality after treatment of the femoropopliteal artery with paclitaxel-coated balloons and paclitaxel-eluting stents, the SVS VQI has analyzed the mortality signal within the Peripheral Vascular Intervention (PVI) registry. The SVS VQI PVI was

started in 2010 and began collecting device-specific information with linkage to GUDID (Global Unique Device Identification Database) in fall 2016. VQI PVI was the first registry of its kind to record detailed device information, including the use of PCDs, putting it in a unique position to address the mortality signal in the United States.

An analysis of 8,375 patients undergoing peripheral intervention of the femoropopliteal artery from October 2016 to December 2017 was first reported at the SVS Vascular Annual Meeting and did not show an increase in 1-year mortality in patients treated with PCDs. In propensity-matched analyses, mortality was not significantly different between groups: 9.6% with paclitaxel angioplasty versus 12.6% with plain angioplasty (HR, 0.84; 95% CI, 0.66–1.06; $P = .14$). In propensity-matched groups, mortality was similar after use of BMSs (9.8%) and paclitaxel-eluting stents (8.8%) (HR, 0.93; 95% CI, 0.62–1.41; $P = .75$). In the matched analysis that combined stents and balloons, mortality was significantly lower in the PCD group (8.5%) compared with the non-PCD group (11.5%) (HR, 0.82; 95% CI, 0.68–0.98; $P = .03$). There was a lower mortality rate in patients with intermittent claudication after treatment with PCDs, whereas patients with chronic limb-threatening ischemia had similar mortality.

Importantly, this analysis did not extend to the 2-year mark, where the mortality signal was first detected by Katsanos et al and later verified by the FDA. Additional VQI analysis is planned in two studies. First, the SVS VQI database will be matched to Medicare claims using the methodology of the Vascular Implant Surveillance and Interventional Outcomes Network (VISION). VISION is a coordinated registry network led by Drs. Art Sedrakyan and Phil Goodney with the support of the FDA's Medical Device Epidemiology Network (MDEpiNet). Matching VQI patients to Medicare claims data will enable the identification of additional VQI patients treated with these devices and extend the analysis retrospectively to the time of approval of paclitaxel stents and balloons in 2012 and 2014, respectively. Second, the SVS VQI is working to embed the Data Extraction and Longitudinal Trend Analysis (DELTA), a risk-adjusted prospective surveillance software, into the PVI registry to monitor mortality after treatment with PCDs. The DELTA surveillance system was developed to monitor clinical data sets such as the VQI in an effort to improve the efficiency of identifying potential medical device safety concerns. This effort is important not only for the present PCDs but also for surveillance of future peripheral device technologies. The SVS Paclitaxel Task Force, chaired by SVS President Dr. Kim Hodgson, is involved with these and other efforts to address the mortality signal.

The recent FDA correspondence to health care providers, dated August 7, 2019, noted the need for additional data including real-world evidence from registries. The SVS VQI aims to add to the totality of evidence by determining if the late mortality risk is present in the PVI registry. The ability to deliver this information and the degree to which it can impact the debate about the safety of PCDs will be a test of real-world evidence from registries.

American College of Cardiology National Cardiovascular Data Registry

BY WILLIAM SCHUYLER JONES, MD

In addition to calling into question the assessment of endovascular devices in the total product life cycle (ie, from development to approval to safety surveillance), the controversy surrounding PCD use for the treatment of femoropopliteal artery disease has heightened the focus on using data collected in everyday practice (often termed "real-world evidence") to support comparative effectiveness and safety studies for patients with vascular disease. Although many argue that participants enrolled in clinical trials (eg, pivotal PCD trials) are "real-world" patients, it is clear that data collection and curation in traditional clinical trials are costly and burdensome, thus highlighting the opportunity to use discrete data elements from EHRs and/or registries to study how to better manage patients.

