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/questions-answers-from-the-aha-2023-symposium/16494/

Released: 11/30/2023
Valid until: 11/30/2024
Time needed to complete: 1h 35m

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

Questions & Answers from the AHA 2023 Symposium

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:
Feel free, there's microphones so you can type in your questions. I know from some of the people in the audience, this is not a shy crowd, so feel free to give me your questions. Okay, I see a question right there. Yes, sir.

Male:
My name is Philip Ansel from Hungary. I'm one of the I lead investigator of the national trial.

Dr. Patel:
Yes. Thanks so much.

Male:
Congratulations for your excellent presentation and you clearly understand the safety of asundexian or all the XIa family. But you know very well the thinking of the general practitioners or the cardiologists, I can give an oral anticoagulant to a patient if we have an antidote. What do you think of the need of antidote? Or do you know any research regarding the XIa antidote?

Dr. Patel:
Yeah, let me make sure everyone heard the question. Thank you so much. By the way, thank you so much for enrolling patients. The only way we learn more is enrolling patients. Thank you for leading in Hungary. The question was, okay, we have these new agents, what do we know about antidotes? And how much does it help with antidotes for these agents? Let me ask you guys, thoughts about antidotes in general? And then antidotes for this? Go ahead, maybe Cecilia, do you want to start and then Elaine?

Dr. Bahit:
The, you know, RE-LY, ROCKET, you know, ARISTOTLE and ENGAGE without an antidote and we – it's just to remember that warfarin and vitamin K antagonists don't have an antidote. So, with these agents, factor XI inhibitors, we expect to see less bleeding as we've seen in phase 2 trials. So, they are ways to treat bleeding whenever it appears, that there's no need for clinical, you know, for a reversal agent.

Dr. Patel:
Yeah. And, Elaine, what are your thoughts?

Dr. Hylek:
We're used to being concerned about reversal, because we've been accustomed to warfarin. And it's important to remember the pharmacokinetics of warfarin in the elderly, the half-life is 60 hours, 40 to 60 hours, think about it, 60 hours. So, when that patient came into the emergency room with an intracranial hemorrhage, you know, giving the sub-q vitamin K, giving the intravenous vitamin K. Now

the FDA has approved Kcentra, or prothrombin complex concentrates. But even when you would give patients all of that, to the warfarin patient with an intracranial bleed, those hemorrhages tended to ooze over the next ensuing 48 hours. So, we believe that there's these reversal agents for warfarin, but in practicality, they don't change the Rankin outcome, at least for intracranial hemorrhage.

So, let's talk about dabigatran. Dabigatran we don't use a lot in the United States. It has an incredible reversal agent. It is amazing, probably the absolute, you know, coup de gras or whatever of reversal agent. It works within minutes. It doesn't have this recovery of the anticoagulant effect like we saw with andexanet alfa, which was what we were hoping would be used in the emergency setting for apixaban- and rivaroxaban-related bleeding.

But I don't see the reversals being used a lot for DOACs. Probably because the half-life is just so much shorter than warfarin. And you know, for most things, I do think you can temporize where you do need reversal agents, is with emergency surgery. The patient that comes in with a bleeding, you know, aortic aneurysm, or you know, you don't want to have any anticoagulant on board. And I think it's the trauma patient who needs to go right to the to the OR, it's the more unusual situations where urgent surgery, you can't wait the 24 to 36 hours. And I think we've been fortunate with the DOACs having such a short half-life, that most of the time you can kind of temporize. But it's a question.

Dr. Bahit:
Yeah, a good question.

Dr. Patel:
You know, I think it’s a key question. Great question. The problem for us is it's hard for us to change our behavior. You know, if I was to say that I had a drug in 2005 that reduced mortality, reduced fatal bleeding, and reduced important bleeding, I would say let's use it. That's all of the new agents. And we even have reversal agents, some not great, let's say, but they exist. They weren't present when we did the trials. I don't know in the new era with the factor XI inhibitors that, outside of PCC and some other things, we can use 4-factor. So that's my answer. You should - you're going to do what you can best do when people come in. Your hope - we know from PACIFIC-AF and tomorrow we'll find out, it's been stopped by the DSMB, so we'll find out from AZALEA, but if you can inhibit something and it bleeds less, then the question is going to be for you, where do we feel comfortable going forward? And we're going to need to see the final trials, but those will be important.

