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Emerging Data in the Management of Acute Ischemic Stroke/TIA

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Dr. Shoamanesh:
Hello, good evening, everyone. Next, I'll be speaking to the emerging data in the management of acute ischemic stroke and TIA. And Manesh has already done quite a nice job laying out the landscape of existing phase 2 and phase 3 trials in this space. As he's already highlighted, there's really three different classes of compounds that have been developed, and that's antisense oligonucleotides, antibodies, and then what we're testing in strokes are small molecule, direct inhibitors of factor XIa, which are oral compounds, which of course improve the ease of use for patients.

I think a couple of things that are worth highlighting is that this is actually the first time for any anticoagulant that we actually had dose-findings studies for stroke prevention. So, I think this is actually a very important step forward for kind of trying to have tailormade doses of anticoagulants for a stroke prevention strategy. And we'll speak to the results of the PACIFIC-STROKE and AXIOMATIC-SSP, which were the phase 2 studies that kind of led to the current doses that are being used in phase 3. In addition, as Manesh has already highlighted, very similar to the DOAC story, many of the phase 2 trials were actually TKA trials. But here, we also had dose-finding AF studies and that was namely PACIFIC-AF. Moving forward, I won't spend much time on the ongoing trials because Manesh did a nice job of it, but I will highlight OCEANIC-STROKE and LIBREXIA-STROKE briefly at the end.

Now, how do the small molecule inhibitors of factor XIa differ in terms of their PK and PKD, or PAPD rather, compared to what we've been used to with factor Xa inhibitors that are listed here, that being apixaban, rivaroxaban, and edoxaban? Well, the first thing to note is that although one of the drugs that was very widely used in this market, rivaroxaban, did have pretty substantial food effect in terms of its bioavailability, this is really minimal for asundexian and modest for milvexian. The half-life here is longer than what we've seen with the factor Xa inhibitors, making us much more confident in the once-daily dosing regimen, particularly for asundexian. Renal elimination is much less, it's actually clinically irrelevant, I would say to some extent. But, what, 14 and 18%, respectively, between asundexian and milvexian, versus ranging between about 25 to 50% with the factor Xa inhibitors. And importantly, for polypharmacy, are here we don't have any metabolism with the CYP3A4 pathway so there's going to be less interaction with asundexian. Although with milvexian, there is still some CYP3A4 metabolism that's going to be implicated for polypharmacy. And in these drugs, similar to what we've seen with factor XI deficient patients in the community, and one way they're actually often diagnosed, is by this detection of elevated aPTT, that then leads to investigations that results in their diagnosis, these drugs do prolong aPTT, whereas they have no effect on PT or thereby no effect on the INR.

Now, across the PACIFIC program, about 4,000 patients were randomized, so a lot of data in patients with vascular disease. And based on the different arms in these trials, actually the vast majority were exposed to a dose of asundexian, so almost 3/4, or 3,000 patients, were exposed to asundexian. And this really increases our confidence in the safety signals that we're seeing consistently across these three trials.

And I'll focus now on PACIFIC-STROKE, which of course was a stroke prevention study in patients with non-cardioembolic ischemic stroke. And this was published in the *Lancet* in September of 2022. And here, we're really targeting patients with non-cardioembolic ischemic stroke. Patients with TIA were not eligible for this study in contrast to AXIOMATIC-SSP which we'll talk about in a second. And this accounts for 75% of all ischemic stroke subtypes. And as Mike has already nicely outlined, these patients remain in a substantial risk of recurrent stroke, despite guideline-recommended treatment at about 6%, or more than 6% per year; that 6% really accrues within the first 90 days and then there are subsequent risks thereafter. And of course, with the consistent data that has been seen between the association of factor XI levels and the risk of stroke as well as the reduced risk of stroke in those that are factor XI deficient that Manesh took us through, stroke prevention seems like a very natural target for factor XI inhibitors. And really, Mike outlined this nicely with the COMPASS results, is where there was a very strong signal that combining an anticoagulant, and in this case, it was a vascular dosing of a factor Xa inhibitor, rivaroxaban 2.5 mg twice daily with aspirin, led to a substantial, close to 50% relative risk reduction, compared to aspirin alone in a population that had stable atherosclerotic disease. Yet, the bleeding really that came along with that made this less appealing for broad use in a very large population of stroke. And really, the promise of factor XIa inhibitors of being able to further reduce stroke without increasing bleeding really makes an attractive candidate for this dual pathway inhibition strategy.

