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Rethinking Secondary Stroke Prevention: The Emerging Role of Factor XI Inhibition

Announcer:
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Dr. Sharma:
Hello, I'm Mike Sharma, stroke neurologist at McMaster University and the Population Health Research Institute. I’m going to be talking about unmet needs in stroke.

Now, as a physician, I tend to think less in statistics and more about people. So let me introduce you to Walter. Walter is a 77-year-old man who is 48 hours out from a lacunar infarct. This is a second ischemic event he's had in 6 months. He does have history of GI bleeding on dual antiplatelet therapy, and has CKD as well, with an EGFR of 35 mils per minute. He presents with right-sided facial weakness, which you see in the picture, and difficulty speaking. Currently he’s treated with single antiplatelet therapy. In his case, clopidogrel.

We do have current therapies available. Dual antiplatelet therapy does carry an increased risk of bleeding, particularly with long-term treatment. And DOACs are indicated for cardioembolic stroke, but we do not have that in Walter's case at present.

Now, ischemic stroke—this may be startling to learn—globally, is the second most common cause of death after ischemic heart disease, and this has increased in terms of prominence over the last decade or so. There are 70 million people in the world with stroke, and 70 million years lost due to death and disability. There are 3.6 million deaths yearly due to stroke in the world.

Atrial fibrillation is also an extremely important condition, with over 50 million people affected, and 8.4 million years lost due to death and disability. The incidence of atrial fibrillation increases significantly with age, and the global population everywhere is aging rapidly.

We think of stroke in terms of subtypes. By the way, hemorrhagic stroke has decreased. When I was a resident, it was about 20% of all strokes; currently it’s 13%, mostly due to improved treatment of blood pressure. Of the 87% of strokes that are ischemic, about 1/4 of them are cardiogenic, and a small percentage, 5 to 10%, are due to other known causes, such as vasculitis or dissections. The main subtypes of ischemic stroke we deal with, however, are large artery atherosclerosis, small artery disease, and cryptogenic, which include the ISA subtype. Each of these have a substantial rate of recurrence per year.

There are a number of unmet needs for secondary stroke prevention. First off is the burden of treatment. Patients that we interview or we plan trials tell us there are problems with medications which cause side effects including bruising or minor bleeding with antithrombotics. Clinical trials sometimes are not representative of the patients that are going to be treated. This includes issues of sex as well as race and geographic spread. There is needed as well an approach to the management of breakthrough bleeding, including intracranial bleeding. Factor XI and XIa inhibitors are being investigated to provide antithrombotic efficacy with less intracranial and major bleeding, which could address an unmet need in the non-cardioembolic and fragile AF populations.

There are a number of existing clinical guidelines. These are two of them from the AHA as well as the European Stroke Organization.

Both of them recommend short term dual antiplatelet therapy with aspirin and clopidogrel, either for 21 days in case of the European guidelines, or 21 to 90 days for the AHA guidelines, for individuals who have had a recent minor event on the NIHSS of 3 or less.

Based on the THALES trial, there's also a recommendation for the use of ticagrelor or an aspirin for 30 days in individuals who have an NIHSS of 5 or less and can be treated fairly soon, that is to say within 24 four hours of onset.

These guidelines have had an impact on prescribing patterns in the US. The green portion of this graph shows the increase in dual antiplatelet prescriptions as the years pass. Long-term anticoagulation has been used in a few clinical trials. These three trials, IST, WARSS, and WASID used different anticoagulants for different periods of time. IST was more acute, with WARSS and WASID being longer, and WASID in particular being directed at symptomatic intracranial stenosis. In all of these cases, you saw either no impact or a decrease in recurrence, which was matched by an increase in bleeding. The previous anticoagulants have not worked well for reducing ischemic stroke.

A new way forward was demonstrated with a COMPASS trial. Now, the COMPASS trial randomized patients who had existing atherosclerotic disease, which could be in the coronary arteries, the carotids, or peripheral vascular disease, to one of three different interventions, either aspirin by itself, low-dose rivaroxaban with aspirin, that is to say rivaroxaban 2.5 mg BID or rivaroxaban by itself.

