DEEPAK BHATT: There have been two large, important, well-done outcome trials for PCSK9 inhibitors-- the FOURIER trial and the ODYSSEY trial. FOURIER examined Evolocumab. ODYSSEY examined Alirocumab.

Both were really well thought out and designed trials though there were differences between the populations studied. FOURIER examined patients with stable atherosclerosis really involving the coronary, cerebral, or peripheral arteries, and that's, of course, a lot of patients in the secondary prevention universe. That's a good chunk of the secondary prevention universe.

ODYSSEY examined patients with a recent ACS. Though recent wasn't necessarily that recent. It was within the past 1 to 12 months. So not someone with a red hot ACS in the hospital but someone that had been stabilized somewhere between 1 to 12 months after that ACS. So two somewhat distinct populations but with the theme of patients in the secondary prevention universe at various levels of risk.

The overall primary outcome results were extremely concordant between the two trials, about a 15% relative risk reduction in important ischemic events. As well, each trial showed a significant reduction in cardiovascular death, MI, stroke as a composite of hard events, so to speak. One difference in terms of the results of the trials is that the ODYSSEY trial actually found lower mortality with Alirocumab versus placebo.

Now, is this due to a difference between the two drugs? That's always a possibility when there are discordant results, but I don't actually think that's the explanation here. Probably, it had to do with differences in the trials, where in The ODYSSEY trial it was a bit longer in terms of the average follow-up with the patients. It was also a different patient population, as I alluded to, and maybe the fact that patients had plaque rupture leading to their acute coronary syndrome relatively recently, in the past 1 to 12 months prior to randomization, maybe that really was a marker of higher risk and therefore greater benefit, that is, a mortality reduction. So a number of possible explanations for why the trials may have differed.

There were also some interesting observations made in the diabetic cohorts. In FOURIER, for example, where there was a consistency of benefit in patients with or without diabetes. So in particular, as we're thinking about diabetes and the very high levels of risk in that patient population, important to realize that PCSK9 inhibition is another trick up our sleeves, so to speak, in terms of addressing their high levels of residual risk.

But getting back though to the FOURIER and ODYSSEY trials and some differences, one subgroup analysis that was done in the ODYSSEY trial that I think was very informative was one looking at baseline LDL cholesterol levels, the randomization, of course, to Alirocumab versus placebo on top of high intensity statin. But then what is the benefit with mortality as the endpoint in the subgroups of baseline LDL? As it turns out, in those patients whose LDL cholesterol at baseline was greater than or equal to 100 in ODYSSEY, there was a large and robust lowering of mortality with Alirocumab versus placebo.

So to me, that's an important finding. Now, some will say, well, it's a subgroup finding, and the mortality in that subgroup is a post hoc analysis. All valid statistical points. Others will say, well, the mortality reduction even in the overall trial didn't strictly meet statistical significance by hierarchical testing. That was the formal statistical analysis plan, meaning you can't go down a list of outcomes after a particular outcome is not significant, so valid statistical points.

Putting that aside though and looking at the data as a clinician and with more of a common sense hat, the mortality was lower. The p-value was less than 0.05 in the overall trial, and in the subgroup greater than or equal to 100, there the p-values were even more significant. Cardiovascular death as an endpoint was significantly reduced, and it makes biological sense that you get the most bang for your buck, so to speak, in patients who have a high baseline LDL despite being treated with maximally-tolerated statin doses. So I really think that that subgroup analysis-- acknowledging there'll be some that criticize such subgroup analysis-- but I personally think that that sheds light on the biological truth of where we get the greatest benefit of PCSK9 inhibition.