

**PHILLIPE**

Our knowledge regarding the use of PCSK9 inhibitors in cardiovascular disease has markedly evolved over the

**GABRIEL STEG:** 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 this 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 alirocumab 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 purposely tried to get them to a range of 25 to 50 milligrams LDL cholesterol. Starting at the 75 milligram dose of alirocumab every two weeks, subcutaneously. And then blindly up-titrated, if needed, to 150 milligrams every two weeks subq.

For those patients who fell consistently below 15 milligrams LDL cholesterol, alirocumab 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 70 to between 25 and 50, allowing levels as low as 15 but not lower than 15. And, again, consistent with Fourier, ODYSSEY Outcomes 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.