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

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# Engineering Safer Antithrombotic Strategies for Secondary Stroke Prevention

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**Chapter 1**

**Dr. Caso:**
Hello, my name is Valeria Caso. I'm a neurologist from Italy. I'm the chief of the Saronno Hospital from the neurology and stroke unit.

These are my disclosures. All fees were paid to my research institution.

So the risk of mortality and the poor outcome increases as after each recurrent stroke. So it means when you have a second stroke, you have a ninefold greater risk of being hospitalized. So the most important issue, that up to 37% of stroke occurs at 3 years, and these patients are 2.4 times likely to be hospitalized follow-up compared to control. So it means their quality of life is different from a patient who did not have a stroke.

When we're talking about stroke, you have to think that stroke is much more a container of different diseases, we can have 26% of cardioembolic stroke, which are associated with atrial fibrillation, and the rest, the 75%, are included: small vessel disease, large artery disease, cryptogenic—so-called cryptogenic, which means we don't have really the cause, unknown causes, more than one cause. Sometimes you have atrial fibrillation, you have large vessel disease, so it's very difficult to give them the correct cause.

For this, we have clear guidelines, and especially for minor stroke. So if we have a minor non-cardioembolic ischemic stroke or TIA in the past 24 hours with low NIH less than 5, the guidelines recommend to start a dual antiplatelet therapy with aspirin and ticagrelor and maintain it for 30 days. In a NIHS below 3, to have a dual antiplatelet therapy with aspirin and clopidogrel for 21 days. TIA ABCD more than 4 or ABCD more than 6, again, to maintain; when you have more than 6, aspirin plus ticagrelor for 30 days; more than 4, aspirin and clopidogrel for 21 days.

Then the continuation of the single antiplatelet therapy is based on the local protocol. In some countries you prefer aspirin, in other clopidogrel. It's also due to patients' preference.

And then the long-term antiplatelet therapy is single antiplatelet therapy for the rest of the life. If there is a presence of CAD or PAD, then there is a recommendation to a start low-dose DOAC with aspirin, or in some cases when we have intracranial stenosis, you can have a


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long-term DAPT.

So here I show you how complex the world of stroke is. Here we have Marco, a 65-year-old man, sudden onset of aphasia, right hemiparesis. He was admitted after to a hospital. He could not perform any kind of revascularization. He had a clinical history of smoking, hypertension. So you see a very severe vascular compromised feature. He had a stenosis of the left cerebral artery. We started clearly DAPT because NIH was 0. We gave him all the good indication to lose weight, start statins. But he had a worsening of the hemiparesis, and you can see that what we did was not enough for him.

But life is not very easy in stroke medicine. You can also have the opposite situation that you have a mild NIHSS of score like in this patient 72 year with a conjugate gaze deviation and right homonymous hemianopia and vertebral stenosis. We did the same, and what happened was a severe bleeding, and unfortunately, the patient died.

So this led us to sit together. This is something that we did together, not only as a physician because it's easy; we like the science. But when you speak with patients and they tell you what they feel, their fears of getting a new stroke, and how you have to live with the sequelae of stroke, we create this expert consensus where we clearly said that there need to be a sustained investment on the secondary stroke prevention management, support new treatment options. They are needed to improve the quality of life of patients, carriers, and achieve long-term savings. And national plans should include secondary stroke prevention, and clear guidelines and policies will be required to support this goal.

Thank you very much for your attention.

**Chapter 2**

**Dr. Shoamanesh:**
Hello, I'm Ashkan Shoamanesh. I'm a stroke neurologist at McMaster University, and I'm pleased to be speaking today on factor XI inhibition, the results of the OCEANIC-Stroke trial, and what this means for secondary stroke prevention of non-cardioembolic ischemic stroke moving forward.

These are my relevant disclosures. And most importantly, I served in the leadership roles of the PACIFIC-Stroke and OCEANIC-Stroke trials that tested asundexian for this indication.

