Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/the-path-forward-whats-on-the-horizon/16493/

Time needed to complete: 1h 35m

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

The Path Forward: What's On The Horizon?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Patel:
Thank you all. Just to remind you all, I'm going to give a brief overview. Although it may not feel brief; I hope it'll feel brief. You've had a long day at the American Heart Association, so, we'll try to make sure you feel brief. And then we're going to open it up for questions. And there is also some feedback we want. So, thank you so much.

I'm going to talk about the path forward. You've heard about the session tomorrow morning with late-breaking clinical trials, so we hope that you get to it. My goal over the next 15 minutes is to talk about what is factor XI hemostasis, preclinical data mechanism, and some of the things with the ongoing trials.

I know you went to medical school; I know this might make you fall asleep, so, I won't go into it deeply. Some of my hematologists in the audience may not be so fired up about it; they think it's good. I see Scott saying that. It's important to recognize when we think about the clotting cascade, or at least what's going on, there's an intrinsic and an extrinsic pathway, there's contact activation, and factor XI and factor XII do play an important role.

I've used this demographic, this sort of image for others. And I know when it sounds simplistic, it's easier, but I just feel like we have to get to the place where we can describe it to each other. There is much more going on than the cartoon on the slide. And it doesn't go in the steps as it does; it often happens as one. But that being said, when we think about normal hemostasis, our body is often trying to figure out how do we form clots to prevent bleeding without having too many clots to form strokes and other things? And so, this is what I'll call normal physiology. Hopefully, where no anticoagulant is present, you have a clot form through the thrombin tissue factor pathway. There's not too much thrombin amplification, so you don't get a pathologic thrombus downstream.

We do know that things like Xa inhibitors or others, like apixaban and rivaroxaban, inhibit Xa, and that prevents some of that actual downstream thrombosis, which is great, but some of that thrombin that we needed for hemostasis may not happen. And so, we may still have some bleeding, even though that's way better than warfarin, which might affect many of these pathways. So, the hope with factor XI was that you could potentially inhibit this thrombin amplification loop so that you would still allow thrombin to affect itself and to actually have normal hemostasis, what we're calling uncoupling hemostasis from thrombosis, or I've simply said is letting good clots happen and not have bad clots happen. And that might be a way to think about what's happening here if it works the way we want. And I'll say this is a holy grail, we don't yet know if that happens with trials. But the hope is that factor XI inhibition will do this.

So, what are the preclinical and observational data that made us think about factor XI as a target for therapy? And tomorrow morning, we're going to hear a phase 2 study. So, it's important for us at least think about the pathway of what's going on. Some of this you may hear again. So genetic predisposition for lower levels of this associated, were associated with reduced levels of ischemic stroke and VTE. And you can see the stroke subtypes there. And so, if you have a genetic deficiency, you have less stroke. And then the actual level was related to less levels of risk of thrombosis in these patients.

And then importantly, it seemed to be pronounced in patients with atrial fibrillation. And patients that have atrial fibrillation, seem to have less risk of stroke when they have genetically lowered levels of factor XI. So that's important. And then what was most important in these studies, which is not described on the slides, is that their levels of bleeding was similar, if not a little less. So, the current preclinical evidence was that we had mice experiments, which I won't go into deeply. We had animal models, but we had inherited deficiency models that also made us think about it.

So, we've talked a little bit about the mechanism. Why did we choose factor XI instead of factor XII? I won't go into it except to say some have thought about factor XII. Many in the hematologic group have. And there are other things that factor XII does, and so does factor XI, which includes some inflammatory things, some kallikreins, some other things. I'm not going to go deeply into it except to say that you can see here from a review from Jeff Weitz and others, that there was some stronger epidemiologic data, lower risk of bleeding, and potentially less off-target stuff.

So where is the world? What are the potential targets for factor XI? I'll show some of this maybe potentially tomorrow, too. You can see on the slide there are many ways we might think about inhibiting factor XI. And when I say factor XI, I'm talking about inhibiting factor XI's conversion to factor XIa and potential ways that small molecules on the top right, as you can see some names there, asundexian and milvexian, or actual antibodies, abelacimab, as you can see, there is an antibody or actual monoclonal human antibody that binds the actual site for factor XI to be converted. And then on the right is actually you could have a ASO, an antisense inhibition that would go to the liver and prevent this. And all of these are being studied in phase 2. And all of these have some data that I will try to go through in not excruciatingly painful detail, given that it is AHA, and I know you guys want to see the data without having to think about it too deeply.

