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Evolving Our View of the Coagulation Cascade and Stroke Management

Announcer:
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Dr. Caso:
One of the challenges we face as providers is how to navigate the complexities of antiplatelet therapy within the context of acute ischemic stroke. Today, we will review the pathophysiology of anticoagulants and antiplatelet therapy, discuss the role of factor XI inhibitors, and explore results of the PACIFIC-Stroke trial.

This is CME on ReachMD, and I'm Dr. Valeria Caso.

Dr. Shoamanesh:
And I'm Dr. Ashkan Shoamanesh.

Dr. Caso:
Ashkan, what can you tell us about the physiology of anticoagulants and antiplatelet therapy and how this affects the standard of care?

Dr. Shoamanesh:
So of course antithrombotics and anticoagulants are targeting the hemostasis in the coagulation cascade. And hemostasis is the body's physiologic mechanism that stops bleeding from injured blood vessels. Normal hemostasis can be divided into 4 stages. The first is constriction of the blood vessel; 2, formation of temporary, weaker platelet plugs; 3, activation of the coagulation cascade; and then finally, formation of a stronger fibrin plug, or the final clot.

So when a blood vessel is injured, vascular spasm initially occurs, leading to vasoconstriction to minimize blood loss. The disrupted endothelial lining also exposes extracellular matrix and collagen to blood components, leading to an inflammatory response that triggers platelet adhesion and aggregation and the formation of a primary and weaker platelet plug that seals the area of bleeding. These initial platelets then become activated and undergo structural changes and release several factors that can then cause the aggregation and activation of many additional platelets, and this is where antiplatelet medications work in that they target this platelet aggregation stage.

In parallel, tissue factor, which normally lives in the vessel wall and is not exposed to circulating blood, binds to circulating factor VII, creating the tissue factor/factor VII complex leading to activation of factor Xa and cleavage of prothrombin into thrombin through a sequential enzymatic cascade. This part of the coagulation cascade is targeted by medications such as a factor Xa, like rivaroxaban, apixaban, and edoxaban, as well as direct thrombin inhibitors such as dabigatran. The final step in the coagulation cascade involves the conversion of fibrinogen to fibrin, which forms a fibrin mesh and results in a stabilized and much stronger cross-linked fibrin clot.

Now, although the hemostatic cascade is meant to control bleeding and be a protective mechanism, at times, for instance, in the setting

of endothelial injury from atherosclerosis, this process is triggered inadvertently without any bleeding, leading to a pathologic thrombus formation that can cause ischemia from either locally obstructing blood flow or embolism to occlude distal vessels that then lead to stroke, for instance.

Of course, the larger the clot, the greater the likelihood for it to cause ischemia. And clot propagation is driven by a positive feedback loop through which the activation of factor XI by thrombin leads to a thrombin burst that we believe is important to pathologic thrombus formation. And this is what is really exciting about factor XI and factor XIa inhibitors that are currently being tested in clinical trials, because theoretically, by blocking clot propagation and having a lesser subsidiary role in the formation of the initial fibrin clot, they can prevent pathologic thrombus formation without compromising hemostasis. And this is in contrast to factor Xa and direct thrombin inhibitors that are more upstream and also interfere with hemostasis.

In addition, the greater safety profile of factor XIa inhibitors allows us to combine them with antiplatelets for potentially greater efficacy in certain conditions where platelet aggregation is a key driver of pathologic thrombus formation, such as in the setting of atherosclerosis.

Now it would be great for our audience to also gain some insights on emerging treatments and their potential effects on patients. Can you share some of that with us?

Dr. Caso:
There's a high risk that 1 in 4 will have a stroke, which means 12 million new strokes globally. And still we have too many recurrent strokes. We know that 10% of our stroke patients will have a recurrent stroke after 1 year and 25% will have a recurrent stroke after 5 years.

And over the years we witnessed a wonderful evolution of treatment. You mentioned aspirin, antiplatelets. We now know that antiplatelets can be combined with other antiplatelets, dual antiplatelet therapy, or with aspirin plus clopidogrel, aspirin plus ticagrelor. We have evidence from COMPASS trial, which was not specifically designed for stroke patients, but we know that patients with a stable coronary disease have a 75% relative risk reduction of having ischemic stroke. So there are good data that we can do a lot in order to reduce the stroke risk.

However, we know one increases the bleeding risk; two antiplatelets will even more increase the bleeding risk. And this is the major challenge that we have. So as we mentioned before, there is space for the dual pathway combination with anticoagulation. But still we now have to understand how much space we have for this in stroke prevention.

Currently, the combination of antiplatelets, we know that we can use them only for a certain time period, 21 days following the European guidelines. They cannot be used in patients with severe stroke, so a large entity of patients are excluded from treatment.

Dr. Shoamanesh:
Indeed it seems, although we've had great strides in the past few decades at improving stroke prevention, there's still a lot of work to be done and there's a need for new therapies that could even further prevent stroke in our patients, given the major global burden of death and disability attributed to stroke that will also increase with our aging population.

Dr. Caso:
Absolutely.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Caso, and I'm here today with Dr. Ashkan Shoamanesh. We are discussing factor XI inhibitors and how results of the PACIFIC-Stroke trial can improve the outcome for patients.

And what are the insights that you can provide us from the PACFIC-Stroke data?

Dr. Shoamanesh:
PACIFIC-Stroke was a trial that that Dr. Valeria and I worked on together. And in this trial, we were targeting patients with non-cardioembolic ischemic stroke, which account for about three-quarters of all ischemic stroke patients. And these patients remain at the substantial recurrent rates of recurrent stroke despite best guideline recommended treatment, and that's over 6% per year.

