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CHET RIHAL: Hi, I'm Dr. Chet Rihal, former chair of the Department of Cardiovascular Medicine, and a practicing interventional cardiologist at Mayo Clinic in Rochester, Minnesota. Today, I'm joined by my colleagues Dr. Naveen Pereira and Dr. Michael Farkouh, the principal investigators of the recently presented TAILOR-PCI trial, that was presented at the late-breaking clinical trial sessions of the Virtual ACC 2020.

First of all, Naveen and Mike, congratulations on the trial coming to fruition and the very exciting presentation this past weekend.

NAVEEN PEREIRA: Thanks, Chet. It's really been a privilege and pleasure to present the trial at the ACC, virtually. It's amazing job done by the ACC. And of course, congratulations to you as study chair of TAILOR-PCI, and my good friend and colleague at the Peter Munk Cardiac Centre at the University of Toronto, Mike Farkouh.

CHET RIHAL: So Mike and Naveen, I really want to ask both of you-- we've seen the presentation-- is, how do clinicians like me take these results, digest them, and apply them to our patients? Maybe Naveen, I'll start with you, and then I'll turn it over to Mike for your comments on the real practicality of the trial.

NAVEEN PEREIRA: Right. So Chet, as you know, patients who carry the CYP2C19 loss of function genotype, there've been a lot of studies showing a significant association of that particular genotype when they take clopidogrel with increased ischemic events. So this is a high-risk population identified by their genetic makeup.

So what we did with TAILOR-PCI is really focus on that group and attempted to demonstrate whether genotype guidance in that group would be better than just giving everybody clopidogrel. And the results basically showed that there was a 34% reduction in events. So there were about 5.9% events in everybody getting clopidogrel, versus a 4% event rate in those getting a genotype guidance treatment.

So there was still a pretty significant difference, but it was statistically, not significant, because we were expecting a 50% reduction. We saw a 34% reduction, so it was, I think, a modest effect. But it was not statistically significant.

CHET RIHAL: So with a p-value of 0.055, I mean, we just missed it, but the fact remains that there was a reduction in events in the genotype-directed arm. So my question-- and maybe I'll turn to Dr. Farkouh now-- Mike, you've been interested in precision medicine for some time. And it's been difficult to demonstrate the clear benefits for individualization of pharmacotherapy. How, in your estimation, should clinicians take the results of TAILOR-PCI and incorporate them into their day-to-day management of their patients?

MIKE FARKOUH: Well, again, Chet, we've tried to explore the opportunities from a research perspective, the advantages of a personalized approach. And of course, this is quite attractive to health care providers, certainly to insurance and to government agencies and state-run health care systems to find ways in which we can target therapies that are emerging to the populations most likely to benefit.

And I think here we have a simple bedside test. It's very cost effective, and we're using it in patients who are largely being managed with clopidogrel. And that was a big surprise to us from the beginning is that the majority of patients, up to 70% of patients in our centers, in the TAILOR trial, which include Canada, US, Mexico, and Korea, are being treated with clopidogrel.

And therefore, there was a real advantage to [INAUDIBLE] putting patients who may be at highest risk for not being able to metabolize the drug. And therefore, they were the patients that could be designated for the newer therapies.

CHET RIHAL: Naveen, how does this trial compare and contrast with popular genetics?

NAVEEN PEREIRA: That's a great question, Chet. So one of the questions that's been raised is, why bother with genetic testing at all? Why not give everybody ticagrelor or prasugrel. And so popular genetics basically did just that. One arm was giving everybody ticagrelor. The other arm was very similar to our arm. It was a genotype-guided arm.

So most of the patients got clopidogrel. Those with the CYP2C19 loss of function genetic makeup got ticagrelor. And so if you look at the event rates in the genotyping-guided arm of popular genetics, just the ischemic event rates, they reported a composite endpoint of ischemic and bleeding. But if you'll just look at the ischemic rates, it was roughly, for the genotype-guided arm where most got clopidogrel, it was about in the mid 4% range.

