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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

FXIa Remix! Keeping the Flow Without Missing a Beat

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Dr. Sharma:
Thanks for joining us for a fresh look at factor XIa inhibition in secondary stroke prevention. Today, we're diving into how this emerging class of antithrombotics might disrupt and uncouple the traditional link between thrombosis and bleeding risk. We'll unpack the science, scrutinize the latest data, and discuss what all this means for our patients.

This is CE on ReachMD, and I'm Dr. Mike Sharma.

Dr. Shoamanesh:
And I'm Dr. Ashkan Shoamanesh.

Dr. Mac Grory:
And I'm Dr. Brian Mac Grory.

Dr. Sharma:
Okay, let's get started. Dr. Shoamanesh, what makes factor XIa such a compelling target in thrombosis, and how is its role in the coagulation cascade different from what we typically target?

Dr. Shoamanesh:
So what's really exciting about the factor XI story, Mike, is really this potential, and you've alluded to this in the introduction, of these agents from uncoupling pathologic thrombus formation from hemostasis. And really, without getting into the weeds from a top level, basically factor XI has a minor subsidiary role in hemostasis, right? You don't need factor XI at a time of vessel injury to prevent bleeding because you already have so much tissue factor being exposed to circulation in that setting that that results in hemostasis with really a really minor role from factor XI.

Where factor XI is really strategically placed and it's important is in pathologic thrombosis formation where, for instance, in the context of plaque rupture, we have relatively less tissue factor being exposed to your circulation. So factor XI plays a part in this thrombin amplification loop, or maybe more clinically relevant, a clot propagation cascade that actually leads from a small clot to becoming a bigger clot that either occludes a vessel or becomes a larger, more mobile vessel that then can embolize downstream. And of course,

for us, downstream would be the brain.

And what kind of really differentiates this from what we're typically used to, which is either common pathway inhibitors like direct thrombin or factor Xa inhibitors, or even more potent are vitamin K antagonists where you have knockout of 2, 7, 9, and 10, is that these are more upstream. So they affect both that hemostasis tissue factor pathway as well as our upstream to this thrombin amplification loop, so by inhibiting them, you still compromise the safety or the bleeding at the time of vessel injury, whereas factor XI's positioning avoids that.

Dr. Mac Grory:
Yeah, and so I think one of the most important things is that when it comes to secondary prevention of cardiovascular disease, there's already such aggressive measures taken by the medical community in general. That certainly includes antiplatelet therapy, very often dual antiplatelet therapy. So it's not enough for a new strategy to simply be additive or incremental on top of that, but you have to find a way to sort of decouple from merely increasing bleeding risk.

And as we all know, down through the history of stroke medicine, almost always, increased efficacy has come at the price of increased bleeding. And so that's why I think a kind of a new approach is needed, targeting a distinct mechanistic pathway.

Dr. Sharma:
That's been a real limitation for us, hasn't it? For about 50 years, we've been trying to replace or add to aspirin, but in the long term, nothing's worked that well. Either it's ineffective or we have increased bleeding and sometimes, tragically, both. So it's very nice to target a pathway where we can uncouple these 2 things, get the benefit without the hazard.

So building on that, one of the main promises of factor XI inhibition is its ability to prevent thrombotic events without tipping patients into dangerous bleeding. How exactly does this strategy walk that fine line, Dr. Shoamanesh?

Dr. Shoamanesh:
Well, I think we've kind of covered this in the original question, Mike, but it's worth restating just because how novel this strategy is, right? Because what we want for our patients is to prevent the pathologic thrombus, the least stroke, right? What we want to maintain is the body's ability to stop bleeding if there's vessel injury or hemostasis. And again, based on factor XI's kind of strategic location in this thrombin amplification loop, by inhibiting it, you can maintain the hemostasis while actually preventing that clot propagation cascade that leads to pathology.

Dr. Sharma:
Thanks very much. It’s complicated enough that sometimes it bears repetition, as a whole thing. For sure.

Dr. Shoamanesh:
And you can imagine the clinical impact of that, right? How important this is to have a safer drug available. Many of our stroke patients have mobility issues that makes them prone to falling. They're elderly, they have hemorrhage-prone small vessel disease of the brain. They have other systemic factors that lead them to bleeding, including the background antithrombotic kind of exposure they're already on with either single dual antiplatelet therapy.