This was a prospective, randomized, double-blind, multicentered, placebo-controlled, phase 2 dose-ranging study where patients with non-cardioembolic ischemic stroke, presenting within 48 hours of symptom onset, were randomized 1:1:1:1 to 3 doses of asundexian, 10, 20 and 50 mg daily, or placebo. All patients were also receiving background antiplatelet treatment as part of standard of care.

Patients underwent an MRI at baseline up to 72 hours post randomization, as well as at 6 months or end of treatment, and in total, we enrolled 1,808 patients at 196 sites in 23 countries.

Our primary efficacy outcome of this trial was the composite of symptomatic ischemic stroke and covert infarcts at 6 months. It was a dose-dependent response analysis, and we did not observe a dose response and for our primary outcome. However, this lack of response seemed to have been driven primarily by a complete lack of effect of asundexian on covert brain infarcts that monopolize the primary outcome that accounted for three-quarters of all the primary outcomes. And 70% of these covert infarcts were small subcortical infarcts that we believed were due to cerebral small vessel disease.

Now with a total study follow-up, when we exclude covert brain infarcts, there was a suggestion of a 20% risk reduction with the highest dose of asundexian, 50 mg daily, versus placebo.

And when we looked at the post hoc exploratory outcome of the composite of ischemic stroke or TIA [transient ischemic attack] at total study follow-up of 10 and a half months, we did observe the suggestion of a dose-dependent reduction with the rate of this combined outcome being reduced from 8.3% in the placebo arm to 7.7% with asundexian 10 mg daily, 6.2% with asundexian 20 mg daily, and 5.4% with asundexian 50 mg daily, with this highest dose leading to a statistically significant 36% relative risk reduction for this combined outcome.

Now also on the basis of the COMPASS trial results that you highlighted, Valeria, we were very interested in looking at treatment interactions when looking at patients who entered the study with stroke due to atherosclerotic disease. And we did this in 2 ways.

First, we looked at those that met the classical TOAST criteria for large artery atherosclerotic-related ischemic stroke. And in this subgroup of 320 individuals, the rate of recurrent stroke and TIA was reduced from 16% to 9%, leading to a numerical trend for a 44% risk reduction for this outcome. And then, those that had any degree of extracranial or intracranial atherosclerosis identified on vascular imaging of their arch cervical vessels or intracranial vessels, and this was in the sample of 791 participants who had vascular imaging, the rate of stroke and TIA was reduced from 8% to 3%. And this was a statistically significant robust 61% risk reduction for this outcome in this subgroup.

And importantly, these suggested benefits were not seen with any excess rate of major bleeding. And when pooling all asundexian doses versus placebo, there was no statistically significant excess risk of bleeding, and there was also no suggestion of any excess all-bleeding. And importantly, when we're introducing a new antithrombotic agent on top of background antiplatelet treatment early after ischemic stroke, it is the concern about potential hemorrhagic transformation or bleeding into the vulnerable tissue that has been infarcted. And we saw absolutely no suggestion of any excess risk of hemorrhagic infarction or parenchymal hematoma formation with the use of asundexian at any dose on top of background antiplatelet therapy. And this is compared to placebo.

So to conclude kind of our findings from PACIFIC-Stroke, in this phase 2 trial, inhibition of factor XIa with asundexian did not reduce the composite of covert brain infarction or ischemic stroke, and no dose response could be shown in patients with acute non-cardoembolic ischemic stroke. However, this was driven by a lack of effect on covert brain infarction, which was largely due to small vessel disease and there's good biological plausibility as to why small vessel disease may not be responsive to factor XI inhibition.

However, treating with asundexian and, in particular, 50 mg of asundexian, reduced recurrence of traumatic ischemic stroke and TIA, particularly amongst those with atherosclerosis. And this was seen with no significant increase in major intracranial bleeding with asundexian. And really these results, we find, are very promising and exciting, that it could perhaps establish a new paradigm for secondary stroke prevention in patients with non-cardioembolic ischemic stroke. However, of course, they first require validation in an aptly powered phase 3 randomized trial, and we're currently in the process of completing that study which is the OCEANIC-STROKE trial.

Dr. Caso:
And we should also mention that a patient included in PACIFIC-Stroke also received thrombolysis, so they were not only very mild stroke. They were also, in the second part of randomization, they were treated after thrombectomy. This also did not influence the rate of bleeding.

Dr. Shoamanesh:
Yes, indeed. And I think this really speaks to the potential safety of these agents and that even when used on top of antiplatelet therapy, and 40% of this population was receiving background dual antiplatelet therapy initially, or if tested in moderate-sized strokes, not only mild strokes, or in those that have received revascularization, as I just mentioned, we're not seeing any concerning signals of major bleeding. And this is compared to placebo.

Dr. Caso:
Well, this has been certainly a fascinating conversation, but just before we wrap up, Ashkan, what's your one take-home message?

Dr. Shoamanesh:

We've done a great job in the stroke community in improving the care of our patients, but we can still do better. And hopefully factor XI inhibition will be a new tool that we'll be able to use towards that goal. And we're in the process of trying to establish that through the OCEANIC-STROKE trial.

Dr. Caso:
What we have learned is stroke is beatable because we have a now excellent acute treatment. But we don't have to forget prevention. The moment that a patient enters in the stroke unit, we have to take care of this patient not only from the acute treatment, but also setting up the best secondary prevention treatment.

Thank you very much.

Dr. Shoamanesh:
Thank you, Valeria.

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