Highlights From the VIVA Vascular Leaders Forum on Paclitaxel Safety

Points of consensus, contention, and paths forward.

To further explore the findings of a recent meta-analysis that showed an increased risk of long-term mortality in patients treated with paclitaxel-coated balloons and stents, VIVA Physicians, a not-for-profit organization, convened a Vascular Leaders Forum (VLF) March 1–2, 2019, in Washington, DC. The VLF brought together an international community of physicians representing a broad variety of national and specialty backgrounds, as well as regulatory and reimbursement officials.

For those new to the current questions facing the use of paclitaxel in peripheral artery disease (PAD), we begin with a brief overview of how the vascular community's perspective on a proven therapy was called into question in early December 2018 and how the field has responded with scrutiny, study, and open dialogue.

BACKGROUND

The Meta-Analysis in Brief

The meta-analysis, authored by Katsanos et al and published December 5, 2018, in *Journal of the American Heart Association (JAHA)* ("*JAHA* meta-analysis"), collected summary-level data from published or presented randomized controlled trials (RCTs) of paclitaxel drug-coated balloons (DCBs) and drug-eluting stents (DESs). Although the collective mortality rates were similar at 1 year of follow-up, a statistically significant increase in mortality was seen in the paclitaxel arm at 2 years, a trend that increased at a combined 4- and 5-year endpoint comprising data from three RCTs. The meta-analysis further indicated a dose-response finding wherein higher doses of paclitaxel resulted in an increased risk of death. However, although late paclitaxel toxicity was posited, no causal link was determined by the meta-analysis.

Responses in the Immediate Aftermath

News of the findings brought heightened scrutiny to the field of PAD therapy, specifically superficial femoral artery (SFA) intervention, in which drug delivery devices have been increasingly considered the most effective options currently available. Regulatory bodies responded with words of caution, although no official warnings or recalls have been deemed necessary as of yet in the United States. Two randomized trials (BASIL-3 and SWEDEPAD) were halted to examine data collected to date; others such as BEST-CLI have continued enrollment but with a close eye on safety.

Industry Responds With Patient-Level Data Collection

Clinical trial investigators and device manufacturers responded by collecting and reexamining patient-level data from their drug delivery programs to more fully evaluate the *JAHA* meta-analysis, including a specific focus on dose-response. In January 2019, data from several of these studies were presented at the Leipzig Interventional Course (LINC) 2019 in Leipzig, Germany.

To date, these analyses, which include RCTs and single-arm registries, have found no significant increase in mortality in their respective paclitaxel populations nor a correlation between higher dose exposures and mortality risk. These data can be found in *Endovascular Today*'s coverage from LINC 2019 (bit.ly/EVTlinc2019) and as such are not included this summary. Since the time of presentation, IN.PACT SFA investigators have also published their findings in *Journal of the American College of Cardiology*.

The VLF and Independent Patient-Level Data Initiatives

Upon learning of the *JAHA* meta-analysis findings, the VIVA Physicians organization began work on two initiatives: (1) to assemble stakeholders representing vascular physicians, industry, and regulatory and reimbursement bodies for a live, scientifically based meeting to candidly address all available data on paclitaxel-related safety and identify any essential actions and fact-finding initiatives toward ensuring patient safety; and (2) to collect blinded patient-level

data from each of the companies with paclitaxel products available in the United States market, with a goal of independent, inclusive examination and determination as to whether a causal link can be established or refuted.

THE VASCULAR LEADERS FORUM

The 1.5-day VLF summit invited approximately 40 talks related to drug delivery applications, as well as frequent periods for panel and audience questions, suggestions, and debate. The faculty represented a variety of vascular specialties and national backgrounds, as well as oncologists, trialists, statisticians, and regulatory representatives. Konstantinos Katsanos, MD, lead author of the meta-analysis, presented and participated in a session via teleconferencing from Patras University Hospital in Greece.

The organizers emphasized patient safety as the priority, as well as and transparency and open dialogue while airing questions, concerns, and new ideas.

