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Secondary Stroke Prevention: Antithrombotic Strategies for Neurologists, Hematologists, and Cardiologists

Announcer:

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Chapter 1

Dr. Siegal:

Hi everyone. I'm Dr. Deborah Siegal and we're fortunate today to be with Dr. Weitz, Dr. Sharma, and Dr. Barnes to talk about factor 11 inhibition for the treatment of secondary prevention of stroke. And so why don't we just get into the discussion that we're all here to talk about. Dr. Sharma, help us understand the need for improved treatments for patients who've experienced non-cardioembolic ischemic stroke.

Dr. Sharma:

So, Dr. Segal thanks for the opportunity to talk about that. So, when we consider ischemic stroke, it falls into two broad categories. Cardioembolic stroke, most of which is related to AF, has very good secondary prevention anticoagulation. Warfarin is about 66% effective at reducing risk compared to placebo.

And the DOACs have built on that more, convenient to use and somewhat greater safety for intracranial hemorrhage. Non-cardioembolic ischemic stroke, which is about 80% of the total ischemic strokes we see, however, does not have that same option for antithrombotic therapy. So, aspirin is the mainstay of secondary prevention of non-cardioembolic ischemic stroke.

And it's been there for about 50 years. And in spite of attempts with previous trials, we've not managed to build on aspirin. Apart from a short-term dual antiplatelet therapy for about three weeks, which is effective, otherwise for most people, for the long term it's aspirin, which is effective, but modestly so, about a 20% relative risk reduction.

So, we have this large group of patients with non-cardioembolic ischemic stroke [and] we're stuck where we were in the 70s.

Dr. Siegal:

So, it sounds like there's an important gap to meet here. And we're talking about combining therapies with different mechanisms of action in order to treat these patients. So maybe Dr. Barnes, from a cardiovascular point of view, perhaps talk us through some of the data that exist already about using different agents in combination and the lessons that we have learned, for example, from COMPASS.

Dr. Barnes:

Well, Dr. Sharma mentioned that really the mainstay of treatment for cerebrovascular disease has been an antiplatelet strategy, largely with aspirin. The question, of course, is could you bring an anticoagulant strategy or something that targets the coagulation cascade, in

addition, and the COMPASS trial really gave us some promising data to suggest that there could be an advantage.

This was a study of patients with stable atherosclerotic cardiovascular disease. So cerebrovascular coronary and peripheral artery disease. And it showed that when you used a very low dose of a factor 10a inhibitor rivaroxaban, and combined that with an antiplatelet agent aspirin, you could prevent atherosclerotic cardiovascular events, major adverse cardiovascular events.

The problem was, in that population, you ended up increasing bleeding as well. So, there's a little bit of this balance that you have to walk. But it really, I think, got us excited about the potential of targeting the coagulation cascade in addition to having an antiplatelet agent. If we could just find the right agent that would prevent thrombosis without leading to that increase in bleeding.

Dr. Siegal:

Right. So, a nice segway for Dr. Weitz maybe to explain a little bit about how factor 11, factor 11a comes into the picture here.

Dr. Weitz:

And what Geoff is talking about is dual pathway inhibition because you have an anticoagulant that's inhibiting the coagulation pathway and reducing the formation of fibrin, and you have an antiplatelet agent that's keeping the platelets happy. And together they do more than either one alone.

And now we have evidence with factor 11a inhibition that it's actually a very safe strategy. So, whether we look at the phase 2 trials of factor 11 inhibitors compared with enoxaparin for post-operative venous thromboembolism prevention as a proof of concept, any number of these agents produced a greater reduction in the risk of post-operative venous thromboembolism, and there was no associated increase in bleeding.

So those findings suggested that you could dissociate or uncouple the effect on thrombosis from the effect on hemostasis. And now we have data from the OCEANIC-STROKE trial that Mike led, where patients with non-cardioembolic ischemic stroke or high-risk TIA were given a factor 11a inhibitor on top of their standard-of-care antiplatelet therapy compared with a placebo on top of standard of care.