What you see is an effect of the combination of low-dose rivaroxaban and aspirin, which reduce stroke compared to aspirin alone. Rivaroxaban by itself was not effective for this indication. They had reduction in ischemic stroke, was accompanied by an increase in major bleeding, as well as an increase in fatal bleeding, symptomatic critical organ bleeding, as well as bleeding leading to hospitalization. This was a major limitation in implying these results.

So to summarize the COMPASS trial, what we found was compared to anticoagulation by itself, anticoagulants added in the right dose to aspirin were effective, though at the cost of major bleeding with rivaroxaban. Remember that rivaroxaban by itself did not reduce the occurrence of stroke. In the COMPASS trial, we included patients who'd had a stroke in the last 3 months, so these results do not apply to people who've just had an acute event.

So with our current treatments, patients still experience recurrent ischemic stroke, and this is true of all major subtypes. The fear of intracranial hemorrhage and major bleeding often leads to dose reduction, discontinuation, or avoidance of anticoagulation in high-risk patients.

We'll talk now of the role of factor XI and activated factor XI in hemostasis and thrombosis.

Fundamental to the use of these agents, and the ability to uncouple bleeding from hemostasis is the differential effect that activated factor XI has in these two settings. In the setting of vessel damage, which is to say injury to the blood vessel where hemostasis is required, the blood is exposed to large concentrations of tissue factor. Tissue factor, coupling with factor VII and acting through factor X, rapidly produces a hemostatic plug without the involvement of factor XI. In settings of intravascular thrombosis, which produce pathologic thrombi, there is relatively little tissue factor, and in this case the feedback loop, the thrombin amplification loop, which involves factor XI, is much more important. Interrupting factor XI, and specifically activated factor XI, would be expected to affect pathologic thrombosis while leaving hemostasis preserved.

There are a number of routes of evidence which allow us to think of activated factor XI as a target for therapeutic manipulation. About 1 in a million of us have genetic deficiency of factor XI. This is concentrated in some populations, particularly in Israel, where 1 in 450 Ashkenazi Jews have a reduced level of factor XI. In that population, we rarely see spontaneous hemorrhage but do see a reduction in the risk of stroke, specifically, as well as venous thrombosis. Mendelian randomization studies also support a role with higher levels of factor XI associated with an increased risk of stroke and lower levels associated with a reduced risk. Likewise, in animal studies, factor XI inhibition reduces the occurrence of intravascular thrombi and makes the thrombi less robust which is to say not quite as large nor as stable as thrombi with factor XI present.

Our current antithrombotics target different parts of pathologic blood clots. We should remember that every blood clot we deal with is composed of fibrin, platelets, and red cells in different amounts. Antiplatelet therapy particularly prevents the formation of platelet-rich arterial thrombi, while anticoagulants such as the DOACs prevent fibrin-rich clots. Factor XI inhibitors have this potential to uncouple thrombosis from hemostasis, prevent excess bleeding, and certainly in the OCEANIC-STROKE trial, be associated with a significant reduction in ischemic stroke, 26% in that case. The bleeding risk for ISTH major bleeding in OCEANIC-STROKE was not increased with the use of asundexian, coupled with antiplatelet therapy.

There are two oral factor XIa inhibitors currently in clinical trials for stroke, asundexian, where both the phase 2 and phase 3 trials are completed, and milvexian, with a completed phase 2 trial and a phase 3 trial which is ongoing. Asundexian and milvexian are both small molecule inhibitors that block the active site of activated factor XI and are orally administered; once a day in the case of asundexian and

twice a day in the case of milvexian. With asundexian, phase 2 studies with more than 4,000 participants showed more than 90% inhibition of factor XIa at peak and trough levels with no significant increase in major bleeding over placebo with or without antiplatelets. With milvexian, phase 2 studies with more than 2,300 participants showed no significant increase in major bleeding over placebo with or without antiplatelets.

Factor XI enhances the generation of thrombin through the thrombin amplification loop and reinforces clot formation after the initial trigger. Inhibition of factor XIa attenuates thrombin amplification and pathologic clot propagation. Lower factor XI levels are associated with a reduced risk of venous thromboembolism and ischemic stroke, supporting its pathological role in thrombosis. Factor XIa inhibition aims to uncouple thrombosis from hemostasis.