A comprehensive accounting of all of the data, opinions, and conclusions shared over the course of the sessions is beyond the scope of this summary. Complete video of the proceedings has been made available online by VIVA, including videos of each presentation and panel discussion.

We aim to highlight key data and perspectives emerging since the meta-analysis, areas of relative consensus and disagreement about the nature of meta-analysis and the *JAHA* study in particular, and the next steps physician investigators, the *JAHA* study authors, industry, and regulators are taking.

The primary question currently facing the field of vascular intervention is: Does the use of a paclitaxel-delivery PAD application directly affect mortality?

PACLITAXEL SAFETY IN ONCOLOGY

Among the reasons the *JAHA* meta-analysis findings were so surprising was paclitaxel's relatively long and established use in chemotherapeutic oncology settings, dating back to its first FDA-approved indication in 1992. However, there are notable differences in the formulations, concentrations, and means of application, as well as the total cumulative doses administered.

In general, oncologic applications involve a significantly higher dose of paclitaxel, and they are administered more frequently than the PAD applications studied in the RCTs feeding the meta-analysis. In their publication, Katsanos et al acknowledged these differences but expressed concern that the paclitaxel formulations applied in PAD have longer half-lives and may have unknown consequences, especially when landing in nontarget anatomies.

During the VLF, a pair of oncologists described the applications and associated data regarding paclitaxel in cancer patients. Medical oncologist Alfred Vargas, MD, of OhioHealth in Columbus, Ohio, detailed its pharmacology, mechanism of action, toxicity, adverse events, and hypersensitivity reactions. Erica Mayer, MD, MPH, a medical oncologist specializing in breast cancer with the Dana-Farber Cancer Institute in Boston, Massachusetts, shared a deep dive on the data regarding the safety and efficacy of paclitaxel in her field.

WATCH ONLINE

View complete videos of all of the presentations, including those not covered here, at vivaphysicians.org/vlf

Safety Profile

Dr. Mayer briefly reviewed the various FDA-approved oncologic applications and off-label uses but focused the majority of her talk on the adjuvant use of paclitaxel in a curative breast cancer setting among patients with anticipated long-term survival. In these patients, hypersensitivity reactions related to systemic paclitaxel exposure have become increasingly infrequent, and severe reactions are almost unheard of.

Some association with asymptomatic bradyarrhythmias and heart block has been shown, but routine cardiac monitoring is not required. As hypersensitivity reactions became better understood and preventable, the historic risk of serious cardiac events substantially diminished, and there is currently no known increased risk of venous thromboembolic events or long-term cardiac toxicities linked to paclitaxel exposure, she said. Long-term concerns include permanent peripheral neuropathy, possible cognitive change, and early menopause in younger patients.

A handful of breast cancer therapies are known to have cardiovascular toxicities. However, paclitaxel is not one of them, noted Dr. Mayer. "In general, we consider this a safe chemotherapy medication."

Dr. Mayer's presentation drew interest for two primary reasons: (1) it described an acceptable safety profile in the studied population of expected long-term survivors, and (2) it informed the audience of vascular specialists and community members of the exact differences in dose sizes and frequency between oncologic and PAD applications. She presented findings from two major trials of adjuvant breast cancer treatment conducted in the 1990s, each randomizing around 3,000 patients. In this long-term curative setting, the addition of paclitaxel cycles to a chemotherapy regimen was shown to decrease cancer recurrence risk by almost 20% (leading to FDA approval in 1999), and a survival analysis showed a decreased risk of

death from any cause at 7 years in patients who received paclitaxel. "Paclitaxel saved lives here," said Dr. Mayer.

Dosing

Patients undergoing adjuvant paclitaxel treatment for breast cancer typically receive one of two 12-week regimens, explained Dr. Mayer. The first (four 3-week cycles) typically involves 175 mg/m^2 of body surface area for an average cumulative dose of 1,120 mg; the other regimen (weekly for 12 weeks) administers 80 mg/m^2 for an average cumulative dose of 1,536 mg. She then contrasted these figures to the doses associated with two approved DCBs in their 6- X 120-mm sizes—cumulative doses of 8.5 mg for In.Pact Admiral (Medtronic) and 4.5 mg for Lutonix (BD Interventional).