And the factor 11a inhibitor reduced the risk of recurrent stroke by 26%, and there was no significant increase in major bleeding, which was the primary safety outcome, clinically relevant bleeding or even minor bleeding. So, a very safe strategy that gives you a big bang for the buck. And unlike what we saw with COMPASS, where you're walking that tightrope, one of the other things with COMPASS was that the greatest reduction in recurrent event was actually in stroke.

Right. Mike.

Dr. Sharma:

Mhm. That was by far the greatest reduction. And it took us a little while to understand why that happened. But stroke is predominantly an embolic disease. So, if you can cut down the formation of thrombi that embolize, you will prevent stroke.

Chapter 2

Dr. Siegal:

Maybe just following up on that a little bit. Um, Jeff, just, you know, for practicing clinicians out there who may not be as familiar with the mechanisms of these different drugs, people are now familiar with DOACs. You know, here's a new agent coming, new agents now coming down the pipeline. How should clinicians think differently about these medications?

Factor 11, factor 11a inhibitors compared to what they already are familiar with?

Dr. Weitz:

Yeah, I mean they're the most commonly used agents now what we call the direct oral anticoagulants or the DOACs. And they target factor Xa or thrombin, which sits lower down on the coagulation cascade in the common pathway. Factor 11 is positioned in the intrinsic pathway. And it turns out that when there is hemostasis for the formation of a hemostatic plug, it's triggered by high concentrations of tissue factor that cause explosive Xa and thrombin generation, and factor 11 is very important.

In contrast, with intravascular thrombosis there's a little bit of tissue factor. And for that clot to grow, there has to be feedback activation of factor 11. So, if you inhibit factor 11, you attenuate the thrombosis part, but you don't affect hemostasis. Whereas because the DOACs target the common pathway, you get both of those.

And that's why, inevitably with a DOAC, the more of it you give the higher the risk of bleeding. Which was not the case here in the in the OCEANIC-STROKE study and in other studies. We're just not seeing that dose-dependent increase in bleeding. But we are seeing a dose-dependent decrease in thrombosis.

So, we have the possibility then of uncoupling those two processes and having safer anticoagulation therapy.

Dr. Siegal:

And I think that's particularly important for stroke neurologists who are obviously very concerned about the possibility of hemorrhage in the brain, you know, limited volume, and those events are so similar too.

Dr. Weitz:

Especially for someone who's just had an ischemia. So that's what we're always worried about is hemorrhagic transformation.

Dr. Siegal:

So maybe, Dr. Sharma, just maybe a couple of your thoughts on how neurologists, should view these results in terms of the bleeding risk and how they should consider that when they're looking to treat patients in the in the context of these new drugs.

Dr. Sharma:

So, you know, you're absolutely right. We're very sensitized to bleeding especially intracranial. And as Dr. Weitz has pointed out, the acute phase after stroke is the highest risk for hemorrhagic transformation. Bleeding into the infarct, which when it's sizable can be fatal. So, I think for neurologists, we're going to have to adjust our thinking in a couple of ways.

First off, our traditional approach to antithrombotic in general, including dual antiplatelet, has been one of trepidation, looking for reasons not to use them. And currently our patients are undertreated with dual antiplatelet agents for this reason. So, if you look at the guidelines, what they require is a milder stroke.

And NIHSS, which is a measure of stroke severity of four or less, and that has a rough correlation with the size of the infarct. So, I think the one big thing we're going to have to change in our thinking is to stop approaching it with fear of bleeding, because we haven't seen an increase in bleeding, particularly intracerebral bleeding.

The other thing which is going to be peculiar to neurologists and the acute practitioners.

There are three surgical procedures which will probably be the commonest for our patients in the acute phase. And those are external ventricular drainage, where there's a burr hole and a drain inserted to prevent hydrocephalus; hemi craniotomy, which is quite a large surgical procedure for malignant edema of the brain; and carotid and arterectomy. So, you know, in planning antithrombotic therapy, we're going to have to think about all of these things first to avoid overwhelming fear of hemorrhage. And second, to plan for how we're going to approach these in the acute phase.

