

DR. BHATT: There's lots of patients that probably should be started on PCSK9 inhibitors. In fact, given the side effect profile seen in these two trials, which was really no major side effects to speak of, things like neurocognitive dysfunction that some, largely on the internet, had been worried about haven't panned out.

So very safe, effective at lowering LDL, reduce major adverse cardiovascular events in the 15% to 20% range. For that type of benefit, really one could say that everyone that was eligible for Fourier or ODYSSEY should be on a PCSK9 inhibitor. And scientifically and clinically, I'd say that's right.

But obviously, because of the expense of these drugs, that's not feasible. So for that reason, we really do need to target patients at the highest risk level and allocate health care resources to those folks. So it's really patients that are at the highest risk level that we want to target. And one group that always falls into that high-risk category are patients with diabetes, and by that I mean type 2 diabetes, type 1 diabetes.

And those types of folks, if they have evident atherosclerosis, and especially if they've had prior ischemic events, it's critical to try to prevent the next ischemic event. A big driver of that is LDL cholesterol. The epidemiology supports that association. The genetics support that association. And the curvilinear relationship between LDL levels and risk exists in everybody. It exists even just in pure, non-diabetic primary prevention. But that curve is much more muted.

In the patient with diabetes, it really is a risk between LDL and cardiovascular events that is shaped as I just drew in air there. Very high risks of recurrent events as the LDL level gets higher, and that's true even in what we used to call normal LDL levels. Of course, as many of you realize-- or maybe not everybody realizes-- our normal LDL cholesterol, and by normal, I mean what a newborn baby has, is in the 20 to 30 range. People living in sub-Saharan Africa, at least the parts that aren't getting urbanized, have LDL cholesterol levels in that range and are free of atherosclerosis. They're also free of neurocognitive dysfunction and other things people have been worried about with respect to low LDL cholesterol.

So those levels of LDL cholesterol are normal. People that are having LDL cholesterols of 70 or 100 are, in fact, having high levels of cholesterol. And that's particularly true in diabetic patients. It's in that context that even ranges of LDL that I quoted can be toxic, especially if someone already has evidence of atherosclerosis.

And that's why the guidelines, for the most part, say that anyone with diabetes, especially if they're over 40, especially if they've got additional risk factors, ought to be on a statin. And just parenthetically, it surprises me how often I see in clinical practice patients coming in, having diabetes-- perhaps I'm seeing them because they've had an acute coronary syndrome or large myocardial infarction or they're coming in with heart failure after multiple ischemic events-- that that sort of patient hasn't been on a statin. That's actually a real problem in oversight, I think, in the way we have organized and deliver health care.

But at any rate, beyond just being on a statin-- in patients who are on a statin, especially if they've got diabetes, especially if they've got atherosclerosis, even more so if they have prior ischemic events as that manifestation of atherosclerosis, one would want to drive down the LDL level as low as possible. And many times, PCSK9 inhibition finds its sweet spot here, taking that patient who has diabetes, who has evident atherosclerosis, who's having recurrent ischemic events and trying to prevent the next one-- potentially that next one will trigger symptomatic heart failure. Or that next one might be fatal. So, very important to target risk appropriately.

And diabetic patients with elevated LDL are a particularly attractive target. As well, in real life there are patients who don't tolerate statin, or don't tolerate high doses of high-potency statin. Some of that is a so-called nocebo effect-- that is, it's quote, unquote, in their head. But if it's in their head, you can't always get around it.

And randomized trials have shown, in fact, some of those patients, it really is a true intolerance. That is, if you give them blinded placebo, they're not having side effect. If you get them the statin, they are having side effect. So in those sorts of patients, as well-- of course, ezetimibe is a good option for a modest degree of LDL reduction. But if larger degrees are needed, PCSK9 inhibitors can also be very useful.

So in the future, I really see much more targeted use of PCSK9 inhibitors, at least as long as they remain at this particular price point. If the price drops even further, then I think use will be broader. And I think a lot of that use will be with a gatekeeper function-- that is, it'll be cardiologists and endocrinologists, many times, that are the ones that have to pull the trigger and say, OK, let me treat this diabetic patient at risk, especially those with atherosclerosis and prior ischemic events, before the next event occurs.