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The Future of Antithrombotics and Anticoagulation – Perspectives from the ESC 2022 Congress

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Dr. Patel:
Hi, my name's Manesh Patel. I'm a cardiologist at Duke, and I'm joined by a friend and colleague, Jon Piccini, the director of our EP section. Jon, thanks for joining me on this update on antithrombotics from ESC.

Dr. Piccini:
Oh! It's great to be here, Manesh.

Dr. Patel:
Well, it was a busy ESC, and it's always great to get back into meetings and seeing each other, and actually seeing the science. And the science is certainly back. Lots of stuff going on with antithrombotics. Maybe the hottest area at ESC was around factor XI inhibition. Jon, maybe you could just start us off by telling us a little bit about what the theory is behind factor XIa inhibition.

Dr. Piccini:
Yeah, I mean, I think it's really exciting, factor XI inhibition, obviously, as you know, Manesh, offers the possibility of inhibiting the intrinsic pathway and thrombin amplification without impairing coagulation mediated by tissue factor, which is helpful, because bleeding initiated by tissue factors, often the response we require when we experience trauma or disruption of a blood vessel intima. And I think some of the most promising data in factor XIa inhibition, that I think is just really neat and exciting to think about, is when you look at population data and you look at genetic variants that are associated with decreases in factor XI activity, those same individuals at the population level, have a lower risk of thrombotic events, including thromboembolism and stroke. And so, that's the whole premise behind these compounds. So, it's very exciting, the opportunity to prevent thrombotic events at a much lower risk of bleeding.

Dr. Patel:
Yeah, so we worked together a little bit on the PACIFIC-AF program, John, maybe... That was presented at ACC, and it was obviously a study against apixaban, a phase two study, maybe just a brief on what your take home was from PACIFIC-AF. I know you- [indistinct] at ESC to sort of recapitulate some of that at a symposium with Lancet.

Dr. Piccini:
Yeah, I know there was a ton of science presented at ESC, but you're right, before that, PACIFIC-AF completed. And the hypothesis was, if we compare asundexian, a small molecular factor XIa inhibitor, to a direct-acting oral anticoagulants like apixaban, will that lead to a reduction in bleeding? And you know what's interesting, the bleeding rate in the trial was half the projected rate, which just goes to show that, event rates keep getting lower, and lower, and lower, as care gets better. But even with that 50% of the projected bleeding

rate and even with enriching the population for bleeding, we saw that asundexian was associated with a significant reduction in bleeding relative to apixaban, with excellent suppression of factor XIa activity, at peak and trough. So the take for me is that, yes, it appears to lead to less bleeding and now we'll need a phase three clinical trial to test whether it can prevent stroke effectively, and we'll see the same benefits in prevention of bleeding.

Dr. Patel:
So ESC had some data on both milvexian, which is a different factor XI for a stroke, and the same drug, asundexian, for a secondary stroke prevention in patients who had stroke. What was your take home on the PACIFIC side, and maybe I'll speak on the axiomatic or the milvexian side?

Dr. Piccini:
Yeah. I mean, again, Manesh, I'm an electrophysiologist, so my interest is obviously in heart rhythm disorders. And so by under no circumstances, what I consider myself an interventional cardiologist, obviously, since I have not been trained in that manner, and don't follow the literatures closely. But I remember sitting in the audience for PACIFIC-AMI, and as you know, these patients, they bleed all the time. And I was blown away, that factor XIa inhibition in those patients did not lead to increased bleeding. I mean, I just... Going back all the way to my fellowship, every single ACS trial, it seems that there's always increase in bleeding risk. And so, I was really struck by that. I just remember sitting in the audience and being like, "These data are so incredible."

Dr. Patel:
Yeah. Powerful, in the sense that on top of DAPT, asundexian didn't increase bleeding compared to placebo, or at least very similar rates at the... Even in some of the higher doses, so I think, encouraging, obviously. Not as much of an efficacy signal, but it's phase two and a lot of people are having conversations about that. We know that phase two for efficacy is really not, if you believe in the compound, something we're going to follow and see. And we've seen other therapeutics where phase two didn't show much of an efficacy signal and then showed a huge... So, safe, and reasonable to go forward. I'll just highlight for the stroke studies, we saw-

Dr. Piccini:
Yeah, you got it. So, what do us, heart rhythm docs, need to know about PACIFIC, and stroke, and axiomatic?

Dr. Patel:
It's interesting. One of the things I'll say, again, not as a stroke neurologist. I told Valeria a case of our colleague, as a neurologist, interventional cardiologist last person to talk to about stroke. But what I have learned about stroke is that, a lot like heart failure, it's a grab bag term, right? We think about heart failure as one condition, when we know there's a lot of underlying conditions. Same thing for stroke. A carotid stroke, an embolic stroke, a middle cerebral artery stroke, or small vessel lacunar infarcts, might be totally different, pathophysiologically. And I actually think that's what we saw in some of these studies. In fact, in at least the PACIFIC-Stroke study, we saw that the patients who had lacuna infarcts or small vessel strokes, or we were looking for covert strokes, small non-symptomatic strokes, didn't see much of an efficacy signal. But for those large vessel strokes, those probably what I'll call athero-related strokes, not only did we see reasonable bleeding signals, but we also saw a possible efficacy, both with asundexian, and then a dose response relationship. Not exactly clear. We saw it sort of with doses that 200, twice daily dose, seem to be the most outlier for the axiomatic. But again, some dose response, and again, safety with bleeding, all again, information that tells us in a very untreated population, patients with secondary stroke who right now get DAPT and then maybe just monotherapy antiplatelet, big opportunity. But with these opportunities, we might have to be a little bit more careful with the phenotypic description of who should get benefit. Well, Jon, this has been a great update from the ESC. Thanks for telling us about this exciting area. I guess I'll just say, for both of us now, the whole field is ready, a lot of investigators are ready. We're going to have to find out which of the phase three studies are going forward. Hopefully, many of them. But I do think there's a lot of opportunities still for our patients, as many do not get therapy when they have a stroke, or they have atrial fibrillation. And certainly, interventional cardiologist still looks for ways to improve our patients. Thanks for joining me on this update on antithrombotics for ESC.

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