So really being able to improve stroke prevention without compromising safety is really the holy grail, right? As you've indicated, we've been trying to achieve this from, really, the outset of antithrombotic development. And it's really exciting that we're actually there and we'll talk about that in a bit.

So we kind of discussed where we are, where we've been, but let's start looking forward. Mike, can you tell me what were some of the key findings from the OCEANIC-Stroke trial presented at ISC 2026? And really, how does that build on what we saw in PACIFIC-Stroke?

Dr. Sharma:
So you know PACIFIC-Stroke was a landmark phase 2 trial. It was the first time we've done the dose-finding study intended for stroke patients in stroke patients. All of the other doses that we use in antithrombotics are derived in a DVT model and it’s not a surprise that they're not always optimized, sometimes too much, sometimes too little. So in PACIFIC, for the first time, we looked for a dose of an

agent intended for stroke use. The 50-mg once-a-day dose.

A couple of key findings from PACIFIC. First, it seemed like, in PACIFIC, that that dose was the best dose to use and might be effective when we looked at the exploratory endpoint of ischemic stroke in TIA. It wasn't effective for MRI-defined covert infarcts, and that was a finding that trial shared with AXIOMATIC as well. And I think we're going to have to rethink that.

Part of what it led us to do was to believe that small vessel disease might not be impacted by factor XIA inhibition. That turned out not to be the case, but that was one of the key things that we were thinking at that time. So when we designed OCEANIC-Stroke, we designed it in a way that it wouldn't be overwhelmed by small vessel disease. Now, there are a few ways you can do this in a trial. You can put a cap on the number of lacunar infarcts you allow in, and that works, but it's somewhat clumsy to use and sometimes delays the trial. Or you can make the pathways into the trial explicit so that there are some lacunar infarcts but not all of the patients on lacunar infarcts.

So in OCEANIC-Stroke, we designed this trial to include patients who had 1 of 3 pathways, which was either a non-lacunar infarct on brain imaging, a plaque which was visible on vascular imaging, and that plaque needn't be large stenotic or causally related. In fact, we accepted plaques which were contralateral to the area of ischemia. In OCEANIC-Stroke, we randomized 12,327 patients in 2 years, which tells me a couple of things. First, the stroke research community has really matured. I mean, if you think about it, 10, 15 years ago, it would have been an impossible task to do that quickly. And the second thing is there's a real unmet need that we're meeting there. People wanted something better, something additive to long-term aspirin or clopidogrel for their patients. So in both those cases, we succeeded.

The key findings of the trial were, first, a significant reduction in ischemic stroke, which was a primary endpoint with a hazard ratio of 0.74. And the cumulative incidence curves start to diverge early and keep on diverging throughout the treatment period, suggesting that the effect is maintained. And very nicely, and coincident with our hypothesis, we did not see an increase in ISTH and major bleeding. And to my knowledge, that's the first time in an antithrombotic trial we've seen that. Very gratifyingly, the effect was consistent across subgroups, including subgroups which indicated the stroke subtype. So we saw an effect in small vessel occlusion, in stroke of undetermined source, as well as atherosclerosis.

In OCEANIC, we allowed stroke severity up to an NIHSS of 15 or more, and the effect was consistent all the way across the NIHSS scale.

So in all these instances, it looks like it's going to be a very easy drug to use and that we won't have to be terribly selective.

Dr. Shoamanesh:
Yeah, and I think this is really, historic, isn't it, Mike? I mean, you mentioned that this was the first time we haven't seen an antithrombotic, I mean, an antiplatelet be able to prevent major thrombotic event like ischemic stroke without compromising safety. The primary safety endpoint in the trial was ISTH major bleeding, but really there was no excess that we saw in any of the secondary bleeding endpoints, including minor bleeding. I have to say that I was shocked when we first saw that together. And of course, some of these secondary endpoints can be underpowered, but the bleeding event of greatest concern for us is hemorrhagic stroke as stroke neurologists, right? And numerically, there was even less hemorrhagic stroke in the asundexian-treated patients versus those assigned to placebo, which really builds, at least, my confidence and reassurance that we're not compromising safety, which is really revolutionary, I have to say, in the history of antithrombotic development.

