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/driving-progress-in-cardiology-exploring-the-role-of-fxi-in-acute-coronary-syndromes-beyond/32980/

Released: 05/23/2025
Valid until: 05/23/2026
Time needed to complete: 60 minutes

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

Driving Progress in Cardiology: Exploring the Role of FXI in Acute Coronary Syndromes & Beyond

Announcer:
Welcome to CME on ReachMD. This activity, titled “Driving Progress in Cardiology: Exploring the Role of FXI in Acute Coronary Syndromes & Beyond” is provided by TOTALCME.

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

Chapter 1: Preserving and Reducing Thrombosis Without Increasing Bleeding

Dr. Mehran:
Good evening, everyone, and welcome to SCAI 2025. What a wonderful occasion to have all of you here and thank you. After a long day, I hope you're all enjoying your dinner and getting ready to dive in. I'm here with Mike Gibson, professor at Harvard, and we are really, really working together. We're going to have a fun conversation together, but also with you, in driving progress in cardiology. Especially exploring this next Holy Grail of factor XI in acute coronary syndromes and beyond. The idea of preserving and reducing thrombosis without increasing bleeding is very, very exciting, and I'm really looking forward to having a conversation with you, Mike.

Dr. Gibson:
Roxanne, I've got big news. You have been enrolled in a trial that you didn't know about.

Dr. Mehran:
Oh.

Dr. Gibson:
You didn't –

Dr. Mehran:
Did you just start that right now? Did I – did I? Where was I?

Dr. Gibson:
The trial was started about 6 million years ago. It’s enrolled billions of people. It's a randomized trial, and people have been randomized to factor XI deficiency or not.

Dr. Mehran:
Oh.

Dr. Gibson:

By –

Dr. Mehran:
Genetic, by God.

Dr. Gibson:
Yes, and here's what the trial shows. It shows that if you are randomized to factor XI deficiency, you have a lower VTE, lower rate of stroke, and that's why we're doing what we're doing in this field, testing out that hypothesis if we can modify things.

Dr. Mehran:
Yeah. The human genetic deficiency is really incredible. One in 450 Ashkenazi Jews have this genetic deficiency of factor XI, and lo and behold, they have less bleeding and less spontaneous myocardial infarction. And then there are also these animal studies that show that, I mean, imagining that we've been so fixated on reducing thrombosis but exposing – every single time, exposing patients to more bleeding. And then modulating our dual antiplatelet therapy and antithrombotics to try to dance around the timing of bleeding and ischemic events. It's exhausting as a physician. And often, we see that patients do experience bleeding or thrombotic events as we're doing some of these modulations. And I'm excited about factor XI deficiency or inhibition for sure.

Dr. Gibson:
We often talk about NNT, number needed to treat, or NNH, number needed to harm, but in practice, it's really NNB, number needed to blame. No one walks in your office and says, “Thank you, Dr. Mehran, for preventing that MI.” They just walk into your office and say, “I’ve had some nosebleeds.” So it’s a symptomatic, overt side effect, but yet the benefits we don't see. So we've got to deal with bleeding.

Well, this is our disclosures. We both have a lot of research grant support from a lot of different companies in this area. Our goals tonight are really to look at the mechanism of action of factor XI inhibitors. We’re going to talk about the pathway. I know people are very scared when you see these coagulation pathways. We’ll make it simple. We're going to talk about risks and benefits, and we're going to talk about the reason to believe why this might be a viable target.

Chapter 2: Acute Coronary Syndrome: Clinical Challenges and Innovative Therapeutic Approaches
Dr. Gibson:
Roxanna, bleeding and ischemia. Talk to us about the timing of these issues.

Dr. Mehran:
Yeah, I think that's really important when we're evaluating patients now, especially after, let's say, a percutaneous coronary intervention, which is what we interventionalists do. And we are the ones who are driving not only their anticoagulation, but even all of their other risk factors in terms of their glucose control, their lipid control, all of that. We really are in the driver's seat. But the dilemma of figuring out what to do, and as you said, where the patient will always remember, it was your PCI that made me have an antiplatelet anticoagulant on board. If they don't get an MI, they're not saying thank you, but if they start to bleed or, God forbid, in their brain, which would be the most catastrophic, is really something you want to avoid.

