SPEAKER: So I think that faced with this challenge that you've outlined, we have some great clinical cardiovascular outcome studies that suggest that if we can further dramatically and safely lower LDL cholesterol with a fully human monoclonal antibody directed against PCSK9, that we can get a very widespread benefit to a broad range of patients. And yet because of the costs and access challenges that our patients face, we can't currently give this to all the patients that have atherosclerotic cardiovascular disease, even though those were the types of patients included in FOURIER and ODYSSEY outcomes.

So we now need to look at those patients who are at the highest residual atherosclerotic cardiovascular risk, in whom we'll get a relative consistent benefit of PCSK9 inhibition on top of statin, maximally tolerated statin plus or minus ezetimibe. But because they have such a high baseline risk of events, the similar relative reduction that's conferred with this treatment can actually lead to a greater absolute risk reduction, lowers number needed to treat, a better economic argument for our payors. And so who are the folks that I would say, you got to get your foot in the door with somebody? Who are the patients that are going to be sort of most deserving of PCSK9 inhibition therapy?

So I think those whose LDL cholesterol is 70 milligrams per deciliter or above, despite being on maximally tolerated statin therapy. And sure, throw in ezetimibe. And it'll have a modest further relative lowering of LDL cholesterol.

But if you're still above 70 and you have some clinical features, like having diabetes, like being a recent acute coronary syndrome, within the last year or two years' time, as both ODYSSEY outcomes and a subgroup analysis from FOURIER suggested, those whose LDL cholesterol is so far away from a target or so high despite the intensive statin therapy that the patient's on, that there's really no other option that you can safely and effectively lower LDL cholesterol. Those may be patients with undiagnosed familial hypercholesterolemia, for example. So those are folks that, for example, have an LDL cholesterol not only above 70, but above 100 and change milligrams per deciliter.

So those are the types of folks. And then other groups that we should think about, those who have residual atherosclerotic cardiovascular disease, including coronary disease. So the patient may have had an MI and they've been successfully stented. But there's modest disease in the same artery or other arteries that doesn't have enough obstruction, let's say 40% narrowing, doesn't warrant putting in a stent or bypassing around those narrowings. But those patients with residual atherosclerotic coronary artery disease are at high risk for recurrent events and clearly benefit from PCSK9 inhibition.

And then I think the final group sort of clinically identifiable would be so-called polyvascular disease. So those folks that have not only atherosclerotic disease in one vascular territory, like the coronary tree, but also in the cerebrovascular tree or in the peripheral arterial tree. If they've got both CAD and PAD, they're at particularly high risk for cardiovascular events And those are the other group of individuals who I think PCSK9 inhibitors would be a so-called no-brainer to think about initiating.