So what makes factor XI inhibition quite attractive as a potential target for stroke prevention is its ability to uncouple pathologic thrombus formation from hemostasis. Patients with non-cardioembolic ischemic stroke have a high risk of recurrent stroke of about 7% in the first year. And thus far, escalating antithrombotic therapy beyond short duration dual antiplatelet therapy has been constrained by excess bleeding with very little gain in terms of further ischemic stroke prevention.

But factor XI has a unique positioning in the coagulation cascade, allowing its inhibition to theoretically inhibit our ability to develop pathologic thrombi while still preserving hemostasis to stop bleeding if someone has vessel injury. And the main reason for that is that when someone has vessel injury, there's a lot of tissue factor that exists within the vessel wall, and its exposure to the circulation leads by itself to a large thrombin burst through the tissue factor factor VII complex that is sufficient to stop bleeding or create a hemostatic plug. And factor XI has a very minor subsidiary role in this context.

In contrast, in situations where there's less tissue factor, such as in the setting of plaque rupture, the initial thrombin burst is not sufficient in of itself to cause pathologic thrombi. It really relies on a thrombin amplification loop for a small clot to subsequently become a larger clot that either leads to vaso-occlusive or thromboembolic diseases that lead to stroke. And in contrast, factor Xa's inhibitors thus far, for instance, they're actually part of a common pathway for both pathologic thrombi and hemostasis, and that's why inhibiting them will still result in excess in major bleeding.

Now, this was a hypothesis with a strong foundation in the coagulation cascade but also supported by substantive early evidence that what actually got people interested in factor XI as a target was clinical observations in patients with inherent factor XI deficiency who are observed to have lower rates of ischemic stroke and venous thromboembolism relative to their general population without a spontaneous major bleeding phenotype.


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These initial observations were explored further in animal models, where it was shown that you can inhibit or knock out factor XI, resulting in lower clot volumes and weights without excess bleeding, and that also could occur if that the factor XI inhibition was used on top of antiplatelet therapy. And then there were Mendelian randomization analyses that replicated these findings, in that genetic polymorphisms that lead to higher factor XI levels are associated with increased risks of ischemic stroke, increased risk of VTE, but not major bleeding.

So having this information in hand and combining it with some observations from a trial that was conducted at our institution, the PHRI, years earlier, called the COMPASS trial, where dual pathway inhibition combining a factor Xa inhibitor, in that situation it was rivaroxaban 2.5 mg twice daily, with aspirin led to a 50% reduction in stroke in patients with stable advanced systemic atherosclerotic disease. But there, there was some partial offsetting harm from increase in major bleeding.

Having that information in mind, we were very eager to test the hypothesis of dual pathway inhibition, but now with the opportunity to do it with a safer agent, that being asundexian, a factor XIa inhibitor. This kind of evidence across multiple levels of evidence from early clinical observations, animal studies, of course, has generated substantial interest amongst multiple companies in developing factor XI inhibitors. These are either direct factor XIa inhibitors, which are small molecule oral agents, or they're factor XI/XIa inhibitors, antisense oligonucleotides, monoclonal antibodies, and they're being tested across various indications that are shown on this slide.

And for stroke prevention, one thing that was historic is that this was the first time we had dose-finding studies of an antithrombotic agent specifically for stroke prevention in phase 2 prior to moving along to phase 3. That was the AXIOMATIC-SSP and PACIFIC-Stroke trials that we led out of my institution, the PHRI, which ultimately culminated in the OCEANIC-Stroke trial, which is the first completed phase 3 trial that we'll talk about in a second, and the ongoing LIBREXIA-Stroke trial that has yet to complete follow-up.

So OCEANIC-Stroke was a placebo-controlled, double-blind, event-driven, phase 3 randomized trial that was comparing asundexian 50 mg daily compared to placebo. The 50-mg dose was the most promising dose that emerged from the phase 2 PACIFIC-Stroke trial. And this was being tested in patients with non-cardioembolic ischemic stroke or high-risk TIA that were due to receive antiplatelet therapy, either dual antiplatelet therapy or single antiplatelet therapy. And this was a large global initiative conducted at over 700 sites in 37 countries.