And thinking about that, we dance around the timing. The timing is very, very important. What is unbelievably important is that first month to 3 months after the procedure, where we know there's tremendous – and especially when a patient presents with an acute coronary syndrome, there’s a lot of events that happen, both bleeding and ischemic events, that are extremely rich in that first 3 months, especially the first 30 days.

Beyond that, for stent-related events, they kind of go down, and the stents are now so great. And now with imaging, we hardly ever see stent thrombosis. I mean, when was the last time you saw a stent thrombosis? We used to see that a lot. That’s kind of gone away and abolished. But the patients are sicker, there's a lot of disease, systemic disease and, of course, systemic thrombosis, but also outside of the stent, new lesions forming is something that continues to give. But what's amazing is this risk of bleeding—it literally is steady all the way through because it's about the patient's risk profile in terms of bleeding. And if they need procedures that has nothing to do with their heart—non-cardiac surgery, procedures for colonoscopy, dental procedures, etc.—if they're on lots of anticoagulation and antiplatelet therapies, they're going to be at risk.

So the idea is, let's find that sweet spot. Where is that sweet spot? And when can you accomplish it? And who has time to navigate this maze? And so imagining that you could have an agent that could help you get there in terms of the least ischemic events, but also without increasing bleeding events. What we know about the duration of DAPT and what we have done with acute coronary syndromes is we've been up and down this literal roller coaster from prolonging to shortening, prolonging to shortening. And just recently, the HBR according to bleeding risk data came out at ACC, and we found that maybe, in high bleeding risk patients, we're okay maybe with 1 month. But in low bleeding risk patients, you can't really shorten DAPT, especially if they present with an acute coronary syndrome. So it seems like maybe the 3 months is better than the 1 month. But obviously, it needs to be further evaluated. But we really literally have been up and down for acute coronary syndromes. The guidelines are telling us 12 months for everyone. Then we are kind of dancing back and forth, and the last ACC 2025 guideline said go to a single antiplatelet regimen after a short period of DAPT—and especially with ticagrelor, which was the first time that we got that.

And you're running the trials. What's happening right now in the United States?

Dr. Gibson:
You know, it is crazy. I personally like to give shorter duration DAPT. And I thought everyone else was. But we're doing an international trial, and throughout the world, people are giving – 95% of the time they're giving DAPT for a year.

Dr. Mehran:
For a year. DAPT. How about all of you here? How many of you are switching to single antiplatelet therapy after 1 month with an acute coronary syndrome in whom you've placed a stent? How many? Almost no one.

After 3 months?

Anyone using ticagrelor monotherapy? Not even because of me? No. Isn't that something? But they'll go to aspirin and clopidogrel.

Dr. Gibson:
Yeah.

Dr. Mehran:
Isn't that right? That is what we're seeing in the NCDR registry and in our data. But that's the bottom line, though. The longer the duration of DAPT, the higher the bleeding. And bleeding is associated with higher mortality. And I think it's very, very important. And the prognostic impact of bleeding is tremendously important. But yet, what we're seeing and what we're hearing is that people, after an acute coronary syndrome, do not want to shorten the duration of DAPT, especially knowing that in the presence of a potent agent like ticagrelor, aspirin is doing nothing but increasing your bleeding risk.

Dr. Gibson:
We had aspirin, and then we had thienopyridines. The early studies showed the thienopyridine, clopidogrel, was better than aspirin. So what did we do? We combined the 2.

Dr. Mehran:
Yeah.

Dr. Gibson:
What we did is, we said does clopidogrel add anything to aspirin? And it did. But we never tested if aspirin added anything to clopidogrel, and it probably doesn't.

Dr. Mehran:
Yeah. And I certainly know with both prasugrel and ticagrelor, there were really, really good PK/PD studies done, showing that in the presence of these 2 potent agents, aspirin is literally not adding anything. Yet, even everyone in this audience is treating patients for a prolonged duration of DAPT.

Dr. Gibson:
Well, in PLATO, we learned that less was more. Less aspirin was better.

