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RIVER and VOYAGER-PAD Findings from the ESC Meeting

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Dr. Patel:
Hey, this is Manesh Patel, and welcome to this session on ESC updates. I'm the cardiologist at Duke and joined by a colleague and a friend who's going to tell us a lot about some interesting studies that happened there, an interventional star in our program, Jen Rymer. Jen, thanks for joining us.

Dr. Rymer:
Thank you, Manesh. It's a pleasure to be here today, and I'm so excited to get to talk to you about some of the really exciting research that was presented at ESC and that we both got to listen to and learn about, and today I hope to maybe start off with talking a little bit about the RIVER trial. So, many of you are familiar with this already. It was presented by Renato Lopes at ESC. The RIVER trial was rivaroxaban for valvular heart disease and atrial fibrillation. Great trial design, patients randomized, after mitral valve implantation, bioprosthetic valve, who had concomitant atrial fibrillation or atrial flutter, to receiving either rivaroxaban 20 milligrams or warfarin with an INR dose range between two to three. And so, the trial results have already been presented, but what was presented at ESC that I thought was so fascinating was what really happens with these patients in the first three months. So, we know that first three months after valve implantation can be a really vulnerable time for patients, and how do we keep them out of the hospital and avoiding bleeding and stroke. And so, what was shown was during this period of time actually the patients randomized to that rivaroxaban group actually fared better. They had lower rates of stroke, bleeding, and heart failure hospitalization during that period of time, and some of that is thought to be the classic and sort of age-old issue with warfarin is that it's often hard to get those patients in target range. And so, when they looked at the patients, found at a good proportion of them had INRs that were subtherapeutic during that first three months. And so that was thought to really be driving what could potentially be going on with either increased bleeding, increased ischemic risk, stroke risk. So, we're wondering what your thoughts are there. Is rivaroxaban what we should be using in these patients from here on out?

Dr. Patel:
Well, I think, you know, I suspect the data probably tells us that DOACs are probably safe. And this is one of the advantages DOACs had, and certainly rivaroxaban in this trial, compared to warfarin, which is that when you first start warfarin, and we've seen this in the phase, phase three studies, all four of them, that when you first start warfarin in the first six months, you know, 20, 30% of elder patients can't tolerate it. It gets really hard to keep the drug within range, even though we try hard. So, we saw it at the start of the studies. We also saw it at the end of the studies when we came off of study drug and we transitioned people to warfarin cause these drugs weren't on market at that time. We saw that within the first month in all four of the randomized trials, I guess three of them, there was difficulty. In ROCKET and ARISTOTLE, somewhere around 50% of people, it took 20, 25 days to just get them therapeutic, cause dosing people with warfarin in large groups is hard, and it's even harder if they're postoperative with valve disease. So, I guess RIVER adds to our

knowledge that you can use these agents, certainly rivaroxaban in mitral-valve bioprosthetic patients. However, we should be cautious, right? I mean, INVICTUS was also presented at ESC and published in the New England Journal, and, you know, the big question about rheumatic heart disease was tackled in that trial, and we found that in fact, warfarin was probably still the right drug in those patients, specifically when those patients have such a high thrombotic risk or might have slow flow in their atria, where we might need a different dosing strategy for the DOACs that we haven't studied. So, the big picture for RIVER and mitral valve disease, especially when it's a bioprosthetic valve, is DOACs are probably okay. The big other messages is if it's rheumatic heart disease, do not use DOACs, use warfarin. So, maybe I'll switch gears. I mean that's really interesting and important data. Thinking about VOYAGER-PAD, there was a lot of, sort of, endovascular, surgical patients going through revascularization for PAD. What were some of the lessons that we heard from our colleagues there at ESC?