Dr. Mayer also recently presented a subgroup of 15 pregnant patients who were administered paclitaxel with their chemotherapy, with no evidence of adverse toxicity to mother or infant in utero observed to date, which became one of the more referenced moments over the rest of the sessions. Of note, she did point out that the risks of prolonged low-dose paclitaxel exposure are not known, although a Cleveland Clinic publication currently in press will shed light on whether there is any connection between DESs and hematologic malignancies.

In summary, Dr. Mayer believes that paclitaxel has a well-established role as a safe and effective chemotherapy over 25 years of application. "We have no data or a mechanistic explanation to suggest that there is a risk from prolonged exposure to the teeny-tiny amounts of paclitaxel in the device," she said. "Looking at this meta-analysis and finding out what these patients were dying of would be quite helpful in order to see if there really is a connection."

The ensuing panel discussion produced many questions from the audience, including a question that applies to all trials of paclitaxel in any application: how do we adjudicate whether events are related to paclitaxel exposure? Others sought more information on possible unknown mechanisms and sequelae, such as immune- and allergy-mediated responses, potential risks related to arrhythmia, a relative lack of data regarding how long the drug remains active in the system, and the differences between data based on soluble paclitaxel used in oncology versus its more crystalline formation in PAD.

ADDRESSING THE META-ANALYSIS DESIGN AND APPLICATION

Even a cursory review of the VLF agenda revealed that one of its focal points would likely be the presentation of the meta-analysis by Dr. Katsanos, followed by a critical appraisal presented by William A. Gray, MD, and the subsequent panel discussion. This session began with an illuminating overview of the strengths and shortcomings of meta-analyses and their ideal applications by Sue Duval, PhD, a statistician and meta-analysis expert from the University of Minnesota. In short, although patient-level meta-analysis is considered the strongest level of data, literature-based meta-analysis is hugely prevalent, in part due to being more accessible to conduct, she noted.

This session involved disagreements, but it was also noteworthy in its development of several newfound consensus points on previous disparate contentions. The points raised by Drs. Katsanos and Gray served as a jumping off point for discussions on the most critical questions regarding the *JAHA* meta-analysis and how best to evaluate the safety of paclitaxel use.

Update on Continued Data Exploration by the Meta-Analysis Authors

Dr. Katsanos presented the primary findings of his group's meta-analysis, a full summary of which has been previously covered and is beyond the scope of this discussion. He then pivoted to focus on the random-effects model and Bayesian analyses that support the overall meta-analysis findings. Dr. Katsanos described dose-response models, addressing not only the target lesion revascularization benefit, but also increased mortality. He was careful not to overstate the implications of the findings, saying "I don't want to drive debate here, but there is a lot of mathematical evidence to show correlation in both cases." In comments to *Endovascular Today* regarding this point, Peter Schneider, MD, from University of California at San Francisco and Kaiser Foundation Hospital in Honolulu, Hawaii, would later assert that the trials included were not powered to determine long-term mortality, the finding the meta-analysis is seeking to prove.

Dr. Katsanos also briefly touched on a possible—though unexplored—mechanism of action (multipolar divisions and aneuploid daughter cell formation) and his group's ongoing review of clinical events that may be potentially related to paclitaxel toxicity. He qualified this as still a work in progress but "food for thought."

One point of relative consensus among Dr. Katsanos and others voicing opinions in the session was the need to evaluate these findings in a time-to-event analysis, rather than at standard follow-up points alone.

For more on Dr. Katsanos and colleagues' approach to the meta-analysis and his perspectives on the data emerging since its publication, please see *Endovascular Today*'s discussion with him on page 37.

A Critical Appraisal: Potential Issues With the Meta-Analysis and Their Counterpoints

Dr. Gray, who is with Main Line Health and Lankenau Heart Institute in Wynnewood, Pennsylvania, was asked to present a critical review of the *JAHA* meta-analysis. He shared his thoughts and preliminary research regarding several areas of concern, which are described hereafter in detail, along with Dr. Katsanos' responses.