I will say in OCEANIC-STROKE, we did not exclude patients who might be planned for carotid and arterectomy surgery. Now, in the end, we didn't have a lot of those procedures, but we felt based on the phase two data, all of the work with other agents, which either block factor 11 or activated factor 11 or deplete it from the source, all of the other work really hadn't suggested a high risk of waiting.

Chapter 3

Dr. Siegal:

Well, following on those comments, I think it dovetails nicely into the next series of questions about let's dive a little bit into some of the data that we've seen from some of these trials and talk to us a little bit, Dr. Sharma, about what outcomes are really important for neurologists.

And also thinking about if you were a neurologist about to start these medications, what are some things that you would consider? How can someone, like, you know, Dr. Weitz as a hematologist or perhaps Dr. Barnes as a cardiologist help in that context?

Dr. Sharma:

So, you know, I think the results that are most important is first off efficacy. So, it's a 26% risk reduction. The hazard ratio is 0.74 in the occurrence of ischemic stroke. And this applied broadly, so all of the pre-specified subgroups that we tested we saw an effect. And so, size of stroke up to an NIHSS of 15 didn't matter, whether you were on dual antiplatelet or monotherapy early, it didn't matter.

And importantly for neurologists, the stroke subtype didn't matter. You know, we built stroke neurology in a way that we suggested you have to be very expert and sort out the stroke subtype. For factor 11a inhibition, it seems not to be the case. So, it was effective for atherosclerotic disease, for small vessel occlusion, and as well for the cryptogenic strokes where we don't know the source of the embolism. So, I think the efficacy is excellent.

The safety was actually very good as well. So, the primary safety outcome, which was ISTH major hemorrhage, was not increased. And we saw similar rates of the secondary outcomes. Importantly, similar rates of intracranial hemorrhage and similar rates of intracerebral hemorrhage with asundexian compared to placebo.

The other thing that patients told us was very important to them was minor bleeding. So, bleeding like bruising, which, you know, most of us tend to downplay. For patients, it was a sign that potentially something bad was happening. They told us it caused anxiety in a number of people, made them stop their medications.

So very happily, there wasn't an increase in minor bleeding over placebo either. So, I think both the efficacy and safety outcomes are of importance. And as this is a medication meant to be started early and continued over the long term, the fact that we saw these over, you know, follow up of about two years was very helpful as well.

Dr. Siegal:

And so, thinking about now the advent of these medications, there's more studies on the horizon. Maybe, Dr. Barnes, help us understand how these findings, from OCEANIC-STROKE, for example, fit in with some other findings. And how should clinicians like OCEANIC-AF in terms of how clinicians should be thinking about those results?

Dr. Barnes:

You know, the OCEANIC-AF study was really a different study because it looked at a different population of patients. These were patients who had diagnosed atrial fibrillation, which we know puts them at risk for cardioembolic stroke. But it also was a study that went up against an active comparator.

So, they were being compared against apixaban. Very different than the OCEANIC-STROKE study which was the use of asundexian or placebo. So, it was really going up against a placebo on top of standard-of-care antiplatelet. So, I think those are really important differences. What's interesting is that the dose of asundexian studied in both of these trials was the same.

And so, I think what we found in the OCEANIC-AF study that was the study of atrial fibrillation patients going up against apixaban, is that the dose probably wasn't sufficient to fully prevent cardioembolic stroke. We saw that the apixaban arm had a lower rate of the primary composite outcome. But we also saw in that study that safety was definitely confirmed with the asundexian arm, the arm that was using the factor 11a inhibitor.

And so that really, I think, mirrors and supports what we now see in the OCEANIC-STROKE study. Very good safety data. I mean, you talked about no increased risk of bleeding or bruising compared to placebo. That's really quite impressive. But now we are able to lower the rate of the ischemic events. Right. The ischemic stroke events when you add asundexian on top of antiplatelets as compared to a placebo.

Dr. Siegal:

Yeah. So, it sounds like though this question about etiology for example is atrial fibrillation present would actually be something that's really important to ascertain.