Dr. Shoamanesh:
Hello, I'm Ashkan Shoamanesh, and I'm pleased to be sharing with you trial data as well as the clinical implications of factor XIa inhibitors for stroke prevention. We'll begin by reviewing the OCEANIC-STROKE trial, which tested asundexian in patients with non-cardioembolic ischemic stroke or high-risk TIA. For this study, patients needed to be 18 years of age or older, presenting with an acute non-cardioembolic ischemic stroke or high-risk TIA within 72 hours of symptom onset, and planned to be receiving dual antiplatelet therapy.

These patients were randomized 1:1 to receive either asundexian 50 mg daily or matching placebo, and randomization was stratified according to either having planned dual antiplatelet therapy or single antiplatelet therapy for stroke prevention. All patients were followed for a minimum of 3 months, up to 31 months, for a common termination date in this event-driven study.

Here, we're demonstrating the eligibility criteria. Key inclusion criteria, as I mentioned, included being over the age of 18 and being within 72 hours of

symptom onset and presenting with a non-cardioembolic ischemic stroke with a stroke severity quantified on a NIH Stroke Scale up to 15, or having high-risk TIA with a risk of having a stroke post-TIA being quantified on the ABCD2 score with a cut off of 6 or 7. Patients were eligible for this study if they had a non-lacunar stroke. Or if they had a lacunar stroke, they required additional enrichment criteria, which included a history of atherosclerosis, such as coronary artery disease or peripheral artery disease. And if this was not present, evidence of plaque on imaging, and this could have been any degree of stenosis anywhere along the cerebral vasculature in the chest, neck, or brain. Again, this did not need to be proximal to the stroke; it was just some degree of plaque that protruded into the vessel lumen. As I mentioned, all patients needed to be planned for antiplatelet therapy. This was an add-on treatment.

And key exclusion criteria included a history of AF or other cardioembolic sources that required anticoagulation, ischemic stroke within the past 7 days of the index event, stroke following procedures or other specific causes, end-stage renal disease requiring dialysis as well as active non-trivial bleeding. And for instance, post stroke, if there was significant parenchymal hematoma formation as part of hemorrhagic transformation, those patients would have been excluded. But patients with asymptomatic hemorrhagic transformation or hemorrhagic infarction 1 and 2, or those with only MRI findings like microbleeds were permitted, as well as patients who had a history of non-traumatic ICH, significant GI bleeding within the past 6 months were also excluded.

As far as the primary efficacy endpoint, that was time to first occurrence of ischemic stroke, and a primary safety endpoint was ISTH major bleeding.

Secondary efficacy endpoints included all strokes, including hemorrhagic strokes, the composite of cardiovascular death, MI, or stroke, the composite of all-cause mortality, MI, or stroke, ischemic stroke in the first 90 days, as well as disabling stroke, which was defined as an mRS of 3 or greater at 90 days.

Secondary safety endpoints included composite of ISTH major bleeding or clinically relevant non-major bleeding, ISTH clinically relevant non-major bleeding in isolation, symptomatic intracranial hemorrhage, hemorrhagic stroke, fatal bleeding, as well as minor bleeding.

This is the cumulative incidence of the primary efficacy endpoint of ischemic stroke. As you can see, asundexian reduced the hazard of ischemic stroke by 26%, and that separation occurred early, on the Aalen–Johansen curves being demonstrated here, and that there was continued separation, importantly, throughout the duration of follow-up.

When looking at secondary efficacy endpoints, we also see reductions in all stroke, a similar 26% reduction in the hazard of all stroke, a reduction in cardiovascular death, MI, or stroke as a 3-point MACE endpoint. Similarly, the MACE endpoint

using all-cause mortality was reduced with asundexian versus placebo, and that although there was a reduction in ischemic stroke within the first 90 days, with a 16% reduction to hazard of this event, overall this did not reach statistical significance with the upper bound of the confidence interval just crossing the null of 1.02. However, overall, we believe that this was just the lack of power of the

study to demonstrate a difference for this endpoint at 90 days, because the overall effect estimates are consistent across the board, and that the confidence interval is just crossing the null. And importantly, we also saw a 31% reduction in the hazard of disabling or fatal stroke, which are, of course, the strokes of greatest clinical severity for our patients.

