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Released: 09/30/2022
Valid until: 09/30/2023
Time needed to complete: 1h 02m

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Factor XI Inhibition- Milvexian, Asundexian, and AXIOMATIC

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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 here today as we talk about some of the exciting science and information coming from European Society of Cardiology this year. Importantly, we're going to be talking about factor XI inhibition. And just to get that into an idea I want to make sure we talk about how much over the last 10 years my colleague and I have been thinking about this. John Alexander, it's great to have you. I know you round on patients, you take care of a lot of patients with a vascular diseases and atherothrombotic needs. So, thanks for joining me.

Dr. Alexander:
My pleasure. Great to be here. There were a lot of exciting trials at ESC on factor XI inhibitors. Manesh, why don't you tell us about the AXIOMATIC secondary stroke trial?

Dr. Patel:
Yeah. Thanks John. As our audience may know, there's a lot to think about in factor XI. I'll just remind everyone about the factor XI inhibition pathway. You know, prior to recent... Last 10 years, which I guess shouldn't be considered recent. But, you know, we used Warfarin, which was sort of I'll call it indiscriminate inhibitor of vitamin K across many factors in our coagulation cascade. Over the last 10 to 12 years, you and I and others have worked on several compounds that inhibit factor X. That's at the crossroads of actually thrombin activation and amplification. And that's been good cause it's prevented clots, but it also has this risk at the right dose or even in certain patients of bleeding. So, the idea with factor XI inhibition which is after that actual activation happens is the amplification contact pathway is often led by factor XI. And inhibiting that might be an opportunity to prevent that sort of propagating thrombus without having as much bleeding. So that's the general concept.

And then one may say, well who are you going to study it in? And believe it or not, there's still a lot of patients who don't get therapy for atrial fibrillation. There's obviously a lot of patients who you and I take care of with acute coronary syndromes. And maybe one of the biggest unmet needs are patients who have secondary stroke or patients who've had a stroke, who are trying to prevent another stroke. And you know, in those patients who've had a stroke previously, right now, and I'm not a neurologist but my neurology colleagues highly likely have studied many of these therapies. They get, you know, dual antiplatelet therapy for a little while and then monotherapy antiplatelet therapy. So there seems to be an opportunity. So, it's in that background that the AXIOMATIC secondary stroke program study was presented by Mike Sharma at the European Society of Cardiology. It is a study evaluating a therapy called Milvexian.

Milvexian is one of these small molecules that inhibits and it's a potent inhibitor for factor 11. It has an oral absorption of two to four hours, half-life around 11 to 18 hours. The good news is, it's less than 20% of it's metabolized in the urine in healthy subjects. So, it has the potential to really be effective. And our colleagues, I think, in phase two were doing appropriately a dose finding study. And we'll talk

a little bit about what this phase two mean. They enrolled 2,700 patients or so or 2,800 patients. And they randomized over 2,300 patients, 2,366 patients to one of, sort of several arms.

One arm was placebo but then there were five doses of Milvexian that they studied. And they dropped a dose and added a dose at the top end I think, as they were thinking about the bleeding in. So, they studied once daily 25 milligrams but then twice daily 25, 50, 100, and 200. And so looking across those patients on those doses they then looked at importantly, you know, we've had sort of conversations about what people should be looking at in these phases. They looked at these patients, about 75% of them had an ischemic stroke coming in and about 25% had a TIA.

And they were about 36 hours from their symptom onset. And they got randomized into the study and they looked at symptomatic ischemic stroke downstream which I really do think is a powerful and important efficacy endpoint. And they see, as you think about it, placebo had about 5.5% rate. And then from 25, once daily as you go to 25 twice daily 50 and 100, you do see a dose-response relationship going down to from around five and a half to 3.5 for 100 BID. Interestingly the 200 BID dose has Craig doxable sort of elevation of 7.7. Not sure what to make of that very high dose but maybe there's some other issues.