Dr. Mehran:
What if your patient is at high bleeding risk? What do you do then? What are you doing?

Dr. Gibson:
I think shortening duration is one strategy. I think switching depends on your comfort. Switching over from ticagrelor to a less potent drug like clopidogrel is another choice. Personally, I like to get rid of the aspirin more than anything. I know some centers are really testing to make sure someone isn't having trouble metabolizing clopidogrel before they switch to clopidogrel. But I'd say shorter, getting rid of aspirin, trying to get someone on monotherapy, and if they can't tolerate ticagrelor, go to clopidogrel.

Dr. Mehran:
I also think it does have a lot to do, believe it or not, in some really weird way, that a lot of this does have to do with the fact that everyone is afraid of bleeding. And, in fact, they're more comfortable with aspirin and clopidogrel than they are with ticagrelor or prasugrel monotherapy, especially if a patient needs a procedure or a non-cardiac surgery, not knowing what to do around that. But when they're on a DAPT, they'll just say, "Oh, we'll stop the clopidogrel. You could operate on aspirin, and our surgeons are used to that."

Dr. Gibson:
It's not really DAPT. It's like instead of dual antiplatelet therapy.

Dr. Mehran:
It's like one and a half.

Dr. Gibson:
It's like half antiplatelet therapy.

Dr. Mehran:
Yeah. It is.

Dr. Gibson:
It's ticagrelor lite.

Dr. Mehran:
It really is an interesting thing. So we defined high bleeding risk at the time of PCI using this ARC definition. One major, two minor puts a patient at risk for BARC 3 to 5 rate of bleeding of 4% after PCI if you have a high bleeding risk. This has been validated with multitudes of databases, and I think it works very, very well.

And if you actually look at short versus standard DAPT in high bleeding risk patients, this is a meta-analysis of over 11 randomized trials with 9,000+ patients; they used the PRECISE-DAPT. And the bottom line is that what you're seeing is less bleeding when you go to a shorter duration of DAPT, and you're not increasing ischemic risk.

So why is it that even in our high bleeding risk patients, pretty much in most of the cases after ACS, the patients are staying on this dual antiplatelet therapy? So I think the idea here now is how do we go there? And I think physicians in general, especially those here in the US, perhaps, because we are so nervous about lawsuits, are very resistant to change, to innovation, and to innovative approaches.

The Europeans, by the way, have changed. They do have a shorter duration of DAPT. They're down to like 6 months for ACS. I don't know if you've seen that in your clinical trial, but it sounds like even there, when they're high risk, because our ACS, that trial has high risk profile, does it not? You've enriched it, and that's probably the reason that people want to keep those.

But I think one of the things is that we have to, when we are thinking about the risks, is to think about and how we are determining what we're doing with our antiplatelet and antithrombotic regiments, is to kind of look at all of the clinical presentation, the patients' characteristics, those things you cannot change, the comorbidities like CKD, diabetes, PAD, heart failure. But very importantly, we're also looking at the medications. What else are they on? Especially if they're on an oral anticoagulant. And those are the people who are

at a very, very high risk for bleeding. And I think even with the oral anticoagulants, we're still seeing a little bit of triple therapy for the very first 3 months. So, to me, these high bleeding risk patients are going to be the lowest hanging fruit in terms of really, really approaching them.

And we still have a tremendous need in really getting to that Holy Grail, that place, that sweet spot that I showed you with the lowest ischemic risk and lowest bleeding risk. We've not yet met there because since 1939, we've come all the way now to where we are today with this incredible opportunity to explore this pathway with factor XI.

So, we can go on and on, and you've done this now, I don't know, 20 years? Maybe more. Thirty years? So there's elements of both the platelet and coagulation pathways.

Dr. Gibson:
We think of them as separate, right?

Dr. Mehran:
Yeah, but you've taught us about the dual pathway inhibition. Do you want to talk a little bit about how you imagined this in your own brain so that everybody else could simplify it?