And impressively, this occurred without any excess in a primary safety endpoint of ISTH major bleeding. And actually, there was no excess in any of the prespecified bleeding endpoints across the board, whether it was the composite of ISTH major or clinically relevant non-major bleeding, clinically relevant non-major bleeding by itself, symptomatic intracranial hemorrhage, hemorrhagic stroke, fatal bleeding, or minor bleeding. Of note, actually, numerically, hemorrhagic stroke and minor bleeding were less with asundexian versus placebo, which is even more reassuring within the context of these neutral results.

And it's also, I think, quite important that minor bleeding is also not being increased in these patients, because, as we know, our patients are often quite disturbed by minor bleeds, if they have, for instance, easy bruising or epistaxis, and this often leads to discontinuation of their medications and antithrombotic agents, making them more vulnerable to thrombotic events. So not only will this provide a psychological benefit to our patients that there's no excess minor bleeding, but it also will improve adherence compared to other antithrombotics we've used in the past, and also that that would then translate to the efficacy that we're seeing here.

Also when looking at subgroup analyses, particularly when you think about the global context of this study, having enrolled over 12,300 patients from 37 countries, over 700 hospitals, we want to make sure that these findings are generalizable to the entire spectrum of patients that we see with non-cardioembolic ischemic stroke or high-risk TIA. And what was very reassuring and exciting for us was that irrespective of what we looked at in terms of subgroups, whether it was having had a non-lacunar infarct or a lacunar infarct at the time of qualifying event, whether the patient presented with an ischemic stroke or a TIA, whether they had large artery atherosclerosis, small vessel occlusive disease, a stroke of undetermined etiology, if they had, depending on when they came in relative to the timing from their stroke to randomization, whether they received revascularization therapies like intravenous thrombolysis or EVT, which actually occurred in over 1/4 of this population, irrespective of stroke severity, or irrespective of whether patients were to due receive single antiplatelet therapy or dual antiplatelet therapy, we see consistency in these results, in that asundexian provided benefit for ischemic stroke reduction in all these contexts.

So the key learnings from the OCEANIC-STROKE trial is that asundexian reduced the occurrence of ischemic stroke by 26% in this population, and that this efficacy was generalizable to the entire spectrum of patients that we see within this context, irrespective of age, stroke severity, sex, or the index event subtype. And this was seen without any increase in ISTH major bleeding between the placebo group and asundexian group. Anytime I see the safety data, I always have to remind myself that we're testing asundexian here versus placebo, not an active comparator. And very impressively, we're seeing no excess in any of the bleeding endpoints, including minor bleeding. And this is really now proof of principle, and the first kind of phase 3 trial that has shown that we are able to indeed to uncouple pathologic thrombus formation from hemostasis, really opening up a Pandora's box for the potential future indications with factor XI or XIa inhibitors.

I'll also like to highlight some of the ongoing phase 3 trials using another small molecule, the direct factor XIa inhibitor, and that's milvexian. There are two trials targeting stroke prevention with this agent. The first that we're highlighting here is the LIBREXIA-STOKE trial, which is testing milvexian at 25 mg twice daily versus placebo, on top of background standard of care antiplatelet therapy, similar to the OCEANIC-STROKE trial. Here, instead of 72 hours, the window for enrollment is within the first 48 hours, and the NIHSS cut off is a bit more conservative at 7, rather than 15, as we saw in OCEANIC-STROKE. And this trial is due to enroll roughly 15,000 participants, and should be finishing enrollment at the end of 2026.

Similar to OCEANIC-STROKE, the primary outcome for LIBREXIA-STROKE is time to first occurrence of ischemic stroke. And secondary outcomes will include any component of the composite of cardiovascular death, MI, or ischemic stroke, ischemic stroke in the first 90 days, as well as any component of major adverse vascular events.