If you look at the event rate in the ticagrelor group, it was 4.7% something in terms of ischemic events. It just goes to show how much we moved from PLATO, when the event rates were in the 10% to 12% range, with the new drug-eluting stents and improved guideline-directed therapy. So if you look at the event rate in our genotype-guided arm, it's the same. It's about 4.4%. Where just the loss of function patients get ticagrelor, everybody else gets clopidogrel.

So this is just remarkable that if you take it across, [INAUDIBLE] with patients with STEMI, our patients were acute coronary syndrome and some stable patients, the event rates in the mid-4% range all across, which really creates a case for us adopting a precision medicine approach to treating them with antiplatelet drug therapy.

CHET RIHAL: Thank you. Mike, I assume you're going to be doing a pharmacoeconomic analysis as well of these data. And you personally have had experience in the US health care system and the Canadian health care system, and you've collaborated with people from around the globe. Can you tell us what you're either expecting or how important you feel a pharmacoeconomic analysis will be of the TAILOR-PCI data?

MIKE FARKOUH: Well, Chet, obviously, whenever we have an effective management strategy, which I believe this demonstrates here, with the TAILOR-PCI trial-- it's really the proof of concept-- cost effectiveness pharmacoeconomic analysis is always warranted, and I think welcome.

But in this particular case, I think it's even more important because the guidelines across many jurisdictions, Canada being sort of an exception where we have voted for ticagrelor as frontline therapy, but for most other jurisdictions, including Mexico and Korea and the other international sites in our network, patients are being recommended to be treated on one of these therapies, and therefore, a therapy that's generic, well tolerated, given to millions of patients, like clopidogrel, the idea that we can evaluate whether it's cost effective to actually institute a pharmacogenomic strategy is very, very important, because it will have tremendous implications for health care systems, the cost of drugs, and will allow us to spend resources, potentially, in other arenas both in the cardiovascular space and otherwise.

CHET RIHAL: Naveen, a lot of this is predicated on doing a point-of-care genotype test. You mentioned this in the presentation, of course. But I wonder if you could describe how this was done in TAILOR-PCI in a little more detail so the audience can understand what a point-of-care genotype test looks like.

NAVEEN PEREIRA: Right. So this was one of the keys to success of TAILOR-PCI, to be able to use point-of-care genotyping. A lot of the pharmacogenetic clinical trials which were more blood-based-- so for example, if we look at the warfarin trials, et cetera, it took time for the blood sample to go to the laboratory, the laboratory to process it for the genetic variance, and to return it.

And the key with pharmacokinetics is early institution of change in medical therapy based on the genotype information. The shorter the time, especially after PCI in patients with MI, acute coronary syndrome, the better it is. So we used a point-of-care assay that was made by Spartan Biosciences, a Canadian company, actually.

And all that was required was for the study coordinators to get trained on-- initially, what we did was a validation phase. So study coordinators trained on 20 volunteers. They had to take a buccal swab, put it in the solution for PCR. It's a little assay. And then they put it in this box and get a result within an hour.

CHET RIHAL: That's all it is?

NAVEEN PEREIRA: 60 minutes. It's bedside, so potentially, you could have it in the cath lab, like you check for aPTT, for heparin. And it got FDA approved. And in our trial, we showed there was a 99% concordance rate between the genotyping by this point-of-care assay with more laboratory-based testing, what we call Stat1 genotyping.

CHET RIHAL: So this simple point-of-care assay that can be done easily by a technician or a nurse in the cath lab room would really facilitate an individualized approach to antiplatelet therapy following PCI. And for interventional cardiologists, I think in terms of minutes, rather than days, I think that's really important.

NAVEEN PEREIRA: Right. Absolutely, Chad.

CHET RIHAL: Mike, so let me know ask the critical translational question here. If you had a stent, what would you do?

MIKE FARKOUH: Well, again, this is very much based on hospital practice, the use of antiplatelet therapy. But in many of the centers that largely use clopidogrel as the frontline therapy for PCI patients, I believe that the genotyping is warranted and is supported by the evidence in this trial.