Dr. Gibson:
That's scary to think of my own brain. The happy platelet is a nice, round platelet. But when it gets angry – do the angry platelet thing. It sprouts – grr. The thing that makes your platelet the angriest is thrombin. I mean, it's the most potent agonist of your platelet. It makes it the angriest. Now, all the drugs we give, aspirin, ticagrelor, all the thienopyridines, they do nothing to thrombin activating your platelets. Collagen, yes. And all ADP, yes. But not to thrombin. So if you treat the thrombin side of things, you're also in kind of a way treating the platelet side.

We always thought that stent thrombosis was a platelet problem. But when we did ATLAS, we found a 31% reduction in stent thrombosis with the additional rivaroxaban.

Dr. Mehran:
Yep.

Dr. Gibson:
So it just goes to show you that both pathways are there.

Dr. Mehran:
There is a synergism between these 2 pathways, and they're brought together in the formation of the thrombus. So the thrombin inhibition is actually key if we really want to get down there. And of course, this dual pathway inhibition is all about kind of getting to those residual events, trying to get that ACS patient to a place where you have the lowest ischemic event rates. And you achieve that by having these 2 essential components inhibited in a synergistic way. Factor Xa as a thrombin inhibition in the coagulation cascade, aspirin and P2Y12 inhibitors in the platelet side. And so imagining that you can go there. And in ATLAS, we saw fantastic results. And here's ATLAS, and here's COMPASS, 2 trials that showed fantastic results. There is a very important synergism with going through the dual pathway inhibition, as you just hypothesized for us, with the thrombin being central there.

But what is very important is that addition of this really caused a lot of bleeding. The bleeding was there. I mean, with rivaroxaban, with the lower dose, you were okay, but you still have some bleeding. Isn't that right?

Dr. Gibson:
Well, it ended up being over 2 years, 2 years, 1.2% major bleeding excess. But on an annualized basis, that's 0.6 per year. That's the same as what you get with ticagrelor versus placebo. Same as with prasugrel. So you get about a 0.6% uptick in major bleeding. But at the end of the day, people, even though we had a reduction in mortality, they weren't willing to tolerate that bleeding.

Dr. Mehran:
Yeah, and here's the trade-off. You see the major adverse cardiovascular events and ATLAS is in here, in this meta-analysis. You

reduce ischematic events, but there is important additional bleeding events.

In the guidelines, the dual pathway inhibition has gotten, in the 2023 ACC, got a 2a with antiplatelet therapy and low-dose DOAC. In the ESC, you see that here, where we're seeing a IIa in high bleeding risk patients, and a IIb recommendation. So suitable only for those patients who do not have the high bleeding risk.

So here is where we are now. Is it actually possible to uncouple? And I don't want to steal your thunder because you're going to really, really show us this with the details. With factor XI, thinking about hemostasis where there is the extrinsic pathway that comes in that's triggered by tissue factor, factor XI is implicated in consolidation, which is there. And then on the thrombotic side, using the intrinsic pathway, which is an intravascular pathway triggered by contact inhibition. And that also, it brings in factor XI. So factor XI inhibition reduces the formation. If you think about that, you could reduce the formation of pathologic thrombi but preserve the hemostasis. And it almost seems like absolutely amazing that that could happen, but it's this feedback that we see through the pathway. And, Mike, you're going to explain it a little bit.

The bottom line is, we've evolved in our treatment of patients after an acute coronary syndrome from multitudes of antiplatelet therapies, single or dual antiplatelet therapies. But we have gone from vitamin K antagonists – you see all of the trials there – to full-dose DOACs, to low-dose DOACs, and now we're thinking about the future and the present. And there is going to be this phase 3 study led by Mike Gibson in over 16,000 patients where we will actually test this hypothesis. And I'm really excited about that.

Chapter 3: Innovation in Anticoagulation: Factor XI in the Future of ACS/AF/SSP
Dr. Mehran:
So, Mike, what do you think? Are you hopeful about this?

Dr. Gibson:
I am. And I'll now show you why I am, actually, very hopeful. I do think it's more than a number, factor XI. This is what I said at first. This is the daily and randomization data. When I talked –

Dr. Mehran:
I think my factor XI levels are normal.

Dr. Gibson:
That's good to hear. Good to hear.

Dr. Mehran:
I don't think I'm deficient.