Dr. Mac Grory:
I think one of the most important things from PACIFIC-Stroke, speaking as an outsider, but it seemed that there's extremely strong attention paid to safety and risk. And for example, analyses that looked at people who had dual antiplatelet therapy or intent-to-treat with dual antiplatelet therapy, people who had microbleeds, people who had all sorts of other features that might have theoretically increased their bleeding risk, and I think that that sets such a strong foundation for OCEANIC because not only were people on dual antiplatelet therapy tolerated in the trial, but it was actually explicitly permitted and even incorporated as a stratification variable, which I think was the most impressive spotlight that you can shine on a subgroup in a clinical trial. And so it really counters the fear that I think a lot of people have in the stroke community that can we really use factor XIa inhibitors on top of dual antiplatelet therapy? I think that's been comprehensively addressed by making a stratification variable that will permit the most high-quality possible subgroup analysis.

Dr. Shoamanesh:

And on your point, it's quite impressive to see such incremental gain on our existing armamentarium of stroke preventive strategies, right? This is in patients who are getting lipid-lowering treatment, they're getting blood pressure control, the majority are receiving short-term DAPT, and yet we're seeing a 26% reduction in the hazard of ischemic stroke and then translating into about a 2% absolute risk reduction at 1 year in this primary efficacy endpoint, which I find remarkable that even at this point in time, we could have such a big incremental gain, despite all the amazing advances we've had up to this point. It's really gotten me excited for this class and what it could do for our patients.

That's maybe worth mentioning and really repeating just because there is this discrepancy in what we expected from phase 2 from PACIFIC-Stroke to what we saw in phase 3. Is that from PACIFIC-Stroke? There was a suggestion that those with atherosclerosis would have increased treatment effect and would be most likely to benefit. But in a large trial, where we had really good representation of a different ischemic stroke subtypes, right?

So really large numbers of subgroups, to have confidence in these being informative subgroups. And what we saw was consistency across the board. It didn't matter what the underlying stroke etiology was, including benefit in those that entered the trial with small vessel occlusive disease.

So I think that was really great to see as well in terms of how to generalize all these findings with the umbrella of patients with non-cardioembolic ischemic stroke that got into the study.

And even what was really cool was that, for me anyways, is that on the heels of 4 randomized trials that thus far have not shown benefit with escalated antithrombotic therapy in patients with embolic strokes of undetermined source, there was consistency in the findings there, about a 47% reduction in ischemic stroke in that ESA subgroup.

Dr. Sharma:
For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Mike Sharma, and here with me today are Dr. Ashkan Shoamanesh and Dr. Brian Mac Grory. We're discussing the evolving science and clinical trial evidence surrounding factor XIa inhibition in secondary stroke prevention, including new data presented at ISC 2026.

Dr. Mac Grory:
So, Dr. Shoamanesh, we've talked about asundexian in the OCEANIC-Stroke program, but this is a broader field. How do you view the evolving evidence from other factor XIa inhibitors like milvexian and abelacimab and helping us understand the potential role of this class?

Dr. Shoamanesh:
Yeah, for sure. So, Mike, I already alluded to it. So there was 2 dose-finding phase 2 studies. They were conducted at PHRI. One was PACIFIC-Stroke; the other was AXIOMATIC-SSP. Both were very consistent in their findings, right? And this is kind of what's really nice and beautiful about the factor XI story has been the consistency from early clinical observations in factor XI-deficient patients all the way now to phase 3.

What we saw in AXIOMATIC-SSP was that similar to PACIFIC-Stroke, there was no effect on covert brain infarcts, which were predominantly small subcortical infarcts. When looking at ischemic stroke in isolation, there was a suggestion of a dose-dependent effect, and that the dose that seemed to have the best trade-off in terms of efficacy for ischemic stroke relative to bleeding complications was 25 mg twice daily. And that's the dose of milvexian that's now gone on to the phase 3 trial, LIBREXIA-Stroke, which we think we'll probably read out about this time this next year for us to see whether, indeed, that consistency plays out to phase 3 in both these molecules, which we anticipate it will be the case. And milvexian also has an ongoing AF trial called LIBREXIA-AF. So that trial is probably going to read out within the next year, as well.