So, what are the relative pharmacologic features of factor XI that I think are important? You can imagine that there are three ways to do it. And through phase 2 and phase 3, we're going to find out if there's actually a difference. I'm not sure that's why we do these human experiments. But there, antisense OS or ASOs have the ability that that can be delivered and can be a little bit delayed on action, but they can be not renally cleared and be not hepatically cleared; it can be there for a bit. Antibodies, as you can imagine, can be present for immediately acting but be there for longer periods of time, 15, 20, 30 days. Small molecules are immediate action, and smaller and faster turn off. And on this slide, you can see again, from a review, multiple different monoclonal antibodies, small molecules that could be used.

So where are the phase 2 data? And where are we in understanding this promise of hopefully having at least, if not better, reduction in thrombosis, but significantly less reduction in bleeding? I just highlight this review that Josephine Harrington, one of our fellows at the institution did, and others, I think this has been valuable. And I'll go through that in a second.

So initially, Harry Buller and others presented this ASO paper that actually was the early proof-of-concept data that said this could be a target because there's a phase 2 study that demonstrated ASO with factor XI had an effect on thrombosis without a relative increase in bleeding. And I think that's important in people who have venous thrombosis. And one might argue, where are we on that pathway? There may be some studies going on forward with ASO in phase 3, but I have not seen many.

And then next to that was the monoclonal antibody by Peter Verhamme and others who looked again at saying, could we use the monoclonal antibody against those patients undergoing elective unilateral total knee surgeries, and look at it compared to enoxaparin? And what you see here on this slide on the right, is the antibody compared to the composite, which is a thrombotic composite with imaging and others on the right, and you can see that there is a dose response compared to enoxaparin. And on the left, you can see there's not much bleeding, if none. Now, it's a short-term study, so, you know, you're not sure what to make of that, but it does seem promising.

This is AZALEA-TIMI 71. I'm not looking to, you know, steal any thunder here. Tomorrow morning, this will be a late-breaking clinical science study, as I've highlighted on the top right. I think Christian Hamm is going to be presenting this. It's a phase 2 study looking at patients, 1,200 such patients that were 55 years or older with AFib compared to rivaroxaban with two doses of the monoclonal. Looking again at the primary safety endpoint of major clinically relevant non-major bleeding in patients with atrial fibrillation. They had a CHADS2 VASc score of a 4 or 3, and at least one of the following criteria. This study was stopped early by the DSMB, reportedly for overwhelming efficacy or safety issues with bleeding. So, we'll have to go see the results tomorrow.

So how do I think about the non-monoclonal antibodies? This is again from Jeff Weitz. He thinks about what is the target factor X for edoxaban, apixaban, rivaroxaban, asundexian, or milvexian. You can see across here that they have some effects on Tmax. Half-life is a little bit longer with some of the small molecules. Renal elimination looks to be about the same. So, some important data here across the small molecules.

This is key data from milvexian, published again by Jeff Weitz, looking at milvexian in the prevention of venous thromboembolism

published in the *New England Journal*. And if you look across the right screen, again, you think about thrombotic endpoints with enoxaparin. And you can see again, a dose response curve as you get to higher doses, you see some less thrombosis. What's interesting in all of these factor XI studies, is if you look to the left, as the doses go up, after the very lowest dose, you don't see a significant change in bleeding as you go from 25, 50, 100, 200. In fact, at the highest doses, you see similar rates, if not just about the same, or maybe a little bit lighter than - higher than enoxaparin.

So, milvexian has also presented a secondary stroke study that looked at the patients again, in phase 2, you can look at symptomatic ischemic stroke across the doses there on the right compared to placebo. And interestingly across again, a dose response curve until you get to about 100. Once you get to 200, it looks like it goes beyond, it may be a hemorrhagic issue, I'm not sure. But again, AEs and bleeding in the bottom left. Again, you again see that placebo had a bleeding rate of 9.7. And there is an increase but not a significant increase, an important feature for us.

I've been involved with others in the PACIFIC program. This is a phase 2 program looking at asundexian with atrial fibrillation, stroke, and AMI. The hope was that you would be able to learn about this small molecule across a large set of patients to inform yourself as we try to do better than we did 10 years ago when we did these Xa inhibitors.

Asundexian in a phase 2 study in patients with atrial fibrillation was published in *Lancet* by a colleague of mine, John Piccini and others, looked at patients with atrial fibrillation, 750 such patients that received 50 mg of asundexian once daily, 20 mg, or apixaban per dose. We just heard from Cecilia how 20% or some of patients with apixaban sometimes get the 2.5 dose, this was labeled dose, so most got 5 mg twice daily, but unless they had two out of the three, then they would get it. And the primary endpoint here was safety, again looking at bleeding, ISTH major and non-major clinically relevant and quantification of factor XI inhibition, recognizing you need to do a much larger study to look for stroke reduction.