Selection bias. One of the key issues raised by Dr. Gray was that of selection bias created by the lack of complete follow-up in the trials. Specifically, although outcomes from 28 trials were evaluated at 1 year and showed no difference in mortality, only 12 trials were examined at 2 years, where the mortality rates first separated, and only three trials were evaluated at a combined 4- and 5-year follow-up. Because a more appropriate time-to-event analysis could not be performed, this attrition to follow-up becomes an even greater limitation of the analysis, according to Dr. Gray.

Also of note, the trials that had longer-term data available showed a mortality effect even at 1 year, whereas trials without long-term data show no mortality effect at that point, he noted. Dr. Gray said it should not be surprising that the mortality differential of three trials observed at 1 year continued to exist at 5 years, noting that what has changed is that the data from the trials without the differential are not available at the long-term endpoint.

Disproportionate application of the dose-time equation. The dose-time product equation used by the meta-analysis authors was also scrutinized and deemed by Dr. Gray to be problematic in its application, in relation to the aforementioned selection bias. "'Time' is disproportionately available in the studies with longer-term follow-up and worse mortality, thus biasing the calculation," he said. Additionally, the dose-time equation may be confounded by the different sizes of devices included. "Once the study population is divided by DCB length and size, adjustments for possible differences in [the population's] cardiovascular risk factors would need to be made," said Dr. Gray, on the basis that more balloon length would likely be required in patients who have a greater disease burden. "It's no longer a randomized application or trial. It's now a trial of subsets of patients using different lengths and sizes."

Dr. Gray also believes that the patients lost to follow-up or withdraw were not completely or accurately accounted for, an opinion shared by Thomas Zeller, MD, of Bad Krozingen, Germany, who was Lead Investigator of the THUNDER trial, one of the three data sets analyzed at 4 to 5 years. "You can't just carry forward the initial enrollment," said Dr. Gray, disagreeing with the mortality rate calculations and also the relative risk figures. "You have to take into account the loss to follow-up and withdraws." Adjusting the final data from the three trials at 4 to 5 years to account for his criticism, he stated that the difference is no longer statistically significant when a proportionately similar confidence interval as that shown by the authors is used.

Dr. Katsanos acknowledged potential issues in the original dose-time equation, but he believes that even if you remove the 'time' component, the dose-response model remains highly significant. "I agree that there is heterogeneity; there is confounding that we may have missed," he said. "I have shown, however, that the dose-response model is very, very valid for TLR [target lesion revascularization], and it seems to be following the same lines in opposite directions for the mortality risk." Dr. Gray rejected that logic, saying that reduction in TLR is the result of a local paclitaxel effect, whereas any negative outcome is postulated to be due to a systemic effect, so mechanistically, TLR does not demand an offsetting detrimental effect.

Differences in the respective surface areas of balloons versus stents were also discussed, suggesting that dose density calculations alone do not take all exposure factors into account.

Paclitaxel naiveté and the known unknowns of control arms. Finally, Dr. Gray addressed what he considers to be the most critical issue in analyzing the meta-analysis: the likelihood that an unknown number of control patients were, at some point in their lives, treated with a paclitaxel-delivery device. Any such patients are currently counted among the control groups despite having been treated with the drug application in question outside of the designed data collection of the trial, confounding the ability to evaluate their results in true contradistinction to the study arm outside of the original study design.

"The PTA [percutaneous transluminal angioplasty] group is not likely paclitaxel naive for the entirety of the analysis," asserted Dr. Gray. Showing a timeline overlaid with each of the device-approval trial durations and the dates of the respective device approvals, he described a changing landscape in which restenosis was increasingly treated using paclitaxel, a trend that preceded almost all of the 1-year follow-up period of TLR in the trials. The average excess of TLR in the PTA arm across the trials at 1 year is approximately 10% to 15%—a rate that would increase with longer follow-up, he noted. Many operators, Dr. Gray included, likely would have started preferentially using paclitaxel devices for TLR after they came to market. "I think the authors would need to have recognized this and performed some sort of sliding scale analysis of the impact of variable proportions of paclitaxel usage in the TLR patients," he contended. "Without that, I think this whole analysis blows up because it assumes these patients are paclitaxel naive for the duration of the analysis."