And what we saw from the Mendelian randomization data is that we see actually consistent associations between genetically determined elevated levels of factor XI, and Mendelian randomization is basically like nature's randomized trial because of the random distribution of alleles and chromosomes during meiosis. And here, we're seeing that genetically determined elevators of factor XI, are associated with all stroke subtypes except, interestingly, with small-vessel occlusive disease. And I'll show you in our phase 2 results about how we may have actually replicated these findings through our clinical trials in the phase 2 level.

Now, PACIFIC-STROKE was a prospective, randomized, double-blind, placebo-controlled, phase 2, dose-ranging study where patients with non-cardioembolic ischemic stroke, who presented within 48 hours of symptom onset, who were intended to be treated with antiplatelet therapy, were randomized with three different doses of asundexian, that's 10, 20, and 50 mg daily, or placebo. And all patients underwent baseline MRI, as well as again at 6 months or at end of treatment. And in total, we had 1,808 patients who were enrolled between June of 2020 and July of 2021 at 196 sites and 23 countries.

The primary efficacy outcome here was the composite of ischemic stroke or covert infarcts on MRI at 6 months. And what we saw is that actually there was no dose-dependent relationship observed with asundexian for this composite outcome. However, this seemed to be largely driven by a lack of effect on covert infarct, so asymptomatic infarcts detected only on MRI at end of treatment, or 6 months. And the majority of these, 70%, were small subcortical infarcts deemed to be most likely resulted from cerebral small vessel disease. And the covert brain infarct component of the composite actually monopolized the composite, it accounted for 3/4 of all composite primary outcome events.

However, when we looked at the outcome of ischemic stroke in isolation, there was a trend for a 20% risk reduction for ischemic stroke with asundexian 50 mg versus placebo. And then when we looked at the outcome of TIA, there was a large effect size that was consistently seen with the 20- and 50-mg daily doses versus placebo at about an 82% relative risk reduction.

Now, when we did a post-hoc exploratory analysis for the composite of recurrent ischemic stroke or TIA, a total study duration of 10.5 months median, we did find that the event rate went from 8.3% in the placebo arm to 7.7% in the asundexian 10-mg arm, 6.2% in the asundexian 20-mg daily arm, and 5.4% in the asundexian 50-mg daily arm with this highest dose leading to a statistically significant 36% relative risk reduction for this composite outcome.

Moreover, on the basis of the COMPASS trial results that we discussed earlier, we were really interested in seeing how patients fared in this study if they entered the trial with atherosclerotic disease. And we did this in two ways; one, we looked at patients who met TOAST criteria for large-artery atherosclerotic disease. And then second, more broadly, we looked at any degree of atherosclerotic disease detected on vascular imaging of their arch, cervical arteries, or intracranial arteries. Now, the first analysis where we looked at those who met large-artery atherosclerotic disease by TOAST criteria, there was about a 44% risk reduction, that did not reach statistical significance. And then for the any-degree of atherosclerotic disease, we found a 61% relative risk reduction with asundexian 50 mg daily versus placebo, and this was statistically significant.

Now, importantly, we saw these potential benefits without any excess risk of bleeding. And when we looked at a composite primary bleeding or safety outcome of major or clinically relevant non-major bleeding defined by the ISTH criteria, the pooled rate was 3.9% amongst all asundexian doses, versus 2.4% in the placebo arm. The hazard ratio of 1.57 is actually comparing the pooled asundexian doses versus placebo. Now, although this is a numerical increase, this was not statistically significant and it was really driven by an excess risk of clinically relevant non-major bleeding, not major bleeding. And clinically relevant non-major bleeding tends to follow all bleeding. And when we looked at all bleeding, and together, we didn't find any suggestion of excess risk with asundexian versus placebo. When kind of merging this data and looking at the consistent safety signals in PACIFIC-AF and PACIFIC-AMI, we really believe

that this is probably a chance finding, and indeed it is statistically insignificant. And importantly, we also don't see a dose-dependent relationship for our primary safety outcome.

And then when looking at the C. table, one of the bleeding outcomes of greatest concern for stroke neurologists, particularly when introducing an anticoagulant on top of antiplatelet therapy is, was there any hemorrhagic transformation of the qualifying infarcts? And there's actually no suggestion of any excess risk of hemorrhagic transformation with asundexian versus placebo across all three doses.