Dr. Barnes:

Absolutely. And I think anyone who manages patients who have cerebrovascular disease, especially in the setting of an ischemic stroke, you're always asking yourself, could this have been cardioembolic? And a big piece of that is looking for atrial fibrillation. So those patients are very commonly placed on telemetry to make sure there's no atrial fibrillation that's happening while they're in the hospital.

Many of them will go home on extended monitors. I don't know, Mike, if you want to talk a little bit about what your practice is, how long you tend to screen for atrial fibrillation, but it's critical because it changes your treatment path.

Dr. Sharma:

It absolutely does. So, you know, there are a few things I won't change. So, if you see a patient with an ischemic stroke, you have to exclude surgically addressable carotid disease and atrial fibrillation. So, what we tend to do is monitor in-hospital and out of hospital with an external monitor for about four weeks.

Patients where we're very suspicious. So, the topography is embolic. They have an enlarged left atrium on echo. Those are the ones that we target for implanted monitors. Now practice varies across the world. In the US, implanted monitors are very common. One of the things that we know is that the finding of asymptomatic, brief bursts of atrial fibrillation after stroke does increase the risk for recurrence.

We also now know that sometimes it happens only after the stroke, not having been there before, but it doesn't change the treatment recommendations. They still have to look and you should switch to anticoagulation you know in that setting. So those patients will likely have their antiplatelet and other medications stopped and switched to a DOAC most usually.

Dr. Barnes:

And of course we need to look for atrial fibrillation. We need to think carefully about all of the antithrombotic strategies, but we can't forget the other parts of management. Right.

The lipid management, often with statins, we need to think about hypertension management, smoking cessation, all the other important things for anyone who presents with cerebrovascular disease.

Dr. Sharma:

It's critically important right then. And if I was going to ask people to do one thing, that would be treat the blood pressure and then treat it again. So, you know, a reduction in blood pressure of ten over six reduces recurrent stroke risk by 40%. It is a very potent therapy. So do it now, also decreases the risk of hemorrhage.

So, for multiplicity of reasons, you're absolutely right, it needs to be in that basket of care, that whole patient approach to prevention.

Chapter 4

Dr. Siegal:

And so just bringing it back a little bit to the OCEANIC-STROKE results which you've described. Reduction in the risk of recurrent stroke. No increase in the risk of bleeding. And thinking about the patients that were in that study. Patients with non-cardioembolic ischemic stroke. And thinking of the clinicians out there who will be managing these patients.

Maybe talk a little bit about the generalizability of the findings. I know Geoff, if you want to start of how generalizable are those findings to people that you know, you would see in everyday practice?

Dr. Barnes:

Well, I think it's a really great question. And when I read the study, I was really excited because it felt like it applied to a large volume of patients who were coming into the hospital with ischemic stroke. You know, as a cardiologist, I'm often involved in those who have atrial fibrillation. Very clearly, that group was excluded.

We have a different treatment pathway, but outside of that group, many I would argue most of the patients with an ischemic stroke are going to be eligible based on the way the trial was designed. And so, I think it's actually a largely generalizable study, especially given the very positive efficacy and safety findings.

Dr. Weitz:

So, I was just going to say that I think that study has given us new knowledge about the pathophysiology and the involvement of factor 11 in the pathophysiology of strokes of different subtypes, because I don't think I would have expected that it would work in, say, lacunar strokes or ESUS, where the DOACs compared with aspirin were not beneficial.

So, I think we've learned a lot. And as you said, Mike, when you looked at the inclusion criteria, it was almost every subtype of non-cardioembolic stroke, which makes it generalizable to the vast majority of patients. And these are indeed 75 to 80% of the patients with an acute ischemic stroke have a non-cardioembolic type.

And then if you can reduce the risk of recurrence without increasing the bleeding it's a win win situation. So, I think we've learned so much from this study.

Dr. Sharma:

Okay I couldn't agree more. And I'm delighted that you're delighted at the generalizability. So, we sometimes get questions about the stroke severity. So, the median stroke severity was in NIHSS of two. If you look at the non-cardioembolic stroke studies, it is shifted towards that. And the other thing to remember is a third of our patients in OCEANIC-STROKE had a NIHSS of 4 all the way up to 15, which was the cutoff.