Dr. Gibson:
Well, not many people are.

Dr. Mehran:
Yeah.

Dr. Gibson:
And you're so proficient in everything else.

So if you're factor XI deficient, you have fewer venous events and venous and arterial events, so that's good news. Now, you might say, well, are you going to bleed? If you had to have a factor deficiency, this is the one to have.

In red here, you see factor XI deficiency, that dark black box in the very bottom. That is the rate of the bad bleeds. And you have a very low rate of severe bleeding. Not much in the way of spontaneous bleeds. So if you had to have one, this is the one to have.

Now, this is the coagulation cascade for dummies.

Dr. Mehran:
101.

Dr. Gibson:
This is mine – I made this one. So –

Dr. Mehran:
This is a good one, though. I think this is – I've been looking at this slide for a while.

Dr. Gibson:
Yeah. This is the way I think about it. So, the intrinsic pathway, that means the inside-the-vessel pathway. Clots inside your vessel, those are the bad clots, right? And over on the other side is the extrinsic pathway; that's the bleeding outside the vessel. That's where you want clots to stop you from bleeding.

What's the difference? Well, the difference is this positive feedback loop. Do you see thrombin going back over there to act on factor XIA? You said it. There's a positive feedback loop, so that if you kick off that contact pathway, that intrinsic pathway, there's a positive feedback loop.

Dr. Mehran:
Yep.

Dr. Gibson:
And that makes a burst of clot form inside your vessel. So what you're doing is you're blocking that red thing.

Dr. Mehran:
That feedback.

Dr. Gibson:
You're blocking that feedback loop, so you don't get that burst of activity. Now that allows you – there's no block on the other side. I mean, you can keep forming clot through the stopping-the-bleeding side of things.

Dr. Mehran:
So access site, for example.

Dr. Gibson:
Yeah, you can continue to clot there but you don't have that clotting inside the vessel. So that's the idea of how we're going to uncouple this.

I'm going to start off a little bit, just wander over into AF for just a second because these 2 do run together. I mean, we do have more and more people with AF out there. About a quarter of strokes are due to AF. We have reduced the risk of bad ICHs with NOACs, but the problem is that NOACs give you a lot of major bleeding, particularly in the GI tract. And there is some hope that maybe the factor XIs would reduce this, but we all were very disappointed when we saw the results of this trial.

This is one of the factor XI inhibitors, asundexian, and it was harmful.

Dr. Mehran:
What happened there?

Dr. Gibson:
We're not really sure. I wrote an editorial about this, about whether there's even still equipoise after this trial. Was it the wrong hypothesis? I don't think so. That epidemiologic data is so strong. One of the things that's most prominent is the reduction of stroke. So it seems like the biology should work. Was it the wrong dose? I kind of think it was the wrong dose. Remember, too, you've got to give the right drug. I think we have the animal data and epidemiologic data to say this is the right kind of drug. You've got to give the right dose and you've got to nail it right in terms of once-a-day versus twice-a-day dosing. Remember, with once-a-day dosing, you have

high peaks and low troughs. What really gets you on both the efficacy and the bleeding side is the troughs. The biggest predictor of bleeds and efficacy is you're trough level, so you've got to maintain those at a certain level, but not too high. It's really a Goldilocks problem with the troughs. So they gave once-a-day dosing. So they had low troughs and those low troughs may have played a role here.

Right dose, milvexian is about 9 times more potent than this drug, asundexian. We're giving it at a 4-times-higher dose, and we're giving it twice a day in the AF setting. So I think –

Dr. Mehran:
So the trough isn't going as low?

Dr. Gibson:
The trough is going to be higher. So we're all familiar with PTT. Your trough with asundexian is 1.5 times the upper limit of normal. Your trough with milvexian is 2.5 times the upper limit of normal. So you're sitting at higher troughs. So we think hopefully with this drug that's still being tested, we think we will hopefully have nailed it on the peak trough ratio and the dosing, so that's why we're doing the study.

This is the study testing out a dose of 100 mg twice a day of milvexian. Not versus placebo, but versus best-in-class apixaban 5 mg twice a day. This trial has now enrolled 20,000 patients. Not been stumped.