Milvexian is also being tested to prevent stroke in patients with AF in the LIBREXIA-AF trial. In this trial, patients who are 18 years of age or older presenting with atrial fibrillation or atrial flutter who are eligible to receive anticoagulation and have either one or both of the following categories of risk: having an age greater than 75 years of age or a history of stroke, and if these weren't present, two or more of the following kind of CHA_2DS_2-VASc risk factors, which is age 65 to 74, hypertension, diabetes, vascular disease, or congestive heart failure, with the exception of sex, which is not being used due to more data that has come out since the development of CHA_2DS_2-VASc demonstrating that sex, in of itself, is not the strongest independent predictor of future stroke.

The primary efficacy endpoint here is looking at stroke prevention as well as the prevention of systemic embolism in a noninferiority design. And the primary safety objective is to demonstrate superiority in reducing ISTH major bleeding.

So how do we apply what we've learned regarding the clinical trials of factor XIa inhibition for secondary stroke prevention to patients

that we're going to be seeing

in practice? Well, some of the practical and implementation considerations include which stroke subtypes stand to benefit the most. Are factor XI or XIa inhibitors as an add on, or are they a replacement for current therapies? And what would be the optimal combination? The duration of treatment with factor XI and XIa inhibitors. And how should patients taking these agents be monitored? And can procedures be done on this treatment?

But what we've learned is that OCEANIC-STROKE has shown that the efficacy was not impacted by stroke severity, subtype, or patient age, sex, or the qualifying index event. And this means that the results are broadly applicable as long as the patients were eligible for the trial, irrespective of their individual kind of characteristics that were tested in subgroup analyses within the study. And most importantly, I think, when we think about things like safety in older populations, when we think about efficacy across a wide degree of stroke etiologies, we've seen this to be the case with asundexian in OCEANIC-STROKE, and that really, as long as patients were eligible, they benefited. And this simplifies decision-making at the bedside, because you don't really actually need to dissect these patients into categories. Really, if they had a non-cardioembolic stroke or high-risk TIA, with the caveats of some of the enrichment criteria of the trial, these patients benefited.

Regarding the second kind of consideration, the current evidence only supports factor XI inhibition as an add-on therapy for secondary stroke prevention. There's really no data right now as a substitute to antiplatelet monotherapy. This was a trial testing asundexian versus placebo on top of antiplatelet therapy, and that's how it should be implemented.

Now, if there is a patient who you're worried about bleeding with dual antiplatelet therapy, you could make an argument of using asundexian on top of single antiplatelet therapy, based on the results and subgroup interactions that we saw where there was actually no difference whether someone received single or dual antiplatelet therapy regarding the overall efficacy of asundexian as an add-on treatment.

And so far, there has been really no loss of efficacy or safety up to over 780 days. And as you saw in the Aalen–Johansen curves, those curves were continuing to diverge, meaning that this can indeed provide benefit on a long-term scale, and this is not a short-term therapy like, for instance, what we use with dual antiplatelet therapy in these patients.

And we're in the process of really monitoring bleeding events in patients who have bleeding events on factor XI inhibitors. Certainly, the monitoring in terms of drug levels or the effects on coagulation, such as the aPTT, which is affected with factor XI inhibition, will be similar and comparable to what we were doing with DOACs. At present, it doesn't seem like we need reversal strategies, but more information will come up in the future regarding kind of how patients fared in emergency surgeries or if they had major bleeding events on a factor XI inhibitor versus placebo in

secondary analyses of OCEANIC-STROKE and other ongoing studies, and that will provide us with greater reassurance. But at present, really, the overall expert consensus is that we're likely not going to need a reversal agent, because overall hemostasis is not substantially affected with factor XI inhibition. And if reversal agents were to be used, some of the agents that have been used in patients with factor XI deficiencies, such as recombinant factor VII or tranexamic acid, can be considered.

Now, what about going back to Walter? And really, Walter is somebody who's been an ideal candidate for factor XI inhibition on the basis of the OCEANIC-STROKE results due to the efficacy that asundexian has shown across many stroke subtypes, the lack of any excess in bleeding, as well as this low renal clearance, making this an ideal drug to improve stroke prevention and keep the quality of life of Walter as high as possible for as long as possible.

