

**SPEAKER:** Right, so when you're looking at LDL levels, for example, in the clinical trials. There's a meta-analysis, actually, showing that you get a continuous decrease in event rates as you go lower LDL. And so, for example, even under 50, getting under 50, you still see a decrease in event rates.

And so stopping at a certain level, which people had been doing, for example, in ATP 3, is really not a great idea. So the people where you really want to do something would be people who are at incredibly high risk. There are significant advantages in FOURIER, for example, in patients who had had a relatively recent acute event within 12 to 24 months and people with other evidence of diffused vascular disease. So for example, peripheral arterial disease patients are at high risk.

And in FOURIER, those people actually not only did they have a decrease in MI, but they also had a decrease in lower limb ischemic events. And so the PAD group, I think is one group that people have not paid as much attention to and probably should be paying much more attention to right now.

I think that the Odyssey outcomes trial suggests that people with recent acute coronary syndromes are definitely going to benefit. Those people have a very high short-term risk and would definitely benefit in getting the LDL as low as possible. And when people in FOURIER started out with over 100, there was actually an even greater benefit.

So the higher you are in terms of starting LDL on statin-- and I always add ezetimibe, actually-- the higher you are in terms of LDL, the lower you really want to get those people who have recent events or evidence of diffuse vascular disease or evidence that they've had a lifelong high LDL level, as in familial hypercholesterolemia.

The other people that may be also at very high risk would be those with coronary disease, with diabetes, with chronic kidney disease, with high protein A levels. For example, those people are also people that I would tend to position in terms of trying to get the LDL as low as possible. So they may be coming in with LDLs 70 to 100, or thereabouts. And once I've got them, if those are the numbers that they're on already on a high dose statin, plus ezetimibe usually, that's another group that I would consider for a PCSK9 monoclonal antibody.

And in many of those people, you're going to be able to get the LDL down to 20, to 30. And so I think that would definitely provide benefit in terms of decreasing progression and decreasing the rate of further events occurring. So one of the things that really showed up in the data were decreases actually in MIs. And so I think that prevention of further MI, prevention of stroke, prevention of peripheral vascular events became fairly clear from the PCSK9 outcomes trials.