But then milvexian and asundexian are small molecule direct inhibitors of factor XIa. There's also other molecules in development, and that includes monoclonal antibodies, as well as antisense oligonucleotides. The main monoclonal antibody that's being tested for stroke prevention right now is abelacimab. This is by the TIMI group in Boston. And the first phase 2 study was basically testing 2 doses of abelacimab versus rivaroxaban, a factor Xa inhibitor, at standard therapeutic doses of rivaroxaban for stroke prevention and AFib. That study was halted early because it was a safety study and there was an overwhelming reduction in bleeding compared to rivaroxaban with abelacimab. As a result, there was very few ischemic stroke events. Numerically, there was slightly excess in abelacimab versus

rivaroxaban, where really the numbers were too small to really make any real conclusions of it.

However, that 8-molecule is now going into a phase 3 trial called the LILAC study. And that study is enrolling patients with AFib who are not good candidates for anticoagulation. Kind of similar to the AVERROES paradigm that tested apixaban versus aspirin previously. And in that study, that's ongoing, and we hope to see that—we believe, probably from the Mendelian randomization analyses, that cardioembolic strokes benefit from this agent, that that is going to be a positive trial. The big question right now in AF for the class as a whole is whether factor XI inhibition in isolation is enough to beat a factor Xa inhibitor, or does it really need to be in a combined treatment for it to have benefit in AFib? And that's on the heels of the OCEANIC-AF study that was stopped early because the asundexian arm did not have the same efficacy as apixaban. But the safety was impressive.

In AVARROES, apixaban was tested against aspirin and was shown to have similar rates of bleeding as aspirin. And similar results were seen in ARCADIA, similar rates of bleeding than aspirin. And numerically, fairly consistently across several trials, we've seen less hemorrhagic stroke with apixaban versus aspirin. What we saw in OCEANIC-AF was 50% to 70% less bleeding with asundexian versus apixaban. So indirectly, this suggests that, really, these drugs, or factor XI inhibitors as a class, is safer than maybe even antiplatelet therapy.

Dr. Mac Grory:
And that's such a rare thing to find because safety events in general are quite rare and almost always the analyses are underpowered. So to actually see, even though OCEANIC-AF on its face was neutral or negative, but it's to actually see a lower bleeding risk was quite a noteworthy finding in and of itself, in my opinion.

Dr. Sharma:
From the mechanism of action, this is what we should expect, and yet we were quite surprised by what we saw, especially to this degree. It waits to be seen whether the autoantibodies have a role to play here. They're going to be given in an extended time frame, so once every 2 weeks or once a month or so, and what happens if we run into trouble with bleeding, for instance? Once they're on board, they're on board, as opposed to the short half-life of the oral inhibitors.

Now, on the other hand, compliance is better. So if you administer something parenterally that lasts 4 weeks, you don't have to worry about people forgetting their pills or mistaking them for side effects and stopping them prematurely or reducing the dose. So there are pluses and minuses to each approach.

It's not clear to us if affecting factor XI, as opposed to activated factor XI, is going to be better, worse, or the same, so we'll have to see how these trials pan out.

Dr. Mac Grory, how do you think these different agents and clinical trials help us better understand the therapeutic potential of this class of agents?

Dr. Mac Grory:
Well, I think the oceanic stroke was testing asundexian, which I think is one agent out of a broader class. And each agent in that class kind of almost has its own personality in a way. There's a distinct chemical structure for each agent, a distinct mechanism of action. Some agents prevent the generation of activated factor XI, some impede the activity of factor XIa, and they have distinct pharmacokinetics, distinct populations within which they have been discussed. For example, some agents have been examined in people who've had an ischemic stroke. Some have been examined in people with cancer who are felt to be at high risk of thromboembolic disease. Some have been examined in people undergoing major orthopedic surgery. So I think each agent has distinct sort of properties and mechanisms that may make them suited to sort of different patients at different times. So in some ways, we're moving beyond this idea of one-size-fits-all into more of a personalized medicine paradigm.