Patients were eligible if they were 18 years of age or older and presenting within 72 hours of either an ischemic stroke or a non-cardioembolic ischemic stroke or a high-risk TIA. If they had an ischemic stroke, they had to have an NIH Stroke Scale of 15 or less, so mild to moderate stroke severity. And if they were a TIA, they had to have high risk of recurrence defined by an ABCD2 score of 6 or 7.

All patients need to have been planned to receive antiplatelet therapy. And in patients who had non-lacunar strokes, there was no additional enrichment criteria needed. So that is one misconception about the design of the trials that everyone required atherosclerosis, and that simply is not the case. If someone had a non-lacunar stroke, they could get into the trial without any additional enrichment criteria.

However, based on some observations from phase 2 PACIFIC-Stroke study, if someone had a lacunar stroke, they required additional atherosclerotic enrichment criteria to be eligible. That could have either been a medical history of symptomatic atherosclerotic disease in any vascular bed throughout the body, or it could have been any degree of atherosclerosis identified on CT angiography of the arch, cervical arteries, or intracranial arteries. That atherosclerosis did not need to be stenotic. It did not need to be proximal to the infarct or implicated in the cause of it. Just present. So that's actually a large proportion of the lacunar stroke patients.

Key exclusion criteria included a history of AF or other cardioembolic sources requiring anticoagulation, ischemic stroke within 7 days of the index event, strokes occurring surrounding certain procedures, end-stage renal disease requiring dialysis, and if someone had hemorrhagic transformation, they were eligible if it was just minor petechial bleeding. However, if there was a parenchymal hematoma that had formed within the infarct or surrounding its borders or remote from the infarct, those patients were excluded.

We allowed eligibility of patients that had MRI markers of small vessel disease like microbleeds or siderosis. However, we did exclude patients that had a history of non-traumatic intracranial hemorrhage, as well as those that had major GI bleeding within the previous 6 months.

Eligible patients were randomized 1:1 to receive the asundexian 50 mg daily or placebo on top of background antiplatelet therapy, and


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the randomization was stratified according to intention to use either dual or single antiplatelet therapy. In total, over 12,300 patients were randomized in this trial, and the intervention period was between 3 and 31 months to a common termination date in this event-driven study.

The primary efficacy outcome was ischemic stroke, and the primary safety endpoint was ISTH major bleeding. A number of secondary efficacy and safety outcomes were also prespecified, and they're listed on this slide, and we'll go through them during the results tables.

When we look at what proportion of stroke patients received acute revascularization therapy prior to study entry, we see that over a quarter of patients, 27%, received either IV thrombolysis or endovascular thrombectomy, 20% received IV thrombolysis alone, 4% received EVT alone, and another about 4% to 5% received the combination of IVT and EVT. The only caveat here is that in these patients, you had to wait at least 24 hours following the revascularization treatment before they were eligible for randomization.

The Aalen-Johansen curve for the primary efficacy outcome of ischemic stroke is being shown here. And as you can see, there's early separation between asundexian and placebo with lower ischemic stroke in the asundexian arm, and then there is the continued separation in the curves throughout the duration of follow-up. And overall, asundexian was shown to reduce the hazard of ischemic stroke by 26%.

When we look at other secondary outcomes, we also saw a similar reduction in all stroke when combining hemorrhagic with ischemic stroke. We saw a 17% reduction in a 3-point MACE endpoint of cardiovascular death, MI, or stroke. A similar reduction when we substitute cardiovascular death for all-cause mortality in this 3-point MACE endpoint. And we also saw suggestion of a similar effect size for ischemic stroke within the first 90 days. However, due to a lower number of events and reduced power, the upper bound of the confidence interval for this just crosses the null at 1.02. And then importantly, we saw a robust 31% reduction in disabling stroke. And what's not being shown here is that we subsequently in secondary analysis also showed that the breakthrough strokes that occur in asundexian were also less disabling and were less likely to require endovascular thrombectomy, suggesting less likelihood of having a large vessel occlusion.

And we've seen this before in the cardiac literature in patients with AF, where anticoagulation not only prevents ischemic stroke, but the breakthrough strokes that occur in anticoagulation are smaller strokes with smaller clots that are less disabling. And I think this is the first time that I'm aware that we're seeing a similar paradigm in non-cardioembolic ischemic stroke patients.