So, I think this is very, very reassuring data all together. And although we're not showing the data here, there's also been subgroup analyses of patients who entered the study with microbleeds, who are even at higher risk of bleeding outcomes, and no suggestion of any treatment interaction whatsoever with the presence of microbleeds, consistently no excess risk of bleeding with asundexian versus placebo.

Now, moving on to AXIOMATIC-SSP, which was the other trial that was being led by our colleague, Mike Sharma, and parallel to PACIFIC-STROKE. And here, the design was slightly different in that they excluded patients with lacunar stroke. They had to have some degree of visible atherosclerotic disease. So, you could think about that subgroup analysis I showed you where we had any degree of athero from the PACIFIC-STROKE trial being generalizable to AXIOMATIC-SSP as its entire study population. Their NIHSS scale had to be 7 or less at study entry. And here, they allowed TIAs if their ABCD ^{2} score was 6 or greater. And again, they had to present within 48 hours of symptom onset. Now, in PACIFIC-STROKE, we did not mandate a certain regimen of antiplatelet therapy, they just had to receive some antiplatelet therapy, whereas in the population, about 40% of received DAPT. In PACIFIC-STROKE, actually all participants had to receive 21 days of DAPT followed by monotherapy. And they tested various dosing of milvexian ranging from 25 mg once daily, up to 200 mg twice daily, all versus placebo. Now, interestingly, similar to our analysis, they did see a dose-dependent response here in patients that had some degree of atherosclerotic disease for the outcome of ischemic stroke, and this came down from 5.5% in the placebo arm down to 3.5% in 100 mg twice daily arm. There was this paradoxical increase of the 200 mg twice daily dose of this compound, which is really uncertain and may have just been a chance finding because there's a consistent dose dependency for the rest of it. And here, there was a suggestion of a 2- to 3-fold excess risk of kind of BARC type 3 and type 5 bleeding, which kind of falls similarly to clinically relevant non-major or major bleeding based on the ISTH criteria once you got over 25 mg twice daily dosing of this agent.

Now, when we combine both studies and we look at it, I think one thing that comes out is the consistency despite some of the trial design differences, right, in that there was no effect on the outcome of covert brain infarction in other trial, there was a reduction in ischemic stroke, particularly in those that have atherosclerotic disease, and that it was generally safe. And this is important because, remember, we're not comparing these drugs versus an antiplatelet agent, we're not comparing them versus another anticoagulant, we're comparing them to placebo, on top of a population, where 40 to 100% of them received DAPT for a short period of time, at least. And we're still not seeing excess bleeding. I think that's pretty consistent and reassuring for the premise that we can have this uncoupling of hemostasis and thrombosis with these agents. And really, for phase 3, what it has emerged is this atherosclerosis hypothesis in that, really, we went into this trial, largely due to the evidence that we had with the COMPASS trial, which was in a population of stable atherosclerotic disease. We then see consistency in the effect of patients with large-artery atherosclerotic disease based on TOAST criteria, as well as those that had atherosclerosis based on vascular imaging in the PACIFIC-STROKE study. And this is very consistent with the overall trial result of AXIOMATIC-SSP, where they had to have athero at trial entry. The robust effect size on TIA, that 80% relative risk reduction that I showed you is actually consistent with atherosclerosis hypothesis as well because TIAs are actually overrepresented in patients with large-artery atherosclerotic disease, relative to other stroke subtypes. And then again, the lack of effect on covert brain infarction, the majority of which was due to small vessel disease, and again, replicating what was already suggested in a Mendelian randomization evidence we had previous to the phase 2 trials.

And in this particular aggregate meta-analysis, I've chosen the PACIFIC-STROKE data of patients that had any degree of atherosclerotic disease who received 50 mg versus placebo, and combined it with the dose of milvexian that's moving forward into phase 3, and that's the 25-mg twice daily dose. And as you can see, that in patients that have any degree of atherosclerotic disease, when you look at the doses that are going into phase 3, we're seeing for the outcome of just symptomatic ischemic stroke, not including TIA, a suggestion of a fairly large effect size, close to 40% relative risk reduction. But of course, due to the small numbers, still, even with a pooled analysis of these two phase 2 studies, and a subgroup of one and the composite of the other, the confidence intervals are fairly large and crossing the null, but really reassuring direction of treatment effect, and that we're on the right path to see positive results in our phase 3 trials.