So that's moderate to severe stroke. So, we have a much broader range of patients that we can treat rather than with the dual antiplatelet therapy. And I agree with Dr. Weitz. You know the one thing I was surprised by. Well, several things I was surprised by. But one was the effect size on small vessel disease.

So, we hadn't expected that based on our belief that much of this was related to lipohyalinosis. changes in the vessel wall. (Dr. Weitz) Exactly. But clearly thrombosis is important there.

Dr. Weitz:

And we didn't know that before. And so, I think that's exciting. Even in the LIBREXIA-STROKE trial, which hasn't read out yet, they capped the percentage of patients with lacunar strokes because they really didn't necessarily expect it to work. Of course, now we know that factor 11 inhibition works in that. I think it's going to change how we think about these strokes and might lead to even newer therapies.

Chapter 5

Dr. Siegal:

To follow up to those questions, a patient has an acute non-cardioembolic ischemic stroke. We're prescribing asundexian for them or factor 11/factor 11a inhibitor. The window of starting that treatment was 72 hours in the trial. Maybe just talk a little bit about how clinicians can consider treatment. If a patient, for example, within the window, without the window, how is that going to be implemented into clinical practice do you think?

Dr. Sharma:

The window was 72 hours. And the reason for that is the recurrence rate is highest early, and you really want to capture that. It was a wider window than in the dual antiplatelet trials, which were limited to 24 hours because we wanted it to be representative. So, patients who receive thrombolysis, mechanical thrombectomy, were excluded from those earlier trials but are included in OCEANIC.

Now, if you look at the cumulative incidence curves, you see the separation. We see it early and it just continues. So, it seems to us that the effect is ongoing, no matter where in the time course you are. As long as we have data out to two years. So, it's our feeling that even if it's outside that 72 hour window, you'll still get an effect and it'll still be usable.

We openly admit we don't have data yet on patients starting later. That may be part of some data collection that goes on post approval.

Dr. Barnes:

I think this is a really important point for a couple of reasons. The first is not every patient will present to a stroke center where they have a stroke expert within that short time window, and many patients have had a stroke in the past, and now they're seeing their vascular specialist and being able to think about whether or not additional therapy like a factor 11 inhibitor could still be offered. I think it's a really important question. We'll have to see how some of the coverage and regulatory elements play out. But clearly the data from the trials show that continued separation of the curves. There's an added benefit that happens over time from bringing a factor 11 in addition to standard-of-care antiplatelet.

Dr. Weitz:

But this is not infinite Mike because the risk of recurrent stroke, yes, it's front loaded. So, you know how long after the incident stroke would you still consider adding asundexian. If they come to you and they told you, "I had a stroke a year ago, I'm on aspirin," would you want to start everybody on asundexian?

And on the other hand, someone who's having recurrent strokes despite aspirin, no AF, it seems to me that would be a person where you would really think about that or the COMPASS regimen.

Dr. Sharma:

Right. So, you know, I think that absolutely I wouldn't start it on anyone who had a stroke 50 years ago. But you raise a good point. So, the risk of stroke is very high early goes down after about the first year, but then it plateaus. And if you keep on following them, the risk goes higher as people get older.

So, one thing we have to acknowledge is that it is not that the risk ever goes away. It is always there. And if you think about what prevents us from using agents, the first thing is hazard. Here we've not seen that. It's really not the hazard of bleeding or other adverse events. But the second thing is cost.

So, I think at some point there's going to be a tradeoff between the cost of the agent and the residual risk at that time point. So, you're right, it won't be infinite. Then we'll have to come to some resolution on these issues.

Dr. Siegal:

I just wanted to circle back to something that that you said, Geoff, about, you know, patients who may not be a tertiary care stroke center. Lots of other physicians are going to be involved in the management of these patients or are involved in the management of these patients. I guess the question is, how is care going to change with the introduction of this new agent? For example, when Dr. Weitz, or Jeff, when would hematology likely become involved in this?