When looking at our primary safety endpoint of ISTH major bleeding, there was no differences between the two treatment groups. There was also no differences in secondary safety endpoints such as ISTH major bleeding combined with clinically relevant non-major bleeding, clinically relevant non-major bleeding by itself, symptomatic intracranial hemorrhage, hemorrhagic stroke, fatal bleeding, and impressively no difference in minor bleeding, which I find quite remarkable.

And I always have to remind myself when I see the safety data that this is a placebo-controlled trial, in that we're not going against an active comparator; this is a non-active comparator. This is really achieving the holy grail, and the first time in history that we've seen this ability to truly uncouple pathologic thrombus formation from hemostasis, and we're not seeing offsetting increase in major bleeding or other bleeding outcomes with an antithrombotic agent.

These are the Aalen-Johansen curves for the ISTH major bleeding, primary safety endpoint that we discussed.

And then the third important piece of information from this trial is that there was consistency in the treatment effect across all prespecified subgroups. It didn't matter how old you were, your sex, what part of the world you came from, your race, whether you had hypertension, diabetes, history of stroke or TIA, medical history of atherosclerosis, vascular imaging of atherosclerosis, if you had lacunar infarct or not, whether you had an ischemic stroke or TIA as your qualifying event, which stroke subtype you had, whether you had your event within a certain time frame prior to randomization, whether you got revascularization treatment, your stroke severity at onset, or even if you were ultimately deemed to receive dual antiplatelet therapy or single antiplatelet therapy. And two-thirds of the population did get short-duration dual antiplatelet therapy; the overall treatment effect for stroke was consistent.

We're going to dive into a little bit on the data on ischemic stroke subtype, but just if you note, although patients with cardioembolic stroke requiring anticoagulation were excluded, as were patients with stroke of other etiologies like vasculitides, we did have a few patients who were identified to have these etiologies post randomization. And although the numbers are small, it is interesting that the


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effect estimates, even in these other stroke subtypes, favors asundexian versus placebo.

The main prespecified secondary analysis that we did in this trial was looking at treatment effect consistency or a potential for heterogeneity across ischemic stroke subtypes, because in the phase 2 PACIFIC-Stroke trial, there was suggestion that patients that had atherosclerotic disease may benefit more from treatment than other stroke subtypes. So we focused on the key 3 subgroups of hosts that were eligible for the study: those with large artery atherosclerosis, small vessel occlusive disease, or strokes of undetermined etiology. And in this third subgroup, we also broke it down to those that qualified specifically for embolic strokes of undetermined source versus not.

And what we saw is overall consistency in the treatment effects. The cause-specific hazard ratio ranged between 0.61 in patients with strokes of undetermined etiology to 0.82 in those with large artery atherosclerosis, and the p-value for the treatment interaction was neutral.

So effectively, the take-home message is that all stroke subtypes that were eligible for entry into the study benefited similarly. We also saw similar consistency in the outcomes of all stroke as well as disabling or fatal stroke. In addition, we see consistency in safety in that asundexian did not increase the risk of major bleeding, symptomatic intracranial hemorrhage, or hemorrhagic stroke, irrespective of the stroke subtype, including in patients with lacunar stroke who are at highest risk of hemorrhagic stroke.

Actually, what's interesting and, I guess, reassuring more than anything is that we actually see numerically less hemorrhagic stroke with asundexian versus placebo. I'm not implying the drug prevents hemorrhagic stroke but not only are we now seeing a significant excess, we're seeing a numerically reduced rate, which it just builds confidence that there is no excess in this outcome.

And then, lastly, on top, on the heels of 4 randomized trials that thus far were unsuccessful in extending the envelope for secondary stroke prevention in patients with embolic strokes of undetermined source beyond a long-term antiplatelet monotherapy, in our trial dual pathway inhibition combining asundexian with background antiplatelet therapy led to a robust 47% reduction in patients with ESUS, and this approach is with significance, with a p-value interaction of 0.07.