Dr. Rymer:
Yeah, so VOYAGER-PAD, just to recap, and I'm sure everyone's aware of this. So, looking at patients with, like you said, peripheral vascular disease, and looking at low-dose rivaroxaban and aspirin with placebo and aspirin alone. So, outcomes in general for the composite primary efficacy outcome, we know that there was a benefit for the rivaroxaban group versus the placebo group, so that's already been shown. But I thought that there were two really interesting studies that were presented at ESC this year and one was focused on this concept of what's becoming more and more popular to look at in clinical trials, which is this idea of hierarchical outcomes or win ratio. So, not every part, not every component of the composite outcome maybe is as important to both the provider and the patient as others. So, can you rank them, and then what does that show? And so, when they did that, they looked at multiple models of hierarchical ranking, where they put CV death as the most important, or the one that you fear the most, and then various other sort of rankings for the individual endpoints and found that rivaroxaban in each of those models still feared better, was still improved benefit for the patient compared to placebo. I was wondering what you were thinking about this and in general, and in clinical trials, thinking about this concept of win ratios.

Dr. Patel:
Yeah, I think win ratios are really important and interesting, and you know, and several years ago with the late Dr. Hiatt and Sumeet Subherwal at Duke, we actually proposed win ratios in PAD patients. And the reason we did is because not everything should be weighted the same and this is probably true in all of medicine, you know? So in that, an example in peripheral artery disease patients is that of course cardiovascular death may be really something people do not want, obviously. But then, the next thing they may not want is amputation, vascular amputation, because that really limits their quality of life. And then they may not really want a large or long procedure in which they may put their limb at risk, and they may fear that over a heart attack, a small heart attack for example, versus a big heart attack, and potentially stroke is worse than all of those. So that, you know when you start to take these different sort of events and you start to give them what we'll call win ratio, or weighting or giving them a hierarchy, that makes you a little bit more powerful to find differences, or it highlights the differences. So, I think it was useful to do it in VOYAGER-PAD, which we know, no matter how you sort of slice it, whether you look at it from the traditional standpoint or the win ratio, it looks like a strategy with dual pathway inhibition with rivaroxaban seemed to be better for those patients. So that, I think helps the PAD community. But as trialists, I think it helps them. My last piece on this would be to say we really care a lot about what the hierarchy might be, but the best way to inform that might be patients and getting a large group of people to kind of give us their ranking, their weighting of these endpoints. And, I suspect as we go forward, for a lot of these sort of anticoagulants or trade-off studies, we're going to be thinking about that. Yeah, maybe there were some other interesting things you saw again from there or other research.

Dr. Rymer:
Yeah, so there, there's another important study that was presented out, coming out of using data from VOYAGER-PAD looking at hospitalizations. So, you know, 6,500 patients in VOYAGER-PAD, around 7,100 hospitalizations, about 40% of those hospitalizations were related to PAD. That's unsurprising, I think to you and I, about 3% related to bleeding. We know that in general, from the results that were presented, for those patients that got hospitalized for PAD causes, the ones that were hosp-, there were far fewer in the rivaroxaban group versus the placebo group, and they had a shorter length of stay if they did get hospitalized compared to the placebo group. There was a higher risk for bleeding-related hospitalizations for the rivaroxaban compared to placebo. However, important to note about only 3% of the hospitalizations were accounted for by bleeding. So, I think all of this just again points to the fact that patients that get rivaroxaban, we should not be concerned about increased risk for hospitalizations overall. Very few were related to bleeding and if they are hospitalized for PAD causes, tend to do better than the aspirin only group. What are your thoughts on that?

Dr. Patel:
Yeah, no, I, I think this is another, just tells us about the burden of disease and how that burden leads to significant, morbidity, if you will, and a hospitalization is one of the biggest things that takes away some freedom from patients, and 40% of these patients getting a

hospitalization and then having many different concurrent events, might be important for us. So, I really think it just highlights, again the opportunity for us to think about how to better care for these patients. And a lot of it weren't the bleeding hospitalizations we think about, they were probably other hospitalizations that these patients go through. Some of which are obviously related to the vascular disease, but also the comorbidities. This has been great. It's been a great update of the ESC. I hope you all enjoyed this session and I look forward to seeing you on some more of our updates from some of these cardiovascular meetings.

Announcer:
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