**Title:** **ESC 22: Dosing of Asundexian in Pts With Non-Cardioembolic Ischemic Stroke**

**Participants: Dr Ashkan Shoamanesh**

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**Dr Ashkan Shoamanesh**

- Hi, my name is Ashkan Shoamanesh. I'm an Associate Professor of Medicine in the Division of Neurology at McMaster University, and a Stroke Neurologist and scientist at the Population Health Research Institute in Hamilton, Canada.

**Importance of the Study**

There's a large unmet need that's being addressed by the PACIFIC-Stroke trial. We are targeting patients with non-cardioembolic ischemic stroke. This subgroup of ischemic stroke patients accounts for 75% of patients who suffer an ischemic stroke. And in 2019, there was about 12 million individuals with stroke worldwide or incidence stroke worldwide. At present, despite guideline recommended treatment, there is a substantial risk of stroke recurrence in patients with non-cardioembolic ischemic stroke, that is above 6% per year. So our aim and the importance of this study is to be able to address this unmet, large, residual risk of stroke recurrence. And we're also using a novel medication that may be able to further reduce this ischemic stroke risk without increasing bleeding, which is of course, kind of, the offsetting potential harm when you use blood thinning medications in these patients.

**Study Design and Eligibility Criteria**

So the PACIFIC-Stroke trial was a perspective, randomised, double-blind, placebo controlled, Phase two dose-ranging study. Patients with a non-cardioembolic ischemic stroke who presented within 48 hours of symptom onset, were randomised one-to-one, to one-to-one, to three doses of asundexian which is a small molecule direct factor XIa inhibitor. And those doses were 10 milligrammes, 20 milligrammes and 50 milligrammes daily. And they were compared against placebo. Our primary efficacy outcome was the composite of recurrent symptomatic ischemic stroke and covert brain infarction on MRI. As a result, all patients also had to have had an MRI either prior to randomization or up to 72 hours post randomization, and at end study or six months. The eligibility criteria additionally mandated that patients at least planned to be treated with antiplatelet therapy throughout the duration of trial participation, so this was using asundexian on top of background clinical care, antiplatelet therapy.

**Mechanism of Action, and How This Differs from NOACS**

It is a very important question because that's what's really exciting about factor XIa inhibitors and particularly asundexian, is that through direct inhibition of factor XI there's a potential and very exciting potential to be able to reduce pathologic thrombus formation without increasing the risk of bleeding. And the reason for that is that factor XI plays a very direct role in amplification of thrombus or thrombus propagation that we think leads to pathologic thrombus formation. On the other hand, it has a much lesser or subsidiary role in hemostasis. So there is a very strong rationale why these medications may reduce thrombosis without resulting in increase in bleeding. And there's a lot of epidemiologic data in patients who have factor XI deficiency and so forth that support this. In addition, for a population of stroke, it is important because we know that patients with ischemic stroke have higher levels of circulating factor XI. And also those who have inherent factor XI deficiency have lower risk of stroke compared to general population. So it makes it a very attractive candidate for optimising stroke prevention.

**Key Findings**

So our primary analysis did not demonstrate a dose-dependent effect on the composite outcome of recurrent asymptomatic ischemic strokes and covert brain infarcts on MRI. However, this was driven by a lack of effect in covert brain infarcts, which accounted for about 75% of our composite primary outcome. When we look at the more clinically relevant outcome of symptomatic ischemic stroke, there is suggestion of a 20% relative risk reduction with asundexian 50 milligrammes relative to placebo, and this does not reach statistical significance, but there is a strong numerical trend there. And then when we looked at the post hoc exploratory outcome of the composite of ischemic stroke in TIA, we did notice a dose-dependent effect in reducing this composite outcome with asundexian leading to roughly a 35% risk reduction in this outcome with asundexian 50 milligrammes daily versus placebo. And we were also very interested in looking at subgroups of patients that had indication of atherosclerotic disease. And this was based on another trial called the COMPASS trial where patients who were receiving rivaroxaban with or without aspirin actually, sorry, the combination of low dose of rivaroxaban and aspirin and who had systemic atherosclerotic disease. These patients had improved ischemic stroke reduction with combination therapy or dual pathway inhibition when combining a small dose of an anticoagulant with an antiplatelet agent. So for this reason, we were really eager to see our effects in patients that had indication of systemic atherosclerotic disease. And we looked at this in two ways. One, we looked at patients who came into the study and their qualifying stroke met criteria to suggest it was due to large artery atherosclerotic disease. And in these patients, there was a larger effect size of a 45% wealth of this reduction in the composite outcome of ischemic stroke in TIA with asundexian 50 milligrammes daily, versus placebo. And in those that had any indication they had atherosclerotic disease, so they had atherosclerotic disease on vascular imaging of their aortic arch, carotid disease or intracranial vessels. In those patients there was actually a very robust 60% relative risk reduction on the composite outcome of the ischemic stroke in TIA with the 50 milligramme dose versus placebo. And this was all combined with no suggested increase in bleeding. So we did not find a significant increase in our primary safety outcome which was the composite of major bleeding or clinically relevant non-major bleeding as defined by the International Society of Thrombosis or Hemostasis.

**Take-Home Messages**

I think, well, the take home message is one, of course, this was a Phase two study and the results are too preliminary to be implemented in clinical practise at this time. However, very, very exciting results demonstrating potential strong efficacy with asundexian method with placebo, particularly the 50 milligrammes daily dose, for addressing this unmet need of high rate of recurrent stroke in this population, particularly in those with atherosclerotic disease, and importantly without increase in bleeding. So I think these are very promising and exciting results for subsequent Phase three trial to confirm these findings before they're applied to clinical practise.

**Next Steps**

So we're really, of course, excited to see if we can confirm these findings in a Phase three trial. And we're working towards the development of such a trial.