The conservative take-home message is that patients with ESUS benefited similarly from this regimen as patients with non-ESUS. However, there is hypothesis generation here that there may be even more treatment effect in patients with ESUS, where actually the absolute risk reduction was 4%, a number needed to treat of about 25 versus the overall number needed to treat of 50, where there was a 2% absolute reduction in all-comers in this study. And again, these benefits were seen without offsetting excess in ISTH major bleeding.

So to conclude, the phase 3 OCEANIC-Stroke trial enrolled a large global representative sample of non-cardioembolic ischemic stroke subtypes. Asundexian reduced ischemic and disabling stroke without increasing ISTH major bleeding or intracranial hemorrhage, irrespective of the underlying etiology. And asundexian now provides a very novel and also very exciting, efficacious, and safe secondary stroke prevention strategy for preventing stroke in patients with non-cardioembolic ischemic stroke, irrespective of the subtypes that were eligible for study entry. And I think this will be a paradigm-changing, practice-changing new standard of care to safeguard healthy aging without loss of function in these patients.

**Chapter 3**

**Dr. Gibson:**
Hi. Mike Gibsen, coming to you live from ESC 2026, and we're talking secondary prevention after stroke. I'm joined by my expert panelist here today, Valeria Caso. Welcome, Valeria.

**Dr. Caso:**
Thank you. Welcome.

**Dr. Gibson:**
And Ashkan Shoamanesh, welcome.

**Dr. Shoamanesh:**


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Pleasure to be with you, Mike.

**Dr. Gibson:**
Let's get started. Let's talk about the advances that we've seen in this field. I mean, for decades we had aspirin, sometimes DAPT, for prevention after stroke, but I think we had a landmark study that's been recently presented, at least published, talking about how factor XI inhibition may change the landscape. Let's dive into some of the opinions of our panelists.

So let me ask you this, Valeria. You have a patient in front of you. They've had a non-cardioembolic ischemic stroke or high-risk TIA, they're on some antiplatelets, but they're still at risk. How do you identify the right patient for this new therapy?

**Dr. Caso:**
Thank you for this question. This is very important issue because we, as a neurologist, you look at your patient, you feel the brain, you understand when there's a higher risk, especially when there's an intracranial stenosis. This is one of the most feared conditions that we have, combined with respect to such as diabetes, hypertension, when they're smoking, that they are completely in an absolute high-risk situation. Or currently, the guidelines recommend to maintain DAPT for 3 months. But the moment that we stop the DAPT therapy after 3 months, you always feel that something could happen after because even during the 3 months you feel that the patient is not so well protected. You go with statin, every kind of drug that you can add in order to lower the risk, but you still have this feeling: can I do something more in order to protect this patient better?

**Dr. Gibson:**
So, Ashkan, when you're sitting across from that patient, how are you sizing things up? How do you decide?

**Dr. Shoamanesh:**
Well, I think the first thing to appreciate is that all non-cardioembolic ischemic patients have a high risk of recurrence. So about 7% per year. So there is no one where I feel comfortable with existing therapies. I think there's an unmet need in all-comers.

But those that have specific features that Valeria already outlined, they're at even a higher risk. She's already mentioned things like diabetes, smoking, intracranial atherosclerotic disease. Some other risk factors that were identified to predict a higher risk of ischemic stroke in the OCEANIC-Stroke trial were things like older age, Black race, Asian race, a prior history of stroke other than the qualifying event, as well as any medical history of atherosclerotic disease. So these are some additional features that we certainly consider when approaching these patients.

**Dr. Gibson:**
So what's some of the main messages someone should take away from the OCEANIC-Stroke trial, Ashkan?

**Dr. Shoamanesh:**
I think there's kind of 3 key take-home points. At least that's the way I look at the data. One is that, yes, there's this large relative reduction of 26%, but even in today's current era of optimal stroke prevention—that's optimization of glycemia control, blood pressure control, lipid-lowering therapy, and two-thirds of this population having received at least short duration of dual antiplatelet therapy—we see a robust, about 2% absolute reduction, a number needed to treat of about 50 at 1 year, which is quite, I think, remarkable given this incremental gain at this stage in the game for stroke prevention.