Dr. Sharma:
So I think that in a perfect world, we'll have a choice of agents and indications to use it in. As much as we'd like to simplify it, imagine that there will be 1 agent across all indications and patient subtypes, unlikely to be the case. There probably will be some which are better, for instance, for AF or cancer-associated thrombosis, and others which are more useful to us in the stroke field.

Dr. Shoamanesh:

And I think one of the successes, I guess, of OCEANIC-Stroke is also a bit of a limitation in terms of future indications, because there's already such a broad population, right? We're talking about non-cardioembolic ischemic strokes, with the exception of those that have dissections and things, and there is these niche populations that we still can look into this. But I think based on the epidemiology of patients with factor XI deficiency, venous thrombosis and then the fact that they have less venous thrombosis, really makes cerebral venous sinus thrombosis perhaps an interesting target for further stroke prevention, or at least improving stroke care.

I personally think that on the basis of what we saw in WARCEF and COMMANDER-HF, where anticoagulation does reduce ischemic stroke, but if you put into a MACE endpoint where you're also including bleeding, you get an overall neutral effect, that actually patients who have heart failure and obviously those who have already had a stroke, having an ischemic stroke recurrence trial in that population could be quite impactful. Or those with left ventricular dysfunction, even if they don't meet that threshold of reduced ejection fraction.

So I think at this point, given that we have an agent that's so safe and proven to prevent thrombosis, even in the arterial system, the world's the oyster at this point in time. There's so many potential indications that it's really exciting for the field of cardiovascular medicine.

Dr. Sharma:
It's gratifying to have those options. And certainly, we should think about it in stent placements as well. And it's a part of the intrinsic cascade and consequently may be effective there.

Dr. Shoamanesh:
And maybe in mechanical valves on that point, as well.

Dr. Sharma:
Quite possibly.

Well, this has been a fantastic conversation. Before we wrap up, can you share one take-home message with the audience?

Dr. Mac Grory:
Well, I think that factor XIa inhibition is an interesting strategy because it's not just additive or superimposed on existing therapies, but it's actually sort of exploiting a kind of a distinct synergistic and complementary mechanism. So stroke neurologists, it doesn't actually take anything away from your arsenal; it allows you to use your existing therapies but actually could be used in tandem with them. And so for me, that was the big kind of take-home message, particularly around bleeding risk or lack thereof in people with dual antiplatelet therapy.

Dr. Shoamanesh:
For me, I agree entirely. I think this is a game changer. And really what matters is how this is going to impact our patients. I was just on the stroke unit earlier this month, or at least earlier in the year, where you would see patients, right? I'm treating them, they're eligible—or they would have been eligible for OCEANIC-Stroke. Now, the study is completed. And they asked me, Doctor, what's my risk of recurrence? And I say, well, it's about 6% or 7% in the first year with our best treatments. And we're going to do this, this, and this for you to be able to bring it down to that level from your already higher intrinsic risk. But the good news is, is that we've now just proven that there's a drug that's going to reduce that by another 26% and without compromising safety. Like, how amazing is that to be able to provide them? And maybe you see it in the face, the hope that they get, that there's actually more coming to benefit them. And that's what really matters, right? In the end, we're scientists, we talk about the numbers and the trial design, but really what matters in the end is the impact it's going to have at the bedside. I'm super enthusiastic and grateful to have this option now.

Dr. Sharma:
I really like that example. What this will do for us once it's approved, is I think it'll make things easier on both ends. On the prescriber end, we won't have to think very carefully about what type of patient could benefit, and we won't have to concern ourselves with what the hazard of bleeding is. On the patient end, what we've seen is no increase in very similar rates of minor bleeding. Patients have told us that minor bleeding really causes them concern. It's invisible, it's up front, causes anxiety, and not infrequently causes people to stop treatment. So I think that the big message here is easy to use on both sides.

And that's all the time we have today. So I want to thank our audience for listening in, and thank you, Dr. Brian Mac Grory and Dr.

Ashkan Shoamanesh, for joining me and sharing all of your valuable insights. It was great speaking with you today.

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