- Hi, my name's Peter Schneider. I'm a vascular surgeon. I practice at the University of California, San Francisco, and my practice includes both open and endovascular procedures for vascular disease.

Controversies in Paclitaxel RCTs

The paclitaxel RCTs are, of course, we're referring to a number of studies that were performed between the beginning of the 2000s and extending up to the mid 2010s. And in these trials, they were primarily randomised with paclitaxel versus plain devices, either a balloon, drug-coated balloons, or drug-eluting stents, and they were coated with paclitaxel with the intent of improving the patency of these procedures for femoral popliteal occlusive disease. These trials were powered for patency typically at one year. They weren't powered for mortality and they also weren't powered for long-term mortality. However, the controversy came and of course, the open scientific question came when these trials were analysed later using a summary-level meta-analysis. The demonstration among these trials was that there was an increase in mortality, especially in the long-term, at five years. And there are a number of issues around that. As I mentioned, none of them were powered for mortality, even together, they're not powered for mortality. And along with this concept of the potential for increased late mortality, we have to think through, okay, well, what are the other issues that would be part of a causal relationship between paclitaxel and long-term mortality. And those issues are summarised in the Bradford-Hill Criteria, which are criteria which have been around since the mid-1960s and it's how epidemiologists very frequently approach an unknown such as this, is there a causal relationship or merely an association? And those include things like dose response, biologic gradient, whether or not there's a clustering of deaths, which would suggest a mechanism that a particular agent could be causing long-term mortality. And also is the signal consistent? That is, if this is a dangerous material, it should be equally dangerous everywhere that it's used and should be relatively consistent in terms of its causation of mortality. And so, what's happened since the summary-level meta-analysis was published in late 2018 in Journal of American Heart Association, what's happened since then is an accumulation of data, tremendous amount of data, both from the completion of long-term follow-up in the randomised controlled trials and additional completeness of data within those trials, as some of the withdrawn and lost follow-up patients were identified. And in addition, a very much larger patient cohort now has been studied in the so-called real world using real-world evidence. And if I may, I'll just say that real-world evidence is frequently not considered of the same quality as randomised controlled trial data. And I'm not asserting that it is, but if one were to look at real-world evidence for a true, hard endpoint, it would be mortality. So for example, various insurers, government regulatory agencies, they may not know every detail of a patient's life, but the accuracy of mortality data in these databases is extremely high. So the potential then to study long-term mortality, using this so-called real-world evidence, is definitely useful, and of course, real-world evidence now in several hundreds of thousands of patients, who've either been treated with paclitaxel or have been treated with plain devices has not shown any evidence of an increase in mortality. And lastly, I'll just say that there were some other trials that were going on such as the VOYAGER trial and the SWEDEPAD trial. These were also randomised trials. They weren't necessarily designed to look at mortality in patients who'd had paclitaxel versus plain devices, but they have all the controls of a randomised controlled trial situation. And both of those trials, the SWEDEPAD and the VOYAGER also showed no evidence of an increase in mortality going one way or the other.

Katsanos' Meta-Analysis

So just for us, for our purposes for discussion, meta-analysis was performed twice. The initial meta-analysis demonstrated long-term mortality increase, and that was from the end of 2018. Then this past year in European Journal of Endovascular and Vascular Surgery, there was another meta-analysis and this indicated the potential that there could be an increase in amputation in patients who've had paclitaxel. And so, the first meta-analysis is the one I was addressing in these last minutes, talking about the initial meta-analysis, the lack of power, but then also the subsequent data showing no increase in mortality. The second meta-analysis published in 2021 by Dr. Katsanos et al in European Journal of Endovascular and Vascular Surgery. This was also a summary-level meta-analysis of randomised controlled trials. And this particular meta-analysis looked at 21 randomised controlled trials, just a little over half the patients were treated for claudication. So the potential for long-term amputation in those patients is less immediate and probably it bears less on the issue of whether paclitaxel should be used since critical limb patients, which comprised about a little less than half the study are the patients in whom we worry about the immediacy in the potential for amputation in the short term. Nevertheless, more recent meta-analysis from 2021 demonstrated a higher risk of amputation in those who had paclitaxel. The hazard ratio was 1.66 to five years. There are challenges with this meta-analysis as there are with every meta-analysis. And these meta-analyses are performed typically as a hypothesis-generating exercise, not to find the answer, but to find the right questions. Then it's perfectly reasonable to ask this question, is it possible that paclitaxel is causing an increase in amputation risk, particularly in patients who are already at increased risk for amputation, that is, patients with chronic limb threatening ischemia or CLTI? So in the meta-analysis done in 2021, there were 19 randomised controlled trials that reported no events and these were therefore excluded. My sense is that these should have been included because the overall rate at which amputations would have occurred in both groups would have been significantly less had these amputations, or had these randomised controlled trials with no events been included. In addition, I really do believe that the challenge of claudication and the challenge of CLTI are completely different, and I think these should be evaluated separately. And lastly, among the 21 randomised controlled trials included in the more recent 2021 meta-analysis, there were several things that we really should pay attention to. One is that none of the available devices that were studied were in the United States. The largest weight among the trials was using a device which is not commercially actually available anywhere. There were 11 different drug-coated balloon trials that were evaluated in the study, but only six of these are commercially available anywhere. And of the 21 randomised controlled trials, five of them were single centre studies, which it doesn't invalidate them, but just makes it less useful and makes it quality of the data less substantial in a situation where these randomised controlled trials had these specific challenges. Now, it doesn't mean you can't do a meta-analysis. It just means that we have to be realistic about what the meta-analysis is telling us. And I think in the same way that I mentioned that a summary level meta-analysis should be a hypothesis-generating activity. That's I think exactly what what's happened here. And of course, I think this concept is certainly worth looking into, but I also believe at the same time that the weight of the finding would be less if some of these different factors were taken into account that I mentioned.

