Nine Months Later... An Interview With Konstantinos Katsanos, MD

Dr. Katsanos's thoughts regarding the vascular community's reaction to his group's meta-analysis, the potential influence of follow-up and adjudication variables, non-SFA applications, and what comes next.

What was your initial reaction when your group first identified the mortality signal? Did you discuss the signal with colleagues before publication, and what was their reaction?

Our group has been researching paclitaxel-coated balloons and stents in the periphery and dialysis for more than 5 years now. Identification of the signal was based on a combination of ongoing systematic reviews and serendipity as well. We basically happened to note an increased rate of mortality events in case of the IN.PACT SFA and Zilver PTX randomized studies and embarked on further systematic analyses later. We were very much shocked and alarmed ourselves and have since had myriad discussions (initially in confidence) with peers and colleagues trying to understand the so-called paclitaxel-related mortality "signal."

What is your interpretation of the response you have received from the vascular community following the publication of the meta-analysis?

I think that the whole vascular community was taken by surprise and was disturbed by the sudden disruption of its practice. In addition, a lot of doctors were upset by the fact that this signal had gone unnoticed for such a long time. A significant part of the vascular community has been disoriented by the lack of an adequate scientific explanation or presence of a plausible biological link. However, the emergence and collection of more follow-up randomized data over the last few months has strengthened numeric evidence underpinning the presence of the mortality signal, which has been outlined by the FDA panel as well.

Since the publication and presentation of your group's meta-analysis, companies and investigators have worked to gather additional data to address the concerns raised in your findings, and you have presented additional data at several recent meetings. Can you summarize the work you have done since last December and where it fits in the current discussion?

We intend to publish the results of our updated dose-response models, including the Zilver PTX individual patient data in the near future.

At the FDA panel hearing in June 2019, Prof. Yann Gouëffic presented data from the BATTLE trial. Although still in preliminary stages, he suggested that when incorporating these data into the meta-analysis, the outcome could be different. Similarly, the ILLUMENATE trial has not shown a mortality difference to date. Do you have plans to periodically reconduct the meta-analysis as new data such as these emerge?

To quote Sir Austin Bradford Hill in his 1965 Presidential Address, "All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge." The results of the BATTLE study and other ongoing randomized studies will add to the body of evidence and help strengthen or refute our original results. A few negative trials may not dismiss all other positive trials that make up the bulk of the studies of our meta-analysis. However, it is often recommended that meta-

analyses are updated every few years to represent contemporary science and inform current medical practice.

What should we expect in terms of future presentations and publications from your group in this ongoing area of study?

We are continuously monitoring and analyzing old and new data in the lower limbs and in other vascular territories as well. Unfortunately, we cannot disclose the findings of our most recent analyses until they are published in major peer-reviewed journals.

What do you believe is the impact of the relatively high rate of loss to follow-up and incomplete data in the randomized trials that comprised much of the meta-analysis? Is there any concern that this might introduce bias into the analysis?

Incomplete follow-up may indeed severely compromise the internal validity of randomized controlled trials by interfering with the ascertainment of outcomes of interest. This is of utmost importance, especially when the reasons for unavailability of patient data are associated with the outcome of interest, which may apply when examining secondary endpoints such as patient mortality (ie, if someone dies, there is increased chance that the patient may be registered as lost to follow-up if the event is not formally communicated to the study team). However, in our meta-analysis, average dropout rates were similar between study groups, and updated numeric analyses by the FDA did not materially change the direction or consistency of our original meta-analysis.

What role do you think the nature of event adjudication played in the outcomes of the trials? How can this be addressed, either retrospectively with existing data or prospectively in new trials?

All-cause mortality is the hardest and clearest of all endpoints. Patients are either dead or alive. Interrogating cause of death may introduce inadvertent bias. For example, oncology trials taught us that there are major inconsistencies between disease-specific and all-cause mortality in randomized cancer screening trials. Because all-cause mortality is not affected by bias in classifying the cause of death, it is the preferred outcome measure when interpreting the results of safety analyses, such as in our case.

Your meta-analysis findings have raised a critical potential safety concern but provided no clarity on the mechanism of action or causality. What further research will be required to establish whether paclitaxel itself is the cause of the increased mortality signal and, if it is, the mechanism of action?

The results of our meta-analysis have identified a potential causal link between paclitaxel and increased all-cause death. The term "causal" applies here because, by design, randomized controlled trials address causality and not association. However, we do not know whether this is a direct paclitaxel-mediated biologic effect or an indirect result of the different natural histories of the paclitaxel patient arms (less target lesion revascularization, different medications and follow-up, etc). To quote Sir Bradford Hill again, "What is biologically plausible depends upon the biological knowledge of the day." I guess we just do not know.

Do you personally believe that paclitaxel is the cause of the increased mortality rate, and if so, what is your own theory about the possible mechanism of action?

We have some working hypotheses, but it is still too early to discuss these publicly. However, paclitaxel has been unquestionably linked with higher rates of distal embolization that may lead to foot amputations and local vessel toxicity (eg, aneurysms).

In other types of drug toxicity, we see a predictable spike in one particular type of death, such as cardiovascular disease or malignancy. If locally delivered paclitaxel is causing increased mortality, why is it that one increased mortality type has not been observed?

I do not know. This is an interesting question that pertains to potential—currently unknown—mechanisms of systemic effects.

What did you think of the most recent communication from the FDA on August 7, 2019?

I think that it is objective and balanced, it represents current knowledge, and it definitely serves public trust and safety.

What do you think about using paclitaxel in patients with critical limb ischemia (CLI) or dialysis access failure?

Those are completely different patient populations in terms of expected endpoints and background comorbidities. They both represent particularly more morbid patient groups with high recurrence of vessel restenosis and increased risk of adverse cardiovascular events. However, the availability of large-scale randomized evidence is also limited; hence, I would not draw any parallels with our meta-analysis—at least not yet.

What gaps in the data need to be addressed next, and what analyses would you most like to see happen?

I think that the vascular community requires more randomized controlled trials with more patient-centered outcomes, such as walking distance capacity in claudicants and amputation-free survival in CLI. We need to move from industry-sponsored, device-specific studies to more pragmatic society-funded, patient-focused trials.

In your clinical practice, how has the discovery of the signal affected your use of paclitaxel? What is your discussion with patients regarding drug delivery devices and the overall body of evidence as to their safety and efficacy?

I have significantly reduced the application of paclitaxel in patients with claudication, especially paclitaxel-coated balloons. I prefer to use paclitaxel-eluting stents (which have a lower dose of paclitaxel compared with paclitaxel-coated balloons), particularly when treating patients with CLI, in order to combine vessel scaffolding for maximal early hemodynamic benefit and drug elution for late antirestenotic effect. We openly discuss and express our concerns with regard to paclitaxel in intermittent claudication, but we also explain that paclitaxel is the best thing we have for the time being in CLI, which is associated with the highest lower limb and systemic cardiovascular risk. However, I do note that no dedicated randomized trials have yet been conducted (completed) in the femoropopliteal artery of the CLI population.

You must have thought at length about the best way to release contentious scientific results. Would you have done it any differently if you were to do it again?

We published our results after a long and painstaking peer review process of the highest standards. We are happy with the fact that the vascular community has taken our results so seriously from the very beginning, considering that patient lives may be at risk. ■

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