One such possibility is the ACC NCDR PVI registry, which prospectively and pragmatically collects data on individual patients undergoing peripheral interventions at more than 200 participating centers around the United States. Data collection was designed to be comprehensive enough to support meaningful observational analysis, premarket drug and device studies, and postmarket surveillance studies. Like other national registries managed by the NCDR, the PVI registry utilizes the NCDR infrastructure by collecting detailed data on patient, anatomic, and procedural characteristics. A steering committee has guided the registry from inception to its current form, a multidisciplinary data governance committee frequently updates and reviews

the data elements, and a research and publications committee reviews proposals for scientific and strategic priorities. Collaborative work with the SVS VQI and the Society of Interventional Radiology within a public-private partnership with the FDA called RAPID (Registry Assessment of Peripheral Interventional Devices) will ensure that all registries collect similar data elements and will permit apples-to-apples comparisons in future studies.

As it pertains to the paclitaxel controversy, the PVI registry captures detailed information about each device used during peripheral interventions, as well as short- and long-term clinical outcomes. In future versions of the registry, a unique device identifier for each device will be consistently collected and can be linked to individual outcomes. Given the difficulty in performing complete follow-up of all patients undergoing peripheral intervention, the PVI registry will augment clinical outcomes ascertainment by linking to administrative claims data from the Centers for Medicare & Medicaid Services. This linkage is made possible by the use of direct identifiers (rather than probabilistic matching) and will create an exciting opportunity to assess the contemporary use of certain devices and the association with safety endpoints, such as all-cause death. As described, the PVI registry should spur process improvement; study the safety, effectiveness, and appropriate use of devices; and permit the assessment of contemporary treatment and variations in treatment and outcomes of patients with PAD.

I would be remiss not to mention the holy grail of real-world evidence: embedding RCTs within clinical registries such as the PVI registry. Although methods to adjust for differences in observational studies have improved, there is absolutely no replacement for randomization, as the results from RCTs have literally influenced every aspect of cardiology practice—and we should require the same for our patients with vascular disease, including device studies. Examples of embedding randomization within registries are becoming more common in patients undergoing percutaneous coronary intervention (eg, SAFE-PCI for Women, SAFE STEMI, TASTE), and similar methodology can be adopted for patients undergoing peripheral intervention. Using data already collected within clinical registries, linked with public and private insurance claims, registry-based RCTs will permit the robust assessment of technology that we utilize in patients undergoing procedures such as peripheral intervention. This pragmatic approach to device evaluation will significantly propel the science behind vascular intervention, and it should facilitate patient enrollment and reduce the burden on clinicians and health systems (by harnessing already collected information) and be associated with lower overall costs per patient to industry partners. A win for all. ■

Anna Krawisz, MD
Cardiovascular Medicine Fellow
Division of Cardiovascular Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts
akrawisz@bidmc.harvard.edu
Disclosures: None.

Eric A. Secemsky, MD, MSc, RPVI, FACC, FSVM
Director, Vascular Intervention
Investigator, Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology
Assistant Professor of Medicine
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts
esecemsk@bidmc.harvard.edu
Disclosures: Consultant to Medtronic, Cardiovascular Systems, Inc.; research grants to institution from AstraZeneca, BD/Bard, Cook Medical, Cardiovascular Systems, Inc., Medtronic.

Robert Yeh, MD
Katz Silver Family Associate Professor of Medicine
Harvard Medical School
Director, Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology
Beth Israel Deaconess Medical Center
Boston, Massachusetts
ryeh@bidmc.harvard.edu
Disclosures: Scientific advisory board for Abbott Vascular, Boston Scientific Corporation, Medtronic; consultant to Abbott Vascular, Biosense Webster, Inc., Boston Scientific Corporation, Medtronic; research grants from Abbott Vascular, AstraZeneca, Boston Scientific Corporation, Medtronic.

Daniel Bertges, MD
UVM Medical Center
Burlington, Vermont
daniel.bertges@uvmhealth.org
Disclosures: None.

William Schuyler Jones, MD
Associate Professor of Medicine
Department of Medicine
Duke University School of Medicine
Durham, North Carolina
schuyler.jones@duke.edu
Disclosures: Research grant from Medtronic.