Dr. Gray closed by referring back to the pharmacokinetics and toxicity of paclitaxel profiles presented earlier, describing them as well studied and characterized. "There are no prior data that at the very, very low doses that are

present as part of DCB and DES use produce a mortality effect," he said. "Therefore, in order to claim otherwise, and be describing a novel and grave paclitaxel toxicity—never [before] described in the history of the world—one would need to present level 1 evidence: prospective, randomized, and appropriately sized." A non–patient-level meta-analysis will not suffice toward this end, concluded Dr. Gray.

Intention-to-treat versus on-treatment analysis. As previously discussed, one the critical points of contention aired at the forum regarding the clinical validity of the statistical findings from the *JAHA* meta-analysis hinges on the degree to which patients included in control arms ever received paclitaxel therapies. Although study-level meta-analyses typically follow their feeding trials' intention-to-treat randomizations, a decision defended by Dr. Katsanos and affirmed in a general sense by Dr. Duval, several VLF participants believed this to be an invalid way to prove the existence of a safety issue because of the high likelihood that control patients were treated with paclitaxel at some point in their lives. Dr. Duval said that on-treatment analyses are also valid, and there is no reason not to do them.

One documented example regarding the challenges of remaining paclitaxel naive and the application of the intention-to-treat principle comes from the Zilver PTX trial (studying the Zilver PTX DES [Cook Medical]). During the LINC 2019 and VLF sessions dedicated to patient-level data from major clinical trials, it was revealed that 31 patients randomized to the PTA control arm of the Zilver PTX trial are known to have been treated with a DES after failed initial therapy within 1 year of randomization. None are reported to have died through 5-year follow-up. These patients were considered by the original publication and the subsequent meta-analysis as control patients per study protocols and intention-to-treat assessment. Reevaluating the mortality analysis with these 31 patients placed instead in the Zilver PTX group, no statistically significant difference between the arms was found.

Although these patients could not have been known to the meta-analysis authors, Drs. Katsanos and Duval stated that they should be categorized by intention-to-treat either way and thus remain in the control arm, per the standards of this form of meta-analysis. This contention was met with considerable debate.

"It's inconceivable to me that if the thesis is looking at paclitaxel mortality effects by 'exposure to paclitaxel' in Dr. Katsanos' own words, that we are not opening our eyes to who was actually treated with paclitaxel and what effect that has on them," said Dr. Gray, in strong disagreement to using only an intention-to-treat analysis. "The trial [design] was never intended—on an intention-to-treat basis—to look at mortality based on noncrossover."

VIEW FROM THE FORUM

"The mortality concern was addressed in a very objective and sincere way, and not only were key endovascular voices invited, but also oncologists and pharmacologists. The presence of FDA allowed both regulatory and physician concerns to be exchanged. My impression at the end of the VLF was that patient-level analysis is a very positive way to address this issue, and I was pleased that there was no overreacting from either side.

Another positive consequence of this issue will be the more rigorous performance of future PAD trials."

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"I think about determining the value of something new differently than I think about determining the harm of something new," added Joshua Beckman, MD, from Vanderbilt University Medical Center in Nashville, Tennessee. "I completely agree that an intent-to-treat analysis is mandatory if you want to see if a new treatment has value. On the other hand, I feel very strongly we should cast a wide net to understand if a new therapy causes harm and that an on-treatment analysis to understand if there's harm is a valuable exercise."

Dr. Katsanos agreed that there are confounding elements especially in the long term, including that an unknown portion of patients in the control arm were increasingly treated with paclitaxel. But, he remained steadfast that they should remain in the control arm. "It doesn't change the fact that the primary analysis has to be on an intention-to-treat principle," he said. "Now, whether we can actually look at those subsets of patients and see whether the signal is being confirmed, this is another discussion."