And what are those phase 3 trials? Well, OCEANIC-STROKE is going to be comparing asundexian 50 mg daily versus placebo in 9,300 patients who have non-cardioembolic ischemic stroke or high-risk TIA, who are being enriched for atherosclerotic disease based on eligibility criteria. The primary efficacy outcome for this study is going to be the time to first occurrence of ischemic stroke, and a primary

safety outcome is going to be time to first occurrence of ISTH major bleeding.

Similarly, the LIBREXIA-STROKE study is going to be testing milvexian 25 mg twice daily, which is again, a sum of 50 mg daily in total. So, same dose in terms of the milvexian 25 BID and asundexian 50 mg daily, versus placebo on top of antiplatelet therapy, and is going to be 15,000 patients for the primary outcome of time to first occurrence of ischemic stroke.

Now, another question is, as you can see, these are fairly large trials, we're going to have in total, close to 25,000 patients that are going to be treated with or enrolled in these studies, half of which are going to get asundexian or milvexian. And eventually, 75% of our ischemic stroke patients may be on these drugs if we are on the right track, as we believe we are.

So, what will we do if these patients come back with an ischemic stroke? Well, do we have the option of administering thrombolysis? And although we don't, we can't provide any firm direction because we just don't have the clinical data to reassure us that it is safe to do so, what we do have some animal data. And this is what I'm showing here. On the left, in the green figure, you're just looking at thrombus weight according to various doses of tPA. And in the very last bar showing the composite of tPA and asundexian being provided together. And you're seeing that the thrombus weight does go down with tPA, maybe a slight addition to the reduction in thrombus weighed with asundexian on top of tPA, although it was not statistically significant, albeit in the top right, you'll see the dose-dependent reduction in thrombus weight when asundexian is given without tPA. And then when we're looking at bleeding times, what's really interesting is that we see actually no excess risk of gum bleeding time in these rabbits when asundexian has been provided on top of a thrombolytic or tPA. And this at least suggests that we can consider it, what we're recommending to our sites in the phase 3 trial is that if it is a disabling stroke and you don't have a rapid access to endovascular thrombectomy or the distal, that you can consider on a case-by-case basis. And we will be collecting data on these cases throughout the trial so that we could then have some clinical data to reassure us on top of the animal data that I'm showing you right now.

So, to conclude, factor XI and XIa as a target for stroke prevention is supported by robust preclinical and clinical data. The phase 2b stroke prevention trials were largely consistent in their findings, and suggest a reduction ischemic stroke recurrence, particularly in patients with non-cardioembolic ischemic stroke, who are enriched with atherosclerotic disease. And if these results are confirmed in ongoing phase 3 trials, which we hope they will be, a factor XIa inhibition will be established, a new paradigm that will enable us to reduce ischemic stroke without compromising safety in select patients with non-cardioembolic ischemic stroke.

Okay, thank you.

Dr. Sharma:
Just want to thank all of our speakers for some excellent talks and a time for questions. So, we have our first question and I'm going to direct this to Valeria. So, Valeria for patients that you're considering dual antiplatelet therapy in, do you recommend genetic testing for CYP2C19 alleles in patients before you start clopidogrel?

Dr. Caso:
Not really, no, we don't do this. Interesting question. Very good question. But probably in the future, we will do, but not now.

Dr. Sharma:
Okay. And so, let me just ask one question. And it's rare that we have a cardiologist in the mix in these panels, so I'm going to take advantage of that. And Manesh, I almost said you were in Chapel Hill, so please forgive me. It's –

Dr. Patel:
Oh my gosh.

Dr. Sharma:
It's UNC. So, Manesh, you've had, you know, this choice between ticagrelor and clopidogrel for a number of years in cardiology. So, how do you select patients for more intensive therapy with ticagrelor or conversely stepping down therapy? What's the paradigm?

Dr. Patel:
Yeah, so I think it's important to recognize a couple of things in our lectures and talks, where, first as a cardiologist, I grew up in a platelet-centric world, we put a stent in, DAPT, the strongest DAPT use it forever, don't stop. And we've moved away from that. We've gone from a platelet-centric world to a dose-specific or antithrombotic, or mixture world, I think that's where we're moving. That's an important piece here.