Other Research

With respect to the mortality issue that was mentioned earlier, the randomised controlled trials that have been done for devices in the femoral popliteal segment and then the subsequent association with mortality, this research, as I mentioned, is hundreds of thousands of patients now with no evidence of a signal toward mortality, also a dramatic increase in the number of patients that were identified in these trials who previously had been withdrawn or lost to follow-up. A tremendous number of these patients were identified, and as they were identified, the mortality signal decreased significantly anywhere from 30 to 50%. And then lastly, I will just say that the potential for these randomised controlled trials to include treatment bias is one that we can't prove one way or the other, but there is circumstantial evidence to suggest that there was treatment bias. Keep in mind that these trials were planned in a previous era, and these trials did not typically control for medications such as antiplatelet agents and statins. During the past two decades, there have been many dozens of papers and studies that have been written to show that statins and other medications have a significant and positive impact on reducing mortality and in the randomised controlled trials, you can randomise the patients on the way into the trial, but subsequent treatments and subsequent follow-ups are not always randomised and there's no way to blind everyone. There's not possible to do a device study that's double-blinded. And so, I think what ended up happening was that the patients that got plain balloon angioplasty or got a plain stent were more likely to fail and therefore, more likely to follow up and that these patients were overrepresented in the results of the trial.

Impact on Daily Practice

In terms of daily practice, the findings of mortality on the initial meta-analysis have not been confirmed by what I would term larger and more sophisticated study using patient-level data, and also using a massive amount of real-world evidence and further randomised controlled trial followup. Therefore, at this point, I do not believe there's any reason to hold back from using paclitaxel-coated balloons or drug-eluting stents. If from a standpoint of the potential of long-term mortality, there's no evidence at this point that long-term mortality is influenced one way or the other by the use of paclitaxel. With respect to the risk of amputation, I think this particularly is something that we should look at in patients who have chronic limb-threatening ischemia. And the best way to do this, of course, is to risk adjust these patients since they come across a broad spectrum of illnesses, chronic limb-threatening ischemia could be anything from mild rest pain to a severe and nearly untreatable gangrene on the lower extremity. And so, paclitaxel, whether it has an influence in this situation has to be, we have to take into account that these patients' CLTI is a broad spectrum of disease and must be risk adjusted. And I think we'll probably be doing that going forward and be on the lookout for any signal of increased mortality. There's a high chance that there is no effect. There've been previous studies showing adequate wound healing, et cetera, in the setting of paclitaxel usage, even large dose paclitaxel usage. Nevertheless, I think once this question is brought up, I think it bears further study.

Future Research

Well, I think at this point, population-based research is probably the best way to sort through whether there's any risk of increased amputation with paclitaxel. And I also believe that there is a tremendous amount of data out there already. As I mentioned, there are a few caveats, one is it has to be risk adjusted. So for example, we could use WIfI scores in order to categorise the presentations of these patients so that we understand how sick they are and what their wound scores are, which is part of WIfI. The other thing that I think would be extremely helpful in understanding this is the potential to use larger databases that had have, in it, the outcomes of patients who've either had amputation or limb salvage. And I think that's really the place to look though. Those places are the places to look first. And then if we still can't sort through it, we may have to add other studies, but I think that's where I would go with it first.