

ROBERT S. ROSENSON: There's been a lot of discussion about the patient with cardiovascular disease who has an LDL cholesterol level between 70 to 100 milligrams per deciliter. In the ODYSSEY Outcome study, the greatest benefit were individuals who had LDL cholesterol levels greater than 100 milligrams per deciliter.

However, one has to realize that in that study design, if individuals had LDL cholesterol levels that were reduced to less than 15 milligrams per deciliter on two occasions, the therapy was discontinued. We would expect that individuals who start off at the higher LDL cholesterol would be the ones who would continue the therapy. So just based on the study design, one needs to consider that fact.

In addition, there was enough titration of alirocumab from 75 to 150 milligram per deciliter, and one would expect that the higher entry LDL cholesterol would result in greater up-titration in that group versus the other group. So based on the study design, one needs to be cautious about the interpretation of that subgroup.

In the FOURIER trial and in the ODYSSEY Outcome entry criteria, the LDL cholesterol level was greater or equal to 70 milligrams per deciliter. What the PCSK9 inhibitors have allowed us to explore is a relationship between LDL cholesterol and cardiovascular events. And it's a straight line down to the single digits. In other words, the lower the LDL cholesterol, the greater the benefit, not only the relative risk reduction, but the greater the absolute benefit.

And there's no lower limit for lowering LDL cholesterol. I had the opportunity to lead the very low LDL cholesterol analysis from the alirocumab development program, phase 2, 3a, and then also involved with ODYSSEY outcomes, and I thought there would be a problem based on what we knew from the statins and other lipid lowering drugs. And after my very extensive review, case by case of tens of thousands of individuals, I found no problem. And so I am comforted by the results that have been published about the safety of the PCSK9 inhibitors and also my own detailed evaluation over a several year period of time of these cases.