PHILLIPE GABRIEL STEG: [INAUDIBLE] regarding the use of PCSK9 inhibitors in cardiovascular disease has markedly evolved over the past year. We've known for several years now that these agents provide substantial and sustained and dramatic reductions in LDL cholesterol levels over many months, when given either every two weeks or every month subcutaneously. But what we've learned from the Fourier trial last year and from the ODYSSEY outcomes trial this year, just published a few days ago in *The New England Journal of Medicine* is that these LDL reduction actually results in improved cardiovascular outcomes.

Fourier first addressed a stable population with established atherosclerotic cardiovascular disease and demonstrated a 15% to 20% reduction in cardiovascular outcomes, depending on the composite outcome you're looking at. And that benefit seems to accrue over times, be slightly greater as time elapsed after starting therapy. ODYSSEY outcomes tested [INAUDIBLE] in post-ACS patients. So it was a different population, presumably slightly higher risk. But ODYSSEY outcomes had another important distinguishing feature-- it was a treat-to-target trial. So not everybody got the same dose.

Patients were enrolled on the basis of having suboptimal LDL cholesterol levels, or lipoprotein levels, on maximal intensive statin therapy, or maximally tolerated statin therapy. And we did implement in the trial really intensive statin therapy. And we [INAUDIBLE] tried to get them to a range of 25 to 50 mg LDL cholesterol, starting at the 75 milligram dose [INAUDIBLE] every two weeks subcutaneously, and then blindly uptitrated, if needed, 250 milligrams every two weeks sub q.

For those patients who fell consistently below 15 milligrams LDL cholesterol, [INAUDIBLE] was down titrated and everything was done blindly to the lower dose. And if patients were already on the lower dose and had two consecutive measurements below 15, then patients were blindly switched to placebo. So it was really trying to get patients from above between 70 to between 25 and 50, allowing levels as low as 15, but not lower than 15. And again, consistent with Fourier, ODYSSEY outcome showed also a 15% relative risk reduction in major adverse cardiovascular outcomes, defined as CHD deaths, ischemic stroke, myocardial infarction, and unstable angina requiring urgent admission.