Title: ESC 22: PACIFIC-AMI: Asundexian on Top of DAPT After Acute Myocardial Infarction
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- I'm John Alexander. I'm a Cardiologist and Professor of Medicine from Duke University in North Carolina in the United States.

What is the existing evidence on FXIa inhibitors in secondary prevention?

Factor XI inhibitors are a new class of drugs that inhibit one factor, factor XI, in the coagulation pathway and they're really new. And there're about four or five of them that are in development. Asundexian, which is being developed by Bayer, is one of them. And that's what we studied in Pacific AMI. And the hope is that they will have some advantages over existing antithrombotic drugs, like aspirin, like the P2Y12 inhibitors, clopidogrel, ticagrelor and prasugrel, and like other anticoagulants, like vitamin K antagonists or warfarin and rivaroxaban, that have limitations, that have benefits but also have limitations in patients after an acute myocardial infarction.

What is the mechanism of action of asundexian and how does it differ from rivaroxaban?

So, we like to lump all anticoagulants together but they're really different. So, factor XI is in the contact activation pathway and asundexian inhibits it. Rivaroxaban and apixaban and edoxaban inhibit factor 10, factor 10 is necessary for the initial generation of thrombin. And we think that thrombin is key for hemostasis, to cause a blood clot to stop bleeding. But thrombin has a feedback loop and generates this huge explosion in thrombin generation and activity. And that is through the pathway, the contact activation pathway that includes factor XI. And so inhibiting factor XI we think will inhibit this burst of thrombin activity and hopefully prevent recurrent heart attacks and recurrent strokes, but still allow a little bit of thrombin to be generated, to stop bleeding.

What is the study design and what was the eligibility criteria?

So Pacific AMI was a phase two clinical trial. We studied patients with a recent acute myocardial infarction. People could be enrolled within five days after their acute MI. They had already undergone PCI or the initial stabilisation after their acute MI and all patients were treated with aspirin. And one of the three available P2Y12 inhibitors, clopidogrel, prasugrel or ticagrelor, And then patients were randomised to one of three doses of asundexian, 10, 20 or 50 milligrammes a day or placebo. And then they were treated for up to a year and we followed patients for that year. Plus an additional two weeks.

What are the key findings?

Our main outcomes were factor 11 levels, bleeding and recurrent ischemic events. We saw a nice dose response in the level of inhibition of factor 11. So, the 10 milligramme dose inhibited about 70% of factor 11, the 20 milligramme dose about 80% and the 50 milligramme dose more than 90% of baseline factor 11 activity. So that's good. We got the drug work to inhibit factor 11.
There was really no increase in bleeding with factor 11 inhibition, including at 50 milligrammes. So that's consistent with a hypothesis and is really why these drugs are being developed. So no increase in bleeding.
Unfortunately we didn't see a reduction in ischemic events either, but you have to be careful. This is a phase two trial. There were only about 20 to 25 events per arm and the confidence intervals are still really wide. So this sets the stage for the next trial. The phase three trial.

What is next for the PACIFIC trials?

Bayer, the sponsor, has a large phase three trial programme planned that'll include trials in atrial fibrillation and stroke. We're still in discussions with the sponsor, with Bayer, about a phase three trial in acute MI. There's not one planned right now but we're still trying to figure out the perfect design. This is going to be, the next 10 years, you're going to see a tonne of results around factor 11 inhibitors, just like we have for the last 10 years around factor 10 inhibitors. And it's quite likely that they will revolutionise the way we take care of patients, so stay tuned.