Dr. Mehran:
The AF1, yeah.

Dr. Gibson:
The AF1. We've enrolled 10,000 in the ACS study.

Dr. Mehran:
It's amazing because I was a little bit worried that people wouldn't want to be adding on top of the dual antiplatelet therapies, because they're giving dual antiplatelets. And I thought they would go to single antiplatelet, and that's not happening.

Dr. Gibson:
Yeah. They're continuing. And there's 8,000 in the stroke trial. So, when you add it all up, there's 38,000 patients' worth of experience now. DSMB looking at all of it. All the trials continue. So that's in contrast to what happened to OCEANIC.

On the stroke side, after stroke, can we prevent recurrent stroke? Bottom right number. When you lump together recurrent stroke and ischemic and TIA, there was a 36% reduction that was significant in phase 2 for asundexian. So there is a hint there that perhaps, on the stroke side, these drugs may have –

Dr. Mehran:
These are patients who have a stroke.

Dr. Gibson:
A stroke. This is post-stroke management.

Dr. Mehran:
Post stroke, not like – the ACS one is post-ACS, and the Afib patients, they just have Afib.

Dr. Gibson:
And the dose is pretty easy to remember. Everyone knows the 2.5 of rivaroxaban. Milvexian 25 is the new 2.5. So that dose twice a day is being compared to placebo after stroke.

So that's AF and stroke. What about ACS? We still have a lot of events, just like you showed, Roxanna. What I'm going to show you is that factor XI and factor X, they're kind of like the new cholesterol. Thrombin is the new cholesterol. They're chronic risk factors, and they're a good biologic target, we think. We saw earlier that thrombin is the thing that makes your platelets most angry, but our drugs

aren't doing anything to block that. We've won this battle 4 times before. ATLAS 1, ATLAS 2, COMPASS, the vorapaxar experience. All of these have shown a reduction in events by targeting thrombin generation. But we got to do it safely.

Now, this is something I learned recently. I didn't know this. If you look at the factor XI levels in people with an AMI, that's on the left, they're higher than in unstable angina and stable angina, and obviously much higher than control.

Dr. Mehran:
But do you think it gets activated during an acute AMI? Almost like a C-reactive protein type of thing?

Dr. Gibson:
Here, this isn't factor XI. This is thrombin generation, and what I want to point out, 2 years later. This isn't just like right after the event; this is 2 years later. The levels are still high. So that's why a lot of us think of it more as a chronic kind of risk factor. That's why I'm saying thrombin is the new cholesterol. So some people may have a different rheostat in terms of their clotting propensity.

Who cares? Why would we worry about that? Well, if you are one of those people who has elevated thrombin generation, you have a threefold higher risk of death, so it's just not a lab abnormality, it's related to events. As I said before, thienopyridines –

Dr. Mehran:
They do nothing.

Dr. Gibson:
They don't do anything. I mean, this is a gap. At the top, this is your aggregation with ADP. It blocks that, it blocks aggregation response, collagen. But look at the bottom one. It does not block aggregation when you put thrombin in there. So that's the chink in the armor that we're not treating.

Like I said, with rivaroxaban, ATLAS 1, we showed benefit; ATLAS 2, we showed benefit; COMPASS, we showed benefit. The hypothesis that inhibiting thrombin generation improves outcomes seems well founded. And look at this, we had a reduction in cardiovascular death. You'd only need to treat 50 people to prevent 1 death. But people wouldn't do it because of the excess bleeding.

And here is that annualized rate. Even though it's 0.6% per year, even though we had a 2% reduction in mortality, people wouldn't do it. So bleeding really is going to be critical.

We came up with the dose based upon some phase 2 data. The red bar there is intracranial hemorrhage. Things were fine at 25 mg twice a day, but when you hit 50 mg twice a day on top of DAPT –

Dr. Mehran:
On top of DAPT. There was a little bit of a - but this phase 2 to me, just look at the numbers. I mean, it's like almost 2,000 patients here, right?

Dr. Gibson:
Yeah.