And then to the question that somebody asked about CYP2C19 testing for how long and how strong do we use the dual antiplatelets. At least in the coronary world, and we can think about what it means and I'm learning from you all in the, I'll say, small vessel to medium vessel or larger vessel stroke world; in the coronary world, when a vessel in the coronaries that's 3.5 mL or 4 mL, ruptures, or has plaque rupture, or gets a stent, I'll call that at least some biological process that may be similar to what you all deal with with acute

stroke. There's a balance that we're dealing with in that, at least in the heart, unlike the brain, we're trying to really prevent recurrent thrombosis. And we don't have as much a penalty as you all - as we all when we think about brain. So, in the coronary world, acute syndromes, or acute myocardial infarction, ticagrelor and aspirin has been shown to be better than aspirin and clopidogrel in the acute scenario. And we also know in the acute scenario, aspirin and prasugrel was better than aspirin and clopidogrel for ACS up to one year. So, for patients that have an acute coronary syndrome, AMI, that are getting a stent, we often will use a stronger dual antiplatelet regimen. And now, if you go to any cardiology conference, there's multiple studies on when do you back down, how long do you have to have dual antiplatelet therapy, what are the features of the patient? So, instead of a one size fits all, everybody needs the strongest DAPT up to a year, we now know at least in stenting world and others that we can start to back down to monotherapy, or even go to lesser therapy at 3 months, at 6 months. ACS which is a broader and bigger issue, still make it 6 to 12 months for the reasons I've described. Does that help, Mike?

Dr. Sharma:
Yep. Thanks. Thanks very much. That's actually very helpful with all that experience. Look, this is triggering other questions as well. So, maybe I'll direct this to Ashkan, and Valeria can comment as well as anyone else. So, imagine a patient who has an aspirin allergy and resistance to clopidogrel. So, we're imagining here a very unlucky human being, but happens to have both these things. So, aspirin, you can't give them, and clopidogrel won't work. So, Ashkan, in that kind of patient, would you consider ticagrelor monotherapy long-term?

Dr. Shoamanesh:
Yeah, I don't see any reason not to. Right? It's a P2Y12 inhibitor, similar mechanism of action of clopidogrel. Here, you have clopidogrel resistance, so certainly I would. An alternative that's more widely used in East Asia is cilostazol monotherapy. Yeah, either of those, I think would be appropriate for this patient.

Dr. Caso:
Yes, the data from SOCRATES shows you it's quite equivalent. So it's an additional choice for the patient. So, we have another one, but yeah, good suggestion.

Dr. Sharma:
So, anybody who has unlucky patients, ticagrelor is a reasonable option to consider. Let me pose one other question to Ashkan, and Valeria, it would be great if you commented as well. So, you know, we started both of those phase 2 trials with a composite endpoint. You could have either a clinical stroke, or an infarct on MRI that had no symptoms, a covert infarct. And we saw in both trials, a resounding lack of effect on the covert infarcts. So, what do you think happened? I mean, this is an ongoing problem.

Dr. Shoamanesh:
Yeah, no. Of course, Mike is a global expert on this, and he's done several trials beyond just looking at covert infarcts in response to antithrombotic treatment. And in general, we haven't seen the degree of effect that we would have anticipated. But the hope was that if we're looking at MRIs fairly early after the index event, that any covert infarct that occurred during a timeframe would have had a similar mechanism as the index ischemic stroke. In contrast, what we've seen is about 70% of these lesions tend to be small subcortical strokes in patients who are predominant presenting with embolic infarct. So, a large proportion tend to be occurring from a mechanism that's different than their qualifying event. And whether that's due to the inflammation cascades that are being generated after an ischemic stroke, that's all speculative.

Interestingly, though, Eric Smith, who was working with us in PACIFIC-STROKE, did publish a subgroup analysis just in stroke in the past couple of months, where we looked at the different types of covert infarcts that occurred during study participation, and there was a reduction in cortical infarct. So, cortical-based covert infarcts, there was a reduction with asundexian, so again, kind of reinforcing the message that embolic appearing hits, that had similar mechanisms to a qualifying event, were reduced, but it's really this lack of effect and small vessel occlusive disease related symptomatic ischemic strokes and covert events.

Dr. Caso:
I believe that what is going on in the white matter is absolutely different from what we are treating with anti, let's say, platelets or with every kind of new drug approach. And probably we have to study better than white matter, and probably something is going on there that we still not, we are not able to treat, we didn't find the target.

Dr. Sharma:
Thanks. Thank you very much. And, you know, amazingly we're right on time. So, I want to thank all of you for your time, your attention, your participation, your ability to resist cookies, and to withstand them, and enjoy Tuesday night in Phoenix. Thanks so much, everyone.

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