I feel that we would be instituting testing routinely. I think it's very practical. It's cost effective. And I think we've demonstrated-- although our p-value was around the 0.05 level, and not certainly the most robust finding at 12 months-- I do believe that this is warranted, and that it will change practice. And I think that that is sort of the reception that we're getting amongst our investigators.

CHET RIHAL: And Mike, you're extending follow-up now too, right?

MIKE FARKOUH: Exactly. So we have been funded by the NHLBI for follow-up out to 24 months. And it's probable that that will tighten up the confidence intervals, and we will reach statistical significance. Of course, we've always concentrated in the trials of personalized medicine, particularly, on clinical significance. The fact that we see such a robust 35% reduction, I'm hoping that at the 24 months, that by tightening the confidence intervals we'll bring home statistical significance, and we'll still have a robust clinical finding.

CHET RIHAL: Naveen, I'm going to ask you a related question. Trials looking at platelet phenotyping have been negative. Why are these genotype trials more positive than negative?

NAVEEN PEREIRA: Well, the platelet function testing is a very difficult field, I think, in terms of what the assay variability is between the various assays that are used. Like the aggregometry would be excellent to use, but it's so difficult to implement by the bedside. And there's always that controversy that, does platelet function testing always correlate with real cardiovascular outcomes?

I think what led up to TAILOR-PCI was a solid body of evidence showing that there was a remarkable association of having this loss of function CYP2C19 genotype and adverse outcomes. It makes sense from a pharmacological perspective. If you're heterozygous for CYP2C19, you have one third less active clopidogrel in your bloodstream. If you're homozygous it could be up to 50% less active clopidogrel.

And so if you have less clopidogrel, you could be at increased risk of events. And we saw that in TAILOR-PCI. If you look at the composite endpoint breakup, stent thrombosis, there were about eight cases of stent thrombosis within the conventional clopidogrel group, but just two cases of stent thrombosis in the genotyping-guided group. So that's a pure phenotype of the antiplatelet effect of clopidogrel.

The other interesting thing we saw was, in the first three months, there was an 80% risk reduction. 80% risk reduction in the first three months, which I think is a very important perspective, because as we know, in the world of dual antiplatelet therapy, those three-month window post-PCI is turning out to be a very critical point.

And Mike and I have talked about this. If we had to now take a retroscope and say, if we timed our pharmacogenetic trial endpoint to be at three months, when the true effect of your genetic makeup would show up, because you don't expect a long-term effect.

The same thing with warfarin and INR. I mean, the true effect of genetics is when you give your first second dose of warfarin. So the first three months playing an important role in this drug-gene interaction is critical.

Mike, you have this whole pharmacogenomic concept precision medicine trials, your opinion about timing and effect size?

MIKE FARKOUH: I feel the weight of this trial is not just to address antiplatelet therapy of [INAUDIBLE] It really is a proof of concept of the personalized medicine approach. And we learned a lot about it.

The two main challenges we have is the effect size we're trying to detect. It's not in the 20% to 25% relative risk reduction that we traditionally sample size for our statistical assumptions in trials. But it may be in the order of 50% to 60% reduction by targeting these patients at risk.

The second element, of course, is the timing of the endpoint. And we've learned a lot from the cancer folks, having now exercised and conducted the TAILOR trial, that maybe it's the early effects that we're looking for, which shows some promise that we can actually answer many, many questions by performing these kinds of analyses. So I think the methodologic and statistical assumptions that we use for personalized medicine trials will be advanced by the TAILOR-PCI trial, in addition to answering the issue of [INAUDIBLE] pharmacogenomics.

CHET RIHAL: So Mike and Naveen, I'd like to thank you for a very engaging conversation today, and my congratulations to you both and to the entire network of TAILOR-PCI-- the investigators, the coordinators, the international sites that made this, I feel, landmark study possible and feasible. It's been really great.

I hope all of you out there have enjoyed this conversation. I certainly have learned a lot from it, and we look forward to having many more with you. So from the Mayo Clinic, this is Chet Rihal signing off. I hope to see you again. Thank you.

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