Dr. Bahit:
At the moment, we do have right now is tranexamic acid.

Dr. Patel:
Yes.

Dr. Bahit:
As first-line.

Dr. Patel:
Yes.

Dr. Bahit:
A low-dose NovoSeven.

Dr. Patel:
I should say to your point, there's three agents that we can use, we can use them in agents, and we shouldn't shy away from them. I think the good news is our patients are needing it less and less. Now, that doesn't mean they still don't need it. And it doesn't mean patients randomized in trials don't care about it. But it's an important point.

Dr. Hylek:
But you know, one thing I would add is as these next set of trials, you know, go through, it's going to be critical that the investigators, you know, capture the interruptions, capture for, you know, a drug that you get once a month, how does having, you know, your gallbladder removed? I mean, how are these things going to really play out in clinical practice? And I think, obviously, that's going to be an important –

Dr. Patel:
I think, so I would just say that the data that exists so far with AFib, and we'll have more tomorrow, but if the data that exists with AFib really are 30 to 50 to 60% less bleeding, then it will be not only, of course, half-life, but if you really do reduce bleeding that much, then you should have an efficacy effect. But that efficacy effect on bleeding should be significant for you to do it. Now, of course use and

other things will come into play. I have another question here in the audience.

Dr. Chaudhry:
Hi there, I'm sure Sharjeel Chaudhry, vascular surgery resident at BI Deaconess. I just had a quick question. I really appreciate the description of the pathways that you illustrated. I think as a vascular surgery resident that was sufficient for me, not maybe for the hematologists. But I do have a question as you start to sort of apply these tools to the larger set of populations in further clinical trials, taking a step back and looking at the epidemiological data again, for factor XI and the genetics data, I'm just kind of interested to know what the cutting-edge data sort of looks like on factor XI, in terms of reducing the risk of MI and bleeding from finding some of these patients who have loss of function, mutations, and things like factor XI and others?

Dr. Patel:
Elaine is going to answer first.

Dr. Hylek:
I may not be able to answer that directly. But I do think that it was a very astute individual, or individuals, in hematology that observed that individuals with congenital factor XI deficiencies, you know, did not have bleeding issues, and they had reduced stroke, MI, DVTs, PEs. And, you know, once that observation was made, I think then, you know, you make sure that it's, you know, animal models are playing that out. And my understanding of factor XI is that it interferes with the propagation of the clot, not the initiation of a clot; so, it's the propagation. And there were smaller DVTs actually in the ASO study with Harry Buller. It was intriguing that when they looked at these legs, the clots were a lot smaller. And you know, whether or not that has a clinical, you know, reason to be important, it sounds like it would be. But regarding genetics, I don't know.

Dr. Patel:
Yeah, maybe I'll make two comments. First, I'll congratulate you as a vascular surgery resident to come to the AHA, that's good work. And I appreciate you're here to learn about broad things. And the second thing, I'll just say, is your question is very astute. You're right. You know, looking back at the data by itself, you might say, hey, why are we going after factor XI? Now, we've known for some time, it's a rare genetic disorder. And those people with that rare genetic disorder don't seem to have clots as much, but there's a lot of things that happen there. And bleeding, while bleeding, yes, I care about it, but you know, I don't know all the things that might drive someone's bleeding rate as they get to be 70 or 80.

What's interesting is we then look at levels and when we look at UK Biobank data, we start to see interesting information around both genetic issues, maybe potential level data, and to say there's a signal. But you know, past that, I go now we're past that, we actually have agents that are inhibiting it. We have clinical data in patients that are showing significant reduction. So, if that continues, we'll see. It's a big bet. I appreciate that. But the genetic story is just used to tell people how we got to where we are. Whether or not we should be targeting it, I think as it makes sense and now we see clinical data amongst many areas where we could go it.

Others might say, well Manesh, why wouldn't you choose other targets? There are many others? You're absolutely right. And I could go deeper into some of the data I've seen. I think it's a pretty thoughtful argument. It's not purely based on genetics as I showed it, I just want to be very clear about that. There's also animal data. And there's also now phase 1 human data, phase 2 human data. I didn't show all of that given in 15 minutes. So, I think that that's part of it.

