

SPEAKER: PCSK9 drugs have been tested in small numbers as monotherapy. The ODYSSEY Outcomes group, we did some studies prior to ODYSSEY Outcomes where they looked at adding alirocumab in patients who have statin intolerance. And I'm fairly confident the evolocumab group has also tested that. But they've been tested as open label treatment generally or in small numbers in randomized controlled trials, meaning less than 1,000 patients.

So we know they work. We know they reduce LDL by about the same amount as with a statin. But we don't know if they reduce outcomes, because the studies weren't large enough to power that. But I think, and I interpret, the data as showing that the reason PCSK9S and the large outcome trials work is not because they are PCSK9 drugs, but because they lower LDL.

And so if you look at the pooled LDL lowering data as an aggregate, you can be confident that if you lower LDL with whatever tool you have-- statin, ezetimibe, PCSK9, lifestyle, even cholestyramine. You will generally get a risk reduction of about 1% for every 1% you lower LDL.

You know, if you use a PCSK9 remember when you give a statin drug to a patient, the statin inhibits cholesterol synthesis in the liver. And it also sort of up regulates the LDL receptor a little bit but it also causes stimulation of PCSK9 secretion and synthesis in the hepatocyte. So the higher your dose of statin doesn't really help the PCSK9 drug work any more effectively. And in fact the sweet spot may really be a low dose statin with the highest dose of PCSK9 because you stimulate the PCSK9 just enough that you can bind it with the excess monoclonal. And at the same time, you get the benefit of a statin. 80% of the statins benefit's in the starting dose, not in the highest dose, but the starting dose. So that may be the sweet spot.

And if we have future clinical trials, I would like to see sort of starting dose statins with PCSK9 tested against highest dose statin with PCSK9 with regard to lipid lowering. And I think we might be surprised that we lower lipids more aggressively with the lower dose statin.