Dr. BHATT: The amount of data that has now amassed regarding LDL reduction and reduction in cardiovascular risk is enormous. There's really not a debate anymore. Lower is better for LDL cholesterol, at least, down to the 20 to 30-ish range. And it's unfortunate that there was controversy on this point for so many years. But now the data are in. The clinical trial data surely support that lower is better to that range. The epidemiologic data have always supported it. The Mendelian randomization data-- the genetic data-- strongly support it. So multiple converging lines of evidence have proved that lower LDL cholesterol is better.

And whether you get there with statins, as ezetimibe, or PCSK9 inhibitors, it basically reduces cardiovascular risk. Now, of course, of all of those, the PCSK9 inhibitors are the strongest, then high potency statin, and ezitimibe is the weakest of those approaches, though extremely safe and well-tolerated.

What, then, should be our target LDL cholesterol? Well, it keeps dropping every few years based on the data. And I use nature as my guide-- that is, our natural LDL cholesterol is in that 25 to 30 range if we're talking about newborns or people from communities such as rural sub-Saharan Africa non-industrialized areas, where that's their natural LDL, and they are living carefree in terms of cardiovascular disease. And there are other issues-- hypertension and things due to lots of salt intake. But at least as far as coronary artery disease goes, very, very low rates.

So LDL matters, and lower is better. And that relationship is further amplified in patients with diabetes. And I really like from the guideline from AACE, the American Association of Clinical Endocrinology, that say in very high risk patients, target an LDL cholesterol less than 55. And these guidelines pre-date, really, the bulk of data that's now come out, say, most recently from the ODYSSEY trial, the FOURIER trial before that, with PCSK9 inhibitors.

So I think that they've interpreted the data correctly, though now, with the newest data, I would drop that even further. And if someone really wants to target a range, the ODYSSEY trial was a treat to target trial, the first trial to really do that in the contemporary era and show that targeting in that case with a PCSK9 inhibitor-- and it wasn't just diabetics, it was non-diabetic patients as well-- targeting and LDL between 25 and 50 milligrams per deciliter seems to be the sweet spot in terms of reducing cardiovascular risk without creating any bad side effects.

And in fact, in the overall trial, also a lower associated mortality with the PCSK9 inhibitor use, alirocumab, versus placebo on top of high intensity statin therapy. So it really does appear lower is better. At least one endocrine guideline strongly supports that concept in higg-risk or very high-risk patients. And the most recent data support even lower thresholds.