Several panelists expressed concern regarding the ability to retrospectively determine the exact patients and outcomes in the control arm who may have ever received paclitaxel. It was noted that the major trials were not necessarily designed to exclude previous paclitaxel treatment in the contralateral limb nor prevent later revascularization using paclitaxel in the enrolled limb.

Comingling technologies. Another area of disagreement included the decision to comingle data from DES and

DCB cohorts, as well as several different DCB platforms. Dr. Katsanos conceded that the comingling of DES and DCB is a well-taken point that was also raised by the *JAHA* reviewers but that he stood by the decision. His reasoning is that the primary variable is the presence of paclitaxel, regardless of formulation and delivery mechanism, which he believes is confirmed by subsequent analyses isolating stent versus balloon and finding the signal in each. Further, that the findings do not conflict with mortality data from several of the trials.

"That's always been the big question with meta-analysis, about apples and oranges. It's an issue," said Dr. Duval, acknowledging that some heterogeneity is not abnormal, but its impact must be considered. Whether certain variables can be comingled ultimately comes down to a clinical question versus a statistical one, she opined, stating that these factors can be further explored in subsequent patient-level meta-analyses.

ADDITIONAL CONTROL ARM CONFOUNDERS

Whether or not the findings of the *JAHA* meta-analysis ultimately lead to a determination of a causal link between paclitaxel and mortality, there seemed to be consensus that the publication and especially its aftermath shed light on several poorly understood study confounders. Characteristics of control arms, from their numbers to their follow-up, were frequently discussed, as were potentially necessary changes to follow-up protocols both in and out of the trial setting.

Bias

Ramon Varcoe, MBBS, MD, PhD, of Prince of Wales Hospital in Sydney, Australia, addressed concerns regarding the effects of certain biases in the control and study arms of any interventional trial. Agreeing that meta-analyses represent the highest level of evidence, Dr. Varcoe contends that they are not perfect, in particular because they do not reduce biases that may have been present in the source studies. Randomized trials of interventional devices are rarely, if ever, free of performance bias; in other words, the health care team is not blinded to the procedure that the patient receives. This can affect how the patient is followed, with some trials potentially placing more emphasis on the need to closely follow and document patients in the study arm than the control. Conversely, after a few unreturned follow-up calls, control patients may be deemed lost to follow-up, with their actual mortality status unknown, said Dr. Varcoe. If proven, this would indicate that a variable beyond the primary study element (such as paclitaxel) affects outcomes in randomized trials. It is also possible that patients in control arms are more likely to have their medical therapy enhanced due to the need for more frequent office visits, which may affect longevity.

Following the publication of the *JAHA* meta-analysis, Dr. Varcoe's group used a similar model to study interventional SFA trials, excluding drug delivery devices. Cautioning that this analysis is not yet complete and its population sizes are smaller, they found that RCTs comparing experimental nonpaclitaxel SFA devices had additional risk of death compared to control arms at 1 year. There was "a similar direction of effect" at 2 and 3 years, but Dr. Varcoe noted that the study is underpowered and does not show statistical significance. Because these preliminary data identified a similar mortality effect in the study arm—independent of paclitaxel—they cast some doubt as to a causal link, he said.

"It is my view that it is much more likely that the association between experimental SFA therapies and higher risk of death is due to a combination of the introduction of bias, more tenacious follow-up with those patients in the experimental arms, and higher rates of medical interaction and medical therapy in those RCT arms that are associated with more frequent TLR," concluded Dr. Varcoe.

Control Arm Size

Although meta-analyses are designed to pool smaller data sets into a larger one to identify statistically significant findings unavailable in the studies themselves, as Dr. Katsanos described in his recent interview with *Endovascular Today*, several VLF participants voiced concerns regarding the signals derived from small control arm populations. Due to their small sizes relative to those at completion of enrollment, the control arms of the three trials evaluated at the 4- and 5-year combined endpoint were "terribly flawed" at that juncture, commented Dr. Schneider. He noted that they were randomized 2:1 (with efficacy as the primary focus at that point) and many patients were lost to follow-up, including 48% of the THUNDER trial PTA group. "My question is: are we really talking about a 5-year signal here, based on this data?"