In terms of some other cases, just to think about the type of patients you should be considering for asundexian, we also present the case of Dolores, who's a 74-year-old woman who, within past 72 hours, presented with a non-cardioembolic ischemic stroke due to intracranial atherosclerosis. Her NIH Stroke Scale was 13 at presentation, and she's currently on single antiplatelet therapy, and she has a history of hypertension and diabetes, as well as moderate intracranial athero as we mentioned. Some kind of considerations in her case are that, one, she's part of that kind of more severe stroke category of 8 or greater that was tested in OCEANIC-STROKE, where 10% of the population, so about over 1,000 patients, entered the study with an NIHSS of 8 or greater, and there is no suggestion of any increased risk of harm and no loss of benefit in that context.

And in her case, you wouldn't be able to use DAPT because she's above that NIHSS cut-off of 5, which indicates DAPT in patients with minor ischemic stroke. And technically, she doesn't meet that over 70% stenosis that was used for the SAMMPRIS trial, where DAPT duration was used up to 3 months, irrespective of the presenting NIHSS.

So in her, really single antiplatelet therapy would be kind of the current standard of care, but there was a large residual thrombotic risk that remains. Patients with large artery athero have the greatest risk, and I would say in her case it approaches kind of 10% at 1 year.

And really factor XI inhibition will provide a major additional benefit for this patient in its ability to reduce thrombus propagation without markedly affecting primary hemostasis, and it can provide this additional benefit without compromising any bleeding or increasing bleeding risk.

If you were to extend the SAMMPRIS data to even patients with moderate intracranial atherosclerosis, or rather than the SAMMPRIS regimen—not the data because there was no monotherapy comparator in SAMMPRIS, but that was just the regimen used in SAMMPRIS. So if you were to use that for 3 months, still the subgroup analysis of OCEANIC-STROKE suggests that the add-on will be effective,

and it's something that you will be using long term, rather than just a short-term kind of 3-week to 3-month period that we would typically be using with DAPT.

Another case is that of Peter, who's a 72-year-old man with a recent non-cardioembolic ischemic stroke within 24 hours of symptom onset. He presents with a kind of mild to moderate severity stroke with an NIHSS of 4. This is 70% of OCEANIC-STROKE participants fit within this category. His MRI confirmed a right MCA territory infarct, and he had intracranial M1 stenosis, 50 to 60% stenosis. Again, it doesn't meet that 70% stenosis threshold that was used for the SAMMPRIS eligibility. There's no indication here, of course, for therapeutic anticoagulation. We know from the WASID trial that that just increases major bleeding without any benefit for reducing thrombotic events. And here, because of the NIHSS was a 4, he was initiated on DAPT with a target of, let's say, 3 weeks duration. But again, even despite the DAPT, the patient remains at significant risk of recurrent stroke, again, about 10% at 1 year. The DAPT will increase his bleeding risks with limited benefit beyond 3 months. I would say in his case, actually, the data would suggest most of the benefit would be within the first 3 weeks. There's, of course, no role for DOACs in non-cardioembolic ischemic strokes. And again, factor XI inhibition would be a great add-on here for preventing excess thrombotic events as an add-on to antiplatelet therapy and without compromising bleeding concerns for him and his family.

So the key section takeaways are that current therapies to reduce stroke after non-cardioembolic ischemic stroke or high-risk TIA are limited. Factor XI inhibition has the potential to block the thrombosis that leads to stroke without impacting hemorrhagic risk. Asundexian is now proven as an adjunct to antiplatelet therapy for secondary stroke prevention. And the LIBREXIA-STROKE trial is ongoing, but based on these signals of efficacy that we've seen that have been consistent between phase 2 and phase 3, we're fairly confident LIBREXIA-STROKE will also be a positive trial, and it's being tested in a similar population as OCEANIC-STROKE. And really, we're very excited to see all the additional indications that factor XI inhibition can provide and more advances similar to what we've seen in patients with non-cardioembolic ischemic stroke, by further reducing thrombosis without compromising hemostasis. And as we mentioned, the LIBREXIA-AF trial is ongoing, testing a higher dose of asundexian, 100 mg twice daily.

Well, thank you very much, and a kind reminder to please complete your evaluations.

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