ACC 22: Results from the TRANSLATE-TIMI 70 Trial

- My name is Brian Bergmark. I am an investigator at the TIMI Study Group and an interventional cardiologist at Brigham and Women's Hospital.

Importance of this Trial

So, this is the TRANSLATE-TIMI 70 Trial where we looked at escalating doses of vupanorsen, which is an antisense oligonucleotide targeting hepatic ANGPTL3.
The importance of this, is that despite other therapies targeting lipids, there remains high residual risk and need for additional therapies to lower lipid-mediated risk for atherosclerosis.

Study Design and Patient Cohort

Yeah, so we enrolled adults who are on a stable statin regimen and who had a non-HDL cholesterol level of at least 100 milligrammes per deciliter, and a triglyceride level of 150 to 500 milligrammes per deciliter.
We randomised them to placebo or one of seven doses of vupanorsen, dosed every two weeks or every four weeks subcutaneously.
There were 286 patients randomised in three countries. The primary endpoint was the change in non-HDL cholesterol from baseline to 24 weeks.

Outcomes of this Study

So, for the primary outcome, the change in non-HDL cholesterol, vupanorsen did reduce non-HDL cholesterol at all dose regimens studied, up to a 27.7% reduction in one of the dose arms.
We also looked at other lipid parameters including the target ANGPTL3, which was significantly reduced in a dose-response fashion, as were triglycerides.
The effect on LDL and ApoB was variable and more modest.
We did also look at several safety parameters that are important to note. One of them is the content of fat in the liver, as measured by MRI at baseline and 24 weeks. And in the higher total monthly doses, the amount of liver fat increased.
We also found that there were elevations of ALT and AST in a dose-response fashion.

Take-home Messages for Clinicians

Yeah, so a couple. So one again, is to reiterate the importance of examining targets across the spectrum of lipoproteins. Many of the therapies that exist target cholesterol-rich lipoproteins, and this is expanding to new targets into triglyceride-rich lipoproteins for the goal of reducing cardiovascular risk.
This particular compound did not have as much lipid lowering as we might have hoped, and as was suggested to be possible by other data. And there were also important safety concerns that also were not anticipated from genetic preclinical data.
So, I think for this particular compound, there is not an immediate clinical implication that's relevant, but what this does highlight is that this is opening targets in a much broader spectrum of the lipoprotein array. And I think this is where we are headed in a more personalised approach to reducing lipid-mediated cardiovascular risk.

Next Steps

So again, for this particular compound, I don't know that there's an immediate and next study given the safety concerns, but there are other agents in similar or adjacent pathways, other ways of targeting these particular targets. And so for example, an antisense oligonucleotide targeting APOC3 is in development. And so I think there's a lot more to look for in this pathway, related pathways, as this field moves forward.