Dr. Katsanos responded by suggesting that the next research phases should include time-to-event analyses to reduce concerns over comparative population sizes at the prespecified follow-up points.

THE ABSENCE OF A CLEAR CAUSAL LINK

There seemed to be consensus that a clear causal link—a biological mechanism—has not yet been identified. Numerous speakers found this to be the most significant reason that the data should not be considered as having definitively determined a higher mortality risk, regardless of whether the debated statistical methods were valid. One key point was that the deaths are not localized to any single cause. Dr. Beckman pointed out that in past instances of drugs or devices causing harm, their associated mechanisms were typically clear. Gary M. Ansel, MD, from

VIEW FROM THE FORUM

"The VLF performed an outstanding review of all the evidence involving the different treatment options for PAD. I was deeply impressed by the commitment of the VIVA board and the speakers, as well as the support of the members of the FDA and industry.

At this point, the most important points include awareness of this signal, although there is still uncertainty regarding causation/association. We will only find the answers by doing a deep dive into the patient-level data. I was glad to hear that every individual there was supportive of the actions taken by the VIVA group and FDA. Everyone who uses a paclitaxel device needs to be aware of this issue and the work being undertaken to get answers."

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OhioHealth Riverside Methodist Hospital & McConnell Heart Hospital in Columbus, Ohio, agreed. "In the coronaries, there was stent thrombosis and [myocardial infarction]," he said. "But when we were looking at all of the CEC-adjudicated [and] the patient-level data, there wasn't a smoking gun."

Concerns were raised as to shortcomings in the ability to determine causes of death, and the information available for adjudication, acknowledging that the latter are often only a summary (ie, not autopsy level). Additionally, it is difficult to identify deaths later in follow-up as being device- or procedure-related. However, the skepticism regarding a causal link was raised throughout the sessions.

"It doesn't make any sense to indict the drug for having an effect at 5 years," said Elazar Edelman, MD, PhD, of the Massachusetts Institute of Technology, Harvard Medical School, and Brigham and Women's Hospital in Boston, in a panel session following his lecture on drug delivery kinetics. "There is no mechanism that I can envision that would account for mortality." He cautioned that this does not mean there is not a mortality signal, emphasizing the need for continued study and greater future emphasis on preclinical and nonclinical research to better understand the basic science related to current technologies.

Dr. Katsanos confirmed that the *JAHA* meta-analysis did not find a clear biological mechanism to explain its findings. The authors consider their postulation of late paclitaxel toxicity to be theoretical at this time. However, he questioned whether a known biological mechanism is necessary to establish causation. "We should not dismiss it on the grounds that we cannot explain it," he said.

Importantly, the FDA does not necessarily need to identify a biological mechanism to take action, noted the agency's Kenneth Cavanaugh, PhD.

DATA EMERGING SINCE THE META-ANALYSIS

In addition to the study being undertaken by Dr. Varcoe's group and the patient-level data from industry-sponsored trials, the VLF featured the discussion of data from several new analyses aimed at addressing the question raised in the *JAHA* meta-analysis. Those that are complete have been previously covered in *Endovascular Today,* and those that are still ongoing are briefly summarized here.

FDA's Preliminary Review Identifies Signal

Another engaging VLF session began with the acknowledgment that the FDA had completed an initial preliminary meta-analysis of the data from the five trials leading to United States approval of paclitaxel-delivery devices, with further evaluations still ongoing. Misti Malone, PhD, who is Chief of the FDA's peripheral interventional group, described how the agency defines a signal and its approaches to signal management, as well as how it is addressing the current questions facing paclitaxel. This includes conducting its own meta-analysis of the data from United States investigational device exemption RCTs, as well as reviewing any other relevant data. Clarifying the terminology, Dr. Malone said a *signal* represents new information that: may arise from one or more sources; suggests a new potentially causal association or a new aspect of a known association between a marketed medical device and an event or set of related events; and, might justify or require further evaluation and/or action by the FDA.