So interesting to see some of that. And I'll just make one more comment and then get some thoughts from you on I know you presented the Pacific AMI study and just overall the field, they did look at bleeding. Everybody goes, okay, so how did it look for bleeding? What was really interesting is the placebo and the and the 25-milligram months daily had almost exactly the same bleeding the 25 twice daily had similar or less and then saw a little bit more bleeding as you got to 50 or a hundred BID. So again, making you think that you could potentially find that right balance between getting an ischemic effect without much bleeding. And these agents have now, both in some of the AF work we've done and some of the AMI work you presented shown us that they are relatively safe to efficacy and the right dose is going to matter. So, I was excited to see the data. I think they were well presented, and they add to the field. So, I guess the question I have for you is tell us what you make of these phase two data, John, and how axiomatic fits into our understanding of a factor 11 sort of programs.

Dr. Alexander:
So, Manesh, you said there, this is one of several phase two studies that has recently been presented, right? Two in stroke, one with Milvexian and one with Asundexian that was presented in the same session. And then one in AFib that you presented and one in acute MI that I presented. And I think there's a, there's a pretty consistent story across all of them with regard to bleeding that, you know the AFib study was compared to apixaban and so Asundexy and a different factor 11 inhibitor caused a lot less bleeding than an apixaban. And in the three placebo control trials the two-stroke trials, including the one you just talked about with Milvexian but also the Asundexian stroke trial and the Asundexian acute MI trial, there was either a very little or no increase in bleeding compared to placebo and with across a range of doses. And so that's, that's very reassuring to the hypothesis that, that you laid out at the beginning that maybe we can decouple bleeding and prevention of thrombosis with these factor 11 inhibitors. So, one thing I want to caution everyone these are phase two studies and they're small. I mean they're a couple hundred patients per arm. And so, you're talking about 10, 20, 30 events per arm. And so, while we talk about these nice trends or absence of trends they're really wide confidence intervals around all of it. And that's the reality of phase two. And it's really, it's important for safety but it's also important for it's really important for efficacy. So, you know, the AFib trial, which you presented at ACC was designed, was not designed to look at efficacy. It was really designed not to look at efficacy, it was short in duration and there were very few thrombolic strokes these two-stroke trials, you know, the Asundexian one we didn't really see a signal in the overall population but in the people with atherosclerotic stroke the same population enrolled in axiomatic there was a nice signal in the asundexian stroke trial and I think there is a nice signal in this axiomatic stroke trial suggesting maybe some reduction in stroke that needs to be confirmed in a bigger phase three, you know or more than one bigger phase three trial. And then in the acute, my trial, which I ran, you know we didn't see a reduction any hint of reduction in ischemic events. And I think there one, again you just don't know whether that's because AMI is different there's some hypotheses that maybe it's different from stroke or is it just chance and wide confidence interval. So, it's, it's a really exciting time. You know, these are phase two trials but they're setting the groundwork for really important big phase three trials.

Dr. Patel:
Yeah, I think you well summarized for us that the importance of these, these steps in phase two studies, right? Which is we do want to see something around safety we want to understand tolerability really, they're really aimed at dose. So, there's still these questions around dose that I think even after seeing the study and the data, you're never fully confident because you always have to have more information, but you do your best PKPD, you look at your best dose you look at the dose that effect happens. So, I think that's what we're learning. I think the one message across those indications you said is that they do seem to bleed a lot less than other therapeutic we've had. And so, the efficacy is if you believe in them then you have to go test them enough people to find out. And I think we're going to do that. And I think to the credit of a lot of different sponsors academics and clinicians, I think people are ready for that. I think as you go forward and see your patients in clinic and you think about these therapies in trials you're going to want to know how comfortable do I

do get presenting it to my patient. And I think one of the strengths here for several of these programs is that they've been tested they've been tested just even sometimes against the comparator. You're going to see in the phase three and you should feel comfortable that it at least is at least as safe and we're going to find out about efficacy. So those are great. Thanks, John. It was a really great conversation around factor 11 as we said, and we're learning a lot about these phase two therapies and certainly, it's some of it's around dose in this patient's tolerability. And as we get closer to our patients and trials I think we should feel fairly comfortable. I hope this conversation's been useful to you all. We're excited about these compounds and milvexian and the Axiomatic secondary stroke program certainly showed us, again another promise with some opportunity in patients that need it. So, thanks for joining me John and we hope you all continue to check. Check-in with us on these updates from clinical trial meetings.

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