SPEAKER: So let's think-- with all these positive trials we've seen over the last year, let's look at them, reduce it. We've seen that fish oil, 4 gram per day, gives you a 25% risk reduction. Let's think about the data we heard from the APO(a) antisense, giving a reduction of 80% to 90% in LPA levels-- and mind you, elevated LPA is highly prevalent and gives you a risk increase of two to four-fold.

Then we've seen the diabetic drugs-- the SGLT2. We've seen the rivaroxaban in the COMPASS trial, giving us a very highly statistically significant reduction. So this shows us that we should be thoughtful of trying to quantify the absolute risk. And what these trials also tell us is that our old paradigm-- just blood pressure, systolic below 140, LDL below 70-- actually doesn't hold true, because in all these trials where state-of-the-art, mostly high-intensity statin therapy is given, we're still facing a very highly statistically significant residual risk.

So how does it translate to the value which we use? Well, think of PCSK9 first. Yes, it's true the higher the baseline lipid level when you start, the bigger the benefit. If you have an absolute reduction of 80 milligram per deciliter, you actually can expect to have a huge return of investment in reduction of risk. So yes, a high baseline LDL residual burden gives you a very high gain, or cardiovascular benefit.

But the second issue, which is equally important, mind you-- equally important-- is the baseline risk. So that implies if you have myocardial infarction in a 52-year-old and progress no other risk factors, then you can lower LDL, but actually, his absolute risk is not that high, so you're not going to gain a lot. If you have a 52-year-old male with diabetes, obesity, high CRP, then the steepness of his curve of his risk will be so much higher that even when his LDL is low, halving that low value will give you a quite impressive risk reduction, because the absolute benefit is dictated by 1, the LDL on the x-axis, but 2, the absolute risk increase on the y-axis.

So that's why it's always important, if you consider deep intensification-- for instance, with PCSK9 LDL lowering, these two factors are equally important. And then very high risk or preventing residual events-- it actually makes sense to evaporate the LDL to very low levels. And that's what we have seen. Think of the GLAGOV trial, where the subjects-- where actually, the LDL was lower than 60-- you could see that 80% to 85% to 90% showed regression of their coronary atherosclerosic lesions.

And mind you, the Fourier analysis by Giugliano et al-- they show that if you achieve the lowest level-- so if you achieve levels less than 20 milligram per deciliter-- those were the ones where you actually had a relative risk reduction of 41%. So this shows that we should not only stare at the defined threshold, we should integrate the residual LDL burden with the absolute magnitude of the risk, and that dictates how we should actually-- how intensive we should treat a patient.