So, this is the factor XI inhibition data, again based on an activity assay, looking again at asundexian 50 and 20, both trough and peak showing the lower limit of what you can actually identify as 3.7. And you can see near 95% or more inhibition at the 50-mg dose.

What about bleeding? First of all, the bleeding events were less than anticipated. It's a 12-week study, but you can see again, as it's been published that apixaban had a significantly higher rate of bleeding compared to asundexian. The pooled reduction was 67%. The individual 50-mg reduction was over 80% reduction in all bleeding, although there weren't many bleeding events.

PACIFIC-Stroke did some of the same dose-finding studies. Again, a fairly large study, and again shows that compared to placebo, there was ischemic stroke or covert infarcts didn't seem dramatically reduced across some of those doses. When they looked at some of the subgroups, like recurrent ischemic stroke or TIA, here, you start to see 50 mg, 20 mg start to have a difference. And bleeding-wise, again as we saw with milvexian, there's an increase but it's not the largest increase and you're looking for the sweet spot of where you can add on to placebo to find therapy to help patients that have stroke.

So, the summary of the phase 2 data, this is asundexian you can see there, and you can see that. And here you can see where we are, I will call it with the phase 2 data. I've told you about the VTE. I've told you about atrial fibrillation. Tomorrow you'll hear about AZALEA-TIMI 71. AXIOMATIC and PACIFIC-Stroke have been presented. I didn't go into acute MI except to just highlight for you that they had similar rates of efficacy and a little bit larger than placebo, and an important conversation for us to have. So, less bleeding than both enoxaparin and apixaban, PACIFIC-AF and other data, no increase in bleeding with secondary stroke, bleeding with the others.

What are the ongoing phase 3 studies? I think this is important for us to think about. This is published by again Jeff Weitz. This is in the Journal of ISTH. LILAC-TIMI 76 is patients with atrial fibrillation deemed unsuitable for oral anticoagulation with the antibody, the monoclonal antibody from Anthos. You can see there's a cancer-associated VTE study. There's a GI study, again, with GI/GU cancer comparing to dalteparin. The cancer-associated VTE is apixaban. So that agent is looking to get to the market and to study patients that have either no option with atrial fibrillation, or have, I'll call it high-risk populations of VTE. Asundexian, both AFib and secondary stroke looks like 18,000 and 9,000 patients. And then milvexian across three broad indications importantly, atrial fibrillation, secondary stroke, and ACS.

So, there's a lot of interest in this area. And one might say, do we really - do we have to have this? And I would say yes, we do. And there's a lot of reasons to think about it. But I'll start by saying that in the United States, 40% of patients right now with atrial fibrillation do not get a therapy, unfortunately, for a variety of reasons.

And so, there is a need. And those many untreated patients that I have not shown you, have clinical needs, whether it's AF secondary stroke, ACS maybe, renal failure, mechanical valves. The inhibition of factor XI is biologically plausible. We've shown that with inhibition data. Phase 2 data with one agent, at least in AFib showed less bleeding, with multiple agents show less bleeding compared to enoxaparin in VTE, in secondary stroke show more bleeding but show some thrombotic events. ASO antibodies and small molecules are being tested. The keys will be maximizing the compound strengths to the patients, the comparators, and the use in clinical practice.

I'll just say this here at AHA today, we've heard amazing science. The next 30 years of global cardiovascular health is moving from AMI to heart failure to stroke. There's an opportunity for us to bend that curve depending on what we do with these therapies.

So, the last thing we know is, and I'll say this importantly, 10 years ago, we published ROCKET, ARISTOTLE, dabigatran study, all these studies, ENGAGE. We thought we were going to change practice, yet 40% of patients are not treated 10 years later. So, we have to get to implementation of therapies faster. And that likely includes the following: we have to understand what patients care about. We've talked about bleeding, saying, 'oh, bleeding, bleeding, bleeding,' patients care a ton about bleeding, they see going to the hospital to get a transfusion equal to going to the hospital to get an angioplasty, the net benefits will lead to improved antithrombotic therapy. We have to enroll diverse patients from diverse populations. We have to capture relevant endpoints that are not just thrombotic and bleeding, but of course, patients' preferences, and we have to think about ways in which we engage each other to get these therapies to market faster.

Thank you all for listening and we are now open to questions.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, LLC. and is part of our MinuteCE curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.