Dr. Weitz:

I think these patients are older. They often have comorbidities. They might present to the emergency department after a fall and have a fractured hip. Or they might present to the emergency department with an acute abdomen. And then if the emergency doc finds that they're on this medication or happens to measure the activated partial thromboplastin time, the first person they're going to call is hematology.

So, they'll have to be some advice given as to what does the aPTT mean. And we know from the trial that even though asundexian can prolong the aPPT, it doesn't mean much in terms of a bleeding risk, but it might make them afraid to go ahead and do surgery if they

need to have surgery. And I think it's really important that we're dealing here, especially if they're present soon after their incident stroke, that they're at a high risk of stroke.

So, when we're thinking about how to manage them very procedurally, we want to make sure that we maximize safety. But we also we want to make sure that they don't have another stroke. So, I think fortunately, you know, if they came in and they were on dual antiplatelet therapy plus asundexian, if they have a bleed, that's not a major bleed, you know, just stop the clopidogrel and keep on with the aspirin and the asundexian. If they needed to go for surgery, asundexian has a relatively short half-life, you could wait for 12 to 24 hours and go then. Or you could probably do the surgery without having much bleeding. I think we're getting more and more comfortable with factor 11 inhibitors, and this is really a prophylactic dose of a factor 11 inhibitor doing surgery without stopping.

So, I think that's where the hematologist is going to intersect with the patient on these. We have a lot of education to do.

Dr. Siegal:

Yeah certainly. And so similarly I guess from the cardiologist point of view, you know how thinking about these patients often will have concurrent, you know, coronary artery or peripheral artery disease. You know, where does the cardiologist or vascular medicine specialists come into play here?

Dr. Barnes:

Well, some of our interventional cardiologists may even be involved in the acute treatment. Some of the interventions, if there's not a, you know, an interventional radiologist who does stroke work. In the United States, where I practice, there's just a shortage of stroke specialists, especially stroke neurologists.

So, they may be involved in the acute phase, but then it's often a cardiovascular specialist who's going to see that patient long term, thinking not just about the antithrombotic therapies, but all of the other things we talked about, lipid management, hypertension management. And then of course, as you mentioned, these patients have comorbid cardiovascular disease.

So, what happens if they develop an acute coronary syndrome. And now we're treating with dual anti platelets for a different reason. What if they develop symptomatic peripheral artery disease. What happens if they develop atrial fibrillation down the line. Understanding how a factor 11 inhibitor fits in should be continued, maybe should not be continued depending on the circumstance. I think it's really important for the cardiovascular specialists to understand, because we're often going to be that longitudinal connection to managing these drugs.

Chapter 6

Dr. Siegal:

And I think that brings us kind of around to this last part here, you're all experts in your field studying these drugs, specialized care, you know, what advice would you give? Perhaps we'll start with Jeff. Practicing clinicians, what do they need to know? And maybe one kind of thought from each of you as we sort of come to a close.

Dr. Weitz:

I think they need to know first that this is a new medication that is directed toward patients who have non-cardioembolic stroke. They all think about AF related stroke. Those are the people who can't get this medication. And then I think it's a safe medication. They have to know a little bit about it. What does it do, how does it work and how do they manage the potential complications, not from the drug itself, but complications that the patient experienced?

And I don't think we should forget the potential role of pharmacists in this, because patients are going to go into the pharmacy to renew their prescriptions, and the pharmacist has a teaching moment there to impress upon the patient the importance of continuing the therapy. And the fact Mike that this does not increase the risk of minor bleeding or nuisance bleeding, as we often call it, is good because it's often those nuisance bleeds that lead patients to stop the therapy.

So, I think there's a lot of education that needs to happen.

Dr. Sharma:

Look, I couldn't agree more. And I think that knowledge has to be dispersed quite widely so that the patient receives the same message from all of the health care practitioners.

They're saying one big fear is premature discontinuation. And as a result, patients are exposed to increased risk. You know, what Dr. Weitz said earlier, I think is very important.