The other piece is that we've really achieved the holy grail, and we've talked about this before, in being able to see these large benefits without any offsetting harm in major bleeding, and we didn't see excess minor bleeding even, with a large trial, that there was a large number of events to feel kind of confident in the results. I think that's historic.

And then the third piece, which was just the cherry on top, was the level of consistency that we saw along all the different prespecified subgroups. It didn't matter how old you were, it didn't matter whether your stroke was lacunar or non-lacunar, whether you had atherosclerotic disease or not, whether your stroke subtype, there was consistent benefit with asundexian across the board when used on top of existing antiplatelet therapy and compared to placebo.

**Dr. Gibson:**
We have number needed to treat, number needed to harm. You heard me yesterday talk about number needed to blame. We don't want


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to get blamed for bleeding. Here we have a solution where you don't get blamed for bleed because there's no excess bleeding.

**Dr. Shoamanesh:**
Yeah, I don't think we've ever been in a situation like this before with antithrombotic.

**Dr. Gibson:**
There's an NNB of 0, yeah.

**Dr. Shoamanesh:**
Yeah, which is very phenomenal.

**Dr. Gibson:**
So you're a stroke neurologist. What special things do you take home from that?

**Dr. Caso:**
I can only echo what Ashkan already said, but the lack of additional bleeding risk is something that you can bring to the neurological community. Also, general physician because it's easy for me to handle antiplatelets because I'm used to hemorrhagic transformation. I can classify; I can deal with it.

But when you go out of your academic world, where you are using thrombolysis, thrombectomy, you have all very severe patients, then it's easy to manage secondary prevention. But outside of this, there are a lot of physicians who want a safe drug and to say, listen, you can reduce the risk without reducing the safety of the patient. It's too nice to be true. So.

**Dr. Gibson:**
It's true, though. But we call it nuisance bleeding, but it's not a nuisance. Yes, I mean if you're wearing long sleeve shirts because you're embarrassed of all the bleeds, if you're walking around with Kleenex because you have a nosebleed all the time, that's more than a nuisance, right? So that's also reassuring to patients as well as doctors, right?

**Dr. Caso:**
Absolutely.

**Dr. Shoamanesh:**
A huge psychological toll of these minor bleeds, and also it contributes to lack of compliance, which reduces efficacy. So it's a very important finding.

**Dr. Gibson:**
People don't understand, when someone bleeds, well, they're 80 some years old, "I don't know if it's the pink pill, the green pill, or the blue one. I'm just going to stop all of them," and then they stop. They fall off the track of evidence-based medicine. They have worse outcomes.

So, Valeria, as you think about the use of a single antiplatelet agent and guideline-directed dual antiplatelet therapy, the average was about 28 days, for instance, in the trial. Where's factor XI fit in within that whole process? When do you start it? When does it fit in?

**Dr. Caso:**
From the trial we start very early, within 72 hours. We see the benefit not really very, very early, but over time. And what you see, and I think this is also important message that we have to give to the audience that the effect is increasing over time.

So it's still the whole story we need to understand of how long we need to treat these patients because, at a certain point, you cannot say we have a very efficacious drug, very safe drug. Why should I stop it? Especially when the drug curves are diverging over time. So it's not like DAPT because we clearly know from all the trials we did on DAPT that the longer you take DAPT, the higher is the risk of bleeding. This is not the case with factor XI. There is a consistency of maintaining zero additional risk to aspirin.

**Dr. Gibson:**


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You said an average of 4 days, but if some prescribing docs might be nervous about hemorrhagic transformation but there was no excess risk of it, so you can start at 4 days safe.

**Dr. Caso:**
Yes. Especially all—and Ashkan know this very well—all the different severity of strokes, there was no difference. Single duct, there was no difference in bleeding risk. And this is patients who were treated by thrombolysis, some who were treated by thrombectomy. So real patients that we see every day in our stroke unit. So this is something that reassures because it's not the easy world of a randomized trial because you have highly selected patients. Here we had patients all over the world, including China, Asia, South America, so low- and middle-income countries, which is very important because this is a different standard of care, and these results were consistent throughout all the countries.