Dr. Mehran:
So it's not like a small phase 2 with a couple of doses. Multiple doses, multiple once, twice daily. So I think that's another really important thing.

Dr. Gibson:
Now you asked this question. I wish I had a little red thingy around this. At the very, very bottom line, placebo. That 21.3% rate of bleeding, and this is with DAPT. The asundexian, the other drug on top of DAPT, 19% rate. So no increased rate of bleeding. And obviously, we've enrolled 10,000 patients and not been stopped, so it looks favorable.

This is the study we are doing together. We're taking high-risk patients with unstable syndromes, STEMI, non-STEMI. We're treating them with this new drug, milvexian, that new dose, 2 –

Dr. Mehran:
Twenty-five twice a day.

Dr. Gibson:
Twenty-five twice a day. I wanted to say 2.5. Twenty-five twice a day, and we're looking at ischemic events. Good old death, MI, stroke, and bleeding events. All these trials continue as planned. The AF study, 20,000 enrolled; STROKE, I want to say about 8,000 enrolled; and ACS, 10,000 enrolled. We're well over 38,000 patients enrolled at this point and they have met the IDMC and we're still going.

Chapter 4: Questions and Answers
Dr. Mehran:
We're going to open it up to some Q&A from everyone. There is a Q&A online, because we do have a – and many have asked what about abelacimab. So we need to talk a little bit about that, right?

Dr. Gibson:
Yeah. Abelacimab is different.

Dr. Mehran:
And how is it different than asundexian or milvexian?

Dr. Gibson:
Yeah. Those 2 are oral small molecules.

Dr. Mehran:
Small molecules.

Dr. Gibson:
Asundexian is an antibody. Once a month. Whereas the asundexian may give you about 90% inhibition, milvexian about 95% inhibition, abelacimab gives you about 99% inhibition. So, more potent.

Dr. Mehran:
And it's not reversible.

Dr. Gibson:
Not reversible. Now, we talked a lot –

Dr. Mehran:
And it lasts about 30 days.

Dr. Gibson:
It does. Now, we talked about peaks and troughs. There's no peaks and troughs here. It's a consistent level of inhibition. So that's really being tested out in AF. They had some favorable results in their first trial. They stopped it early because they had such – about a 40% –

Dr. Mehran:
Versus rivaroxaban.

Dr. Gibson:
Versus riva –

Dr. Mehran:
There was much less bleeding. It was a really –

Dr. Gibson:

About a 40% reduction –

Dr. Mehran:
40% reduction in bleeding.

Dr. Gibson:
But the ischemic outcomes were not clear, so –

Dr. Mehran:
Well, because they weren't powered for that, right?

Dr. Gibson:
They were not. So doing –

Dr. Mehran:
A bleeding study.

Dr. Gibson:
Similar to what you've proposed, talked about the –

Dr. Mehran:
I had proposed with asundexian to do a study with patients who are in Afib, who are at such high bleeding risk that they're not actually being anticoagulated. There are lots of patients out there for whatever reason that people are very worried about anticoagulation because of intracranial hemorrhage and they really should be on an oral anticoagulant and they're not. And so we proposed that with asundexian, but because of OCEANIC-AF, that has been sort of on a stop until they figure out what they're doing, because, yeah, I mean, even if you showed versus placebo, what do you have to lose? Right. And I think you have to show a reduction in ischemic events without increasing bleeding.

Dr. Gibson:
That's what they're doing with abelacimab.

Dr. Mehran:
And abelacimab, they're doing that. Exactly.

Dr. Gibson:
Yes.

Dr. Mehran:
So that was the question, and I think that was the big question, and I think that was important to really do these differences.

Dr. Gibson:
The other theory that may be good in is this kind of one-for-the-road kind of thing where you give a shot on the way out the door if you're medically ill, or if you had –

Dr. Mehran:
What about TAVR patients?

Dr. Gibson:
Or left atrial appendage closure device, one for the road. So it's appealing for that one-for-the-road kind of shot. I mean, there's good compliance with that.

Dr. Mehran:
Well, let's open this up to you guys. We have another 10 or 15 minutes to any questions that you might have. Anyone online, if they want

to send us a question, please go right ahead and do. I'm waiting for any questions that you might have.