One of the concerns we have is people will overreact to things like the elevated aPTT, but they will overreact in situations where procedures are needed. When you withdraw the medication, you expose that patient once again to a risk of recurrent stroke and stroke

recurrence is associated with high mortality and high morbidity, which we really want to avoid.

So, I'm reminded of that old poster that said keep calm and carry on. So, one of the things we want to prevent is overreaction.

Dr. Barnes:

And I think for the cardiovascular specialist, we really need to be present to support the acute phase with the stroke neurologists who are often going to be the ones initiating. But we need to be there to make sure that the family physicians, the primary care physicians, they have questions when the patients have questions, that they know that they can come to us and say, how does this fit in? How does this fit into the larger cardiovascular risk factor modification we're doing with blood pressure, with lipids, with antithrombotic agents, understanding how they may or may not contribute to bleeding and not overreacting to stop drugs right away. I think we really need to understand how this fits and how it's different from the current DOACs, so that we're not treating it in the same way.

They really are different and distinct, and that means that we're going to be able to treat them differently longitudinally. And when patients present with cardiovascular conditions like a heart attack and require a stent placement or something like that.

Dr. Siegal:

It's that multidisciplinary care is very important. Education is very important. Collaboration is very important. All good principles.

Dr. Weitz:

I think the biggest takeaway is what we started with, and that is that it now looks like it's possible to uncouple thrombosis and hemostasis. And that's always been the holy grail of anticoagulation has been to attenuate thrombosis with little or no disruption of hemostasis. And the DOACs took us one step closer to that compared with warfarin.

But now we've gone that extra mile, and we saw a phenomenal result in OCEANIC-STROKE, with a big reduction in the risk of recurrent stroke and no increase, no significant increase in bleeding.

Dr. Sharma:

So, you know, I think for the first time in 50 years, we have a new option, something other than aspirin, which was the standard. The results apply broadly to patient populations, older, younger, men, women, stroke severity and stroke subtypes. So, you know, I think the biggest takeaway is this will be easier to use than other agents we use before. We don't have to be as selective. And it should apply to most of the non-cardioembolic ischemic stroke patients you see.

Dr. Barnes:

For me the OCEANIC-STROKE trial had two really important takeaways. And the first was not just that it reduced the risk of recurrent stroke, but even in the patients who had a recurrent stroke, it was less severe. And I think that's really remarkable. Not only are we preventing the recurrences, but if they happen, it's less likely to be that long-term disabling stroke.

That's really an important finding. And then secondarily. Not only are you preventing stroke recurrence, but you're doing so with no increased risk of bleeding compared to placebo.

And that's really remarkable. We haven't seen that kind of an efficacy safety balance in most of our antithrombotic strategies to date.

So those are two very exciting outcomes for this trial.

Dr. Weitz:

I'd like to temper that. When you say no increase, no significant increase. Yes. The point estimates for some of the if we're higher, which you would expect with an anticoagulant first but no significant. We've never seen that before. And I guess the other point to make, which you started with Mike, is that, you know, we've had all this action around atrial fibrillation and strokes associated with it with the DOACs, but this is looking at the majority of ischemic strokes, the non-cardioembolic strokes.

And we haven't had much except for maybe the dual antiplatelet therapy for a short period of time has added a little bit of bang, but now we've got something that works. And you know there wasn't really much of a difference in the effects on those who got dual antiplatelet therapy or those who didn't?

I thought this might really have a big effect in patients who got aspirin only. So, you know, is it possible that in the future we'll see monotherapy with a factor 11 inhibitor and you know, drop the aspirin?

Dr. Sharma:

It's a very tempting thing to think of. I would caution people right now that that comparison of dual monotherapy wasn't randomized. So, patients were placed on it for a specific reason. And you're quite right. On top of that, we saw similar efficacy whether you're on two antiplatelets or one.

Dr. Siegal:

So, I think we'll come to a close. It's been a pleasure having this discussion with you all. Thank you so much for your insights. Very enlightening. And we'll talk to you again soon.

Dr. Weitz:

Exciting times.

Announcer:

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