So one of the things that, as a general cardiologist that sees a host of younger and older patients across primary and secondary prevention, clearly patients who are on high-intensity statin who have very elevated LDLs, prior disease, above 100, 120, clearly, those patients are easier to justify putting on a PCSK9 inhibitor. And it's relatively more straightforward.

But I think both what we struggle on the clinical side but also, even, the logistics of all the hassle of the prior authorizations are patients whose LDL are reasonable. Maybe they're close to 70. Maybe they're even a little less than 70. Are there patients who are going to benefit by adding the PCSK9 inhibitor? Is it really worth the hassle of going back and forth with the payers to try to say, insurance, that this patient really is going to benefit?

And the way I look at it is, really, once I have a patient that is at a reasonable target or threshold-- at 70 or a little bit less-- I really look at, well, what's happened to them clinically? And I've had several patients that their LDLs might be 70, 75, 60, 65, but they've really had an aggressive course of progressive athero, that they've had multiple events and revascularizations in the last several years, despite a pretty ideal lipid lowering, as follows cardiovascular regimen.

They have multivessel disease. So they have a NSTEMI. They go to cath. They've had progression of in-stent restenosis in one artery, and they had progression of disease in the other. They're diabetic, particularly patients with polyvascular disease. So they have cerebrovascular disease, or they have claudication. The may even have revasc in the peripheries.

These are patients that just have a tremendous burden of athero. And we know that patients who have athero in multiple vessels or multiple vascular territories that have clinical events that, I don't care what number their LDL is, they're having events on that LDL. And they're going to have less events throughout their vascular tree by driving their LDL lower.

So I've had patients whose LDLs were 60 on high-intensity statins, but I really pushed and went through the additional paperwork to have them approved for PCSK9 inhibitor because they were still having hard clinical events despite a pretty good LDL. And so I think in those patients that, despite maximal therapy, at least with a statin, are having progressive events, particularly, I think, multiple MIs, multivessel coronary disease.

And we know now that diabetes in general, but also the sense of polyvascular disease, is a huge driver of risk. So that's one group of patients where the LDL is really only one piece of it and, I would argue, actually not the most important piece. It's we're treating the patient and clinical events. I'm not treating a number.

But we do know from lots of the PCSK9 inhibitor trials, the ezetimibe trials, that there's nothing magical about that number of 70. In fact, the patients who achieve an LDL of 60, 50, 40, 30, 20, if you can get their LDL down, they do even better, and there are no unwanted side effects.

On the other side of the spectrum, I see a lot of patients who don't necessarily have a lot of those other comorbidities. They're relatively young. They don't have chronic kidney disease. But they have had an early thrombotic event in their early, maybe, late 30s, early 40s. They have an MI.

They often have a family history of early coronary disease. There's clearly a genetic predisposition in these patients. We often don't have a specific variant that we've identified, but we know that these patients have a family history, and they likely have a genetically premediated course of athero.

And in these patients, you really have to be careful about just focusing on LDL. Because if you have a 42-year-old, 45-year-old, sitting in front of you, you're really not just looking at the next five or 10 years. You're trying to look at this patient and say, well, in the next 30 to 40 years, what do we think is going to happen to you, as far as progression of athero?

And we know from the genetic studies, the Mendelian randomization studies, that very small differences in LDL over many, many decades has very profound effects on risk. In fact, if you look at genetic studies versus randomized clinical trials, there's a three-fold gradient of risk for that same amount of LDL reduction. And so it's really an area under the curve.

And so if I have a patient who has early athero family history, if I can make their LDL 65 or 60 instead of 75 or 70, you might say, well, that's modest. OK, over five or 10 years. But if I say, well, what's going to happen to that 45-year-old when they're 65? I've now made a tremendous difference in their lifetime risk.

So I think you can't look at these guidelines-- they're meant to help you categorize patients, but you really have to look at two things. What's happening to that patient clinically? Do they have a lot of risk factors? And then driving the LDL as low as humanly possible is going to benefit that patient. Because even on optimal therapy, they're still having clinical events.

And then, I'd also be cautious in younger patients who have a thrombotic event family history that you have to take a step back and saying that these patients have a lifetime risk of atherosclerosis that's very high. And the only way to lower their lifetime risk is to be as aggressive in lowering their LDL relatively early in life.