Dr. Gibson:
Dr. Petrovic.

Dr. Mehran:
Hi, Dr. Petrovic. Always wonderful to have you.

Dr. Petrovic:
That was all very nice. We were all taught so much that's related to inflammation. What's the integration of this with inflammation, and is there a variation of whether patients are on statins or not, for instance? Because I'm always interested in this aspirin studies that show all this increased bleeding and no benefit, and we all saw benefit in the past. How much of that is blunted now by being on statins, for instance?

Dr. Mehran:
Yeah. Yes.

Dr. Petrovic:
And you never see that in the article.

Dr. Mehran:
No, it's such an important question, Dr. Petrovic, because the ATT collaborators, you remember, that it's a *Lancet* publication almost over 2 decades ago that showed aspirin unequivocally reduces ischemic events. But back then, there was no other treatments for risk factors, no ACE, ARB. Those patients were not on SGLT2 inhibitors, certainly not on GLP-1 agonists, and certainly not on lipid lowering the way we are. And there's no question that lipid lowering has a lot to do with this and so does inflammation. But what this is, is sort of getting to the residual thrombotic risk of the patient. Not separate, but also, we need to think about and not forget about the residual cholesterol risk, the residual glycemic risk, as well as the inflammatory risk, so you're 100% correct.

Dr. Petrovic:
Yeah.

Dr. Gibson:
And the other thing people don't know, and I could never get rid of this in the TIMI studies, if you're on a statin, you had a higher rate of ICH in our trials, and you adjust for everything and it never goes away. Statins actually inhibit a little bit of factor VII, for instance, so there is a little bit of baby anticoagulant effect from statins.

Dr. Petrovic:
So I guess the question is sort of if you're on or not on a statin, how much will that affect, say, some of these?

Dr. Mehran:
Well, most of these patients are on statins because that's a class 1 indication now for both primary and secondary prevention, especially in patients with multitudes of risk factors. And in an ACS patient, we know that even high-dose statins are right up there. We've seen fantastic results with it.

Dr. Petrovic:
But of course, there are always the patients who have some side effect and don't stay on it.

Dr. Mehran:
That's right. And they don't stay on it. And now we have the PSK9 inhibitors, so we can't forget about those. And I think those trials are also ongoing to deal with these residual events, systemic events.

Dr. Gibson:
But in that post ACS setting, in our modern trials, we're talking 85% to 95% are on high-dose statins. So in the trials at least, it's on top of

pretty aggressive medical therapy.

Dr. Mehran:
Yeah. And you know if this works, it literally is on top of all of these very aggressive therapies. But we are not doing a great job in reducing lipids. There's no question in my mind. We see that in our PCI patient populations. And those patients who present with an acute coronary syndrome, we're continuing to see LDLs in 70, 80, and now those LDLs should be below 50 and we are not doing the greatest job on that.

Dr. Gibson:
Roxanna, let me ask you, why don't you think more people are shortening DAPT?

Dr. Mehran:
I think they're afraid of ischemic events. But they're also afraid of bleeding, so they put them on aspirin and clopidogrel, which is not what they should be on. They are supposed to be on aspirin and a potent antiplatelet, but what they're doing is they'd rather keep them on aspirin and a not-so-potent and 30% not working thienopyridine than to put them on a potent. I think we just haven't done a good job in kind of maybe perhaps de-escalating and understanding the timing to de-escalation, that if we actually go to a single antiplatelet with a thienopyridine that's potent, when can I de-escalate to clopidogrel? And then do I have to test that patient to make sure they're actually responding? And then what happens if they go to the operating room? Are they supposed to go to the operating room with nothing? And people are scared of that.

I think it's all of that. That's why.

I think we're almost at time. It is late, and tomorrow's a big, big day for SCAI. And thank you all for being part of this.

Dr. Gibson:
Get your LDL checked.

Dr. Mehran:
Thank you so much for being here with us and I hope that you enjoyed this, too.

Thank you, Mike.

Dr. Gibson:
Thank you.

Dr. Mehran:
Love working with you. Thank you.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by **TOTALCME**.

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