Dr. Chaudhry:
Thank you.

Dr. Patel:
Yeah, yeah. Great question. Very thoughtful. Over here.

Male 2:
Thanks. Thanks, all three of you for your topical and informative presentations. One question for the whole panel. And then the second question for Dr. Patel.

Dr. Patel:
Uh oh.

Male 2:
For the whole panel, anything that you guys have told us tonight, relevant to something I haven't thought about since cardiology fellowship, von Willebrand factor and the people on LVADs who get bleeding from angiodysplasia in the GI tract. So, anything relevant with von Willebrand that you can share with us? Okay.

Dr. Hylek:

I have nothing. No idea.

Dr. Bahit:
Me neither, sorry.

Dr. Hylek:
Very good question though.

Dr. Patel:
Yeah, very great question. And I'll only say the things that we have thought about in this space, is that obviously, mechanical devices activate a lot of things. And that does deplete things like von Willebrand factor, and people with VADs have angiodysplasias for a variety of reasons we may not be able to explain. I certainly can't, you know, but they have high bleeding rates.

One of the holy grails in the space of, I'll call it antithrombotic therapy, has been contact inhibition for mechanical devices. So could we see if factor XI actually works in atrial fibrillation and secondary stroke, working in stents, and AMIs, eventually getting to valves, eventually getting to vents? We could see that. But I don't want to say we know we're going to get there until we've seen these other things. And as you can imagine, if you're in a large clinical community or pharma, you're not going to start with a VAD or mechanical device, because the risk there is just so high. And the reward is so low, because those patients just bleed almost for a variety of reasons.

But your question is spot on. And we all want to not be having to treat our patients with mechanical valves with warfarin. I believe the intermediary, this is now a personal belief, is going to be TAVRs and things like that. So, if AFib and these things work, we might get to those spaces.

Male 2:
And my question for you, specifically, Dr. Patel, you've told us 40% of people 10 years after DOACs who have AFib are still not treated. I'm from Illinois, and I can tell you, one of the main reasons they're not treated is that apixaban marketed as Eliquis is 10 times more expensive than warfarin. What do you anticipate, if you can, I realize that the cost of the factor XIa inhibition elements are going to be? And is it going to be reasonable? Because warfarin is the gold standard in terms of payment, particularly for people who are underinsured or who've got no insurance.

Dr. Patel:
I totally appreciate what - your question is fantastic. And I'll try to answer it in what I hope is both my belief but what I hope is what we're trying to do across the United States, although it is a complicated time right now. I would say the following. I've seen that adoption of therapies takes more than 10 years across every therapy we've seen. And every clinician I speak to gets up and says it's access, it's access, it's access. I absolutely agree, it is access.

But before I get into how we might change access, let me ask you a question. How many of the patients do you think at due cost will get a statin when they're supposed to get a statin? It's free, I'll call it, fair near generic. And so, I would argue for us as a professional group, we should first start by saying let's get everything as fast as possible to the patients that need it even when it becomes generic, because some of it is access for sure. But much of it is physician inertia and patient inertia. It is - why do you think 2.5 of apixaban is used instead of 5 when people can use it? People – why do you think 12.5 of carvedilol is not used instead of 6.25? Why is 20 of atorva more popular than 40 or 80? It's just hard to get patients to the right dose. So, I'm not using the bully pulpit just simply to say it's all our fault. Some of it is our fault. Some of it is access. Some of it is the system. In the United States, the pharmacy benefit managers have put a big, big place in front of the workload we have to do. I have no idea what the price will be. I can't even imagine it right now.

As I would say right now, the key is if you want to run down the price of the therapies, we have to start using therapies much more frequently when they work, because then the number of patients that the therapy could go to goes up and the price could potentially go down. So, our goal should be to say, how do we get therapies to our patients? It doesn't mean we still don't have to advocate for better drug prices. But that seems straightforward and easy when most of the rebates don't go to our patients. They go to these intermediaries.

So, it's a complicated situation. And I would just answer by saying, I don't know the price. If it does reduce bleeding by 50 to 60%, that's a significant reduction for the things our patients care about. Well, we've spent an hour and a half, and I was here a little late, but I appreciate the comments. And thank you all for coming. Thank you for my moderators in town.

Dr. Hylek:
Thank you.

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.