**Dr. Gibson:**
As trials always say, is when something works, it works. It works in everybody, and that was the case here. You look at those forest plots, everyone lines up on our side. I guess I was actually very surprised that all the different stroke subtypes, similar results. All the different DAPT, no DAPT, same results. So very consistent results. So it looks like everyone has a similar benefit. But Ashkan, out in practice, you got to start somewhere.

**Dr. Shoamanesh:**
Yes.

**Dr. Gibson:**
So what kind of patient really kind of rises to the top of your list to bring and start?

**Dr. Shoamanesh:**
So I think, given the robustness of the data and to be a purist, you would start with the trial eligibility criteria. These are patients presenting within 72 hours of symptom onset who had non-cardioembolic ischemic stroke or high-risk TIA. Okay, so that's your starting block. I wouldn't try to reduce or subgroup that any further, just based on the consistency of the results that we saw and the fact that we're going to be withholding a very effective, safe treatment from a large proportion of patients if we were to take that approach.

And then amongst those, with the one enrichment criteria that we did have in the trial that's worth noting and clarifying because there is this misconception out there that you had to have atherosclerosis to enter the trial. That is not true. Only patients who had a lacunar stroke required atherosclerotic enrichment criteria, which could have been any history of symptomatic atherosclerotic disease in any vascular bed, or if any degree of atherosclerosis seen on CT angiogram of their kind of cerebral circulation, whether it be the arch, the neck, or the brain. So that would be the vast majority of lacunar patients as well. And in patients that had non-lacunar strokes, they were eligible without enrichment criteria, right?

So that is the one caveat that needs to be kind of taken and understood, I think, when you refine the data in a pure sense, but that's a starting block.

I think from there, when you look at the Kaplan-Meier curves and you're seeing—or the Aalen-Johansen curves, rather, that were used in the study for primary analysis, you're seeing continued separation of curves over time, you then start to wonder, well, to be honest, this is probably going to work even if I go beyond that 72-hour window. That 72-hour window really came from gap studies where we saw the majority of separation within the first 72 hours, and that's what we were expecting in this trial. That informed the kind of trial design, but we actually saw something very different that the separation and continued benefit over long-term follow-up, which was also excellent to see.

**Dr. Gibson:**
Yeah, so some benefits acutely, as we usually see, but then they went on, and the curves continue to diverge over time.

Now we said there's, quote, no bleeding. I think we've got to be clear. So excess bleeding. Yes, there may be some bleeding. I mean, they're going to be on aspirin. That can cause some bruising, some bleeding, but the thing here is there's no extra bleeding by adding this drug on.


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Any kind of final take-home messages?

**Dr. Shoamanesh:**
I'm really excited to hopefully start using this drug in clinical practice as soon as possible. There was prior review by the FDA and some of the regulatory agencies in China, and I know there's a few that are going in Europe and elsewhere in the world, like my own country, Canada. So a huge advancement, I think, a paradigm change in stroke prevention, and really excited what it's going to mean for patients and maintaining their independence and function by preventing stroke recurrence.

**Dr. Caso:**
Yeah, absolutely. We see now our patients are getting younger. What I see, many males between 50 and 70, high burden of risk factor. And when you look at the low- and middle-income countries, the situation is even worse, all in working age. So we need absolutely to find—we need to integrate and implement the drug as soon as possible in order to protect patients from recurrence. Because the journey through a stroke is such a hard journey. To do it again and again, it's something that you cannot survive. And also the cognition, one lesion, there's physiotherapy. You can do a lot, but the second one, the third one is not. The person, you will lose this person, so we need to protect these persons.

**Dr. Gibson:**
I've been in this field for 40 years. All types of antithrombins, antiplatelets. We've always searched for the holy grail, which is effectiveness with no bleeding. We finally have it for the first time ever. Probably the most important trial in decades in secondary stroke prevention.

Thanks for listening. Thank you, Valeria. Thank you, Ashkan. Hope you enjoyed the show.

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