"Following preliminary review of the data and replicating the meta-analysis, we believe that a signal still persists, and it warrants additional investigation," said Dr. Malone. "We are considering this a potential class effect, while also acknowledging that this may affect other disease states, such as AV [access] and CLI . . . Moving forward, we plan to evaluate potential trends in the cause of death; any adverse events—many of these analyses have also been performed externally; whether there's a trend in the patient-level dose that's associated with mortality; and whether there is susceptibility in particular patient populations."

Although the specifics of the findings and methods were not described, Dr. Malone agreed that the data might be subject to some of the limitations discussed throughout the VLF. However, the preliminary belief is that there is a signal, although there is no "smoking gun." She also emphasized that the device manufacturers have been extremely supportive in the review process. More evaluation, both by the FDA and other parties, is needed, said Dr. Malone.

"Real-World" Medicare and VQI Data Show No Increased Mortality to Date

The data produced in the RCT setting were characterized both for their strengths and their weaknesses, the latter of which include patient populations that do not necessarily represent those seen in most practices. Two of the population-based databases with available long-term follow-up currently collecting data include the Medicare database and the Vascular Quality Initiative (VQI) registry. Although each have their own inherent selection biases and unique weaknesses, their population numbers are large, and in some cases, detailed patient data and longitudinal information are available. Interestingly, the Medicare and VQI data sets can also now be linked together.

Mark Schermerhorn, MD, and Eric Secemsky, MD, both of Beth Israel Deaconess Medical Center in Boston, Massachusetts, described these means of data collection. Dr. Schermerhorn focused on the current data from the VQI, which will be presented at the Society for Vascular Surgery's upcoming Vascular Annual Meeting. Dr. Secemsky recently published the Medicare findings in *JAMA Cardiology* and *JACC* and discussed them with *Endovascular Today*. In short, these analyses of paclitaxel-treated patients and non–paclitaxel-treated patients have not yet found evidence to support a mortality signal in the studied populations, which include claudication and critical limb ischemia. See page 31 for more on these findings.

NEXT STEPS: ENHANCING FUTURE TRIALS AND INDEPENDENT PATIENT-LEVEL DATA COLLECTION

Although there is not yet consensus as to whether paclitaxel itself causes increased mortality after PAD applications, the surprising and controversial findings of the *JAHA* meta-analysis and the vascular community's collective responses to it shed new light on several potential areas for improvement in conducting and evaluating clinical trials. Numerous speakers suggested the need for more robust trial designs, specifically with respect to control arm size and follow-up.

VIEW FROM THE FORUM

"A deeper dive into the meta-analysis needs to be done on a patient-level basis. Is it possible there is a treatment-bias effect (ie, study arm patients were not seen as often as those randomized to PTA)? A per-treatment analysis rather than just intention-to-treat is also needed. Plausible biologic mechanisms for how the devices would increase mortality based upon our current biologic understanding are also lacking. In the absence of a plausible mechanism for increased mortality, the focus should be on the methodologies used in the trials and examination for potential bias.

Nonetheless, we should still be aiming for devices with minimal particulate, given that downstream effects do occur. Although their clinical consequences are not completely understood, these emboli should be minimized. Drug transfer efficiency should also be improved. DCBs, in my opinion, remain an important newer technology whose potential in the vascular space is tremendous, but further improvements also need to be made."

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Also frequently mentioned was the importance of ensuring that patients are on optimal medical therapy and regularly followed up for medical evaluation, both in trials and in clinical practices.

The VLF has begun the process of gathering independent patient-level data from each of the five companies with paclitaxel products available in the United States, with a goal toward "timely, transparent, unbiased, and phased meta-analysis and publication of RCT and adjudicated registry data." Additionally, the VQI and Medicare database analyses will continue as more patients reach longer follow-up. ■