**Dr. BHATT:** Another exciting development, much anticipated at the American Heart Association of Scientific Sessions this year was the release of the guidelines with respect to cholesterol. I can't remember, actually, a guideline that's been as widely anticipated. Of course, the last set of guidelines generated some degree of controversy with the lack of overt recommendation of monitoring LDL over time, though that sort of was in there buried in the text. But at least it was interpreted as don't measure LDL again.

This version of may also generate some discussion. The new target, so to speak, is 70 milligrams per deciliter, which I thought was interesting. But I must say, based on older studies like IMPROVE-IT, I thought we, perhaps, already moved below 70.

I think one, perhaps, limitation that the guideline writers had was that the ODYSSEY outcomes trial just got published in the New England Journal of Medicine three days ago-- or four days ago now. So that might not have been something they could factor in. And the ODYSSEY Outcomes economics-- well, I just presented that yesterday. And that of course, hasn't been peer reviewed or published, so some caveats even with that presentation.

So I think that probably limited their ability to incorporate data from ODYSSEY outcomes, such as a lower all-cause mortality, though that, too, one might debate. Because it wasn't statistically significant in a hierarchical statistical purest sense. But it was lower with a P-value less than 0.05. And some people, at least, would say, well, all cause mortality always counts as an endpoint, whether it's better or worse. That should always factor into decision making.

But the guidelines may not have a full chance to really get the paper or review it. So I think with what they had, 70 seems OK. Though, I might have pushed lower, just even based on IMPROVE-IT, which showed 50-ish was better than 70-ish. But Paul, I'd be interested in your take on this. Obviously, you've been doing a ton of research in the field for a while, helping define new populations that would benefit from LDL and inflammatory marker reduction. Is 70 the right target? Do you agree with the guidelines?

**Dr. RIDKER:** Well, so, I'm not so interested in what the right target is. But I do want to congratulate them at least putting them back in. I think the real issue here was we went through a phase where suddenly measuring on treatment LDL was essentially being retelling our general internist and primary care colleagues not to do it. And I don't think many of us agree with that approach. So I have to--

**Dr. BHATT:** That went over very poorly with the primary care folks, I should say.

**Dr. RIDKER:** Right.

**Dr. BHATT:** They really just thought it was--

**Dr. RIDKER:** So I think this is a correction in the right direction to say look, of course we have to measure. I've often said, if you don't measure something, it's impossible to treat it. If we don't measure LDL, I don't know how to treat it. I don't measure blood pressure, I don't know how to treat it.

**Dr. BHATT:** You don't even know if your patient's taking their medicines, I mean--

**Dr. RIDKER:** And yeah, you've heard me argue for years. If we don't measure inflammation, how do we possibly know who has it? And I think we have a fundamental problem in telling people, don't measure things; just randomly treat. Well, that's not how any of us, as a physician, function.

So first of all, getting a target, any target, back in, I think, was a good idea. Guidelines tend to be conservative. And I think that's expected and anticipated. So the fact that we have biologic data saying, LDL's of 50 are better than 70, and 30 is better than 50, I think is true. Most of us believe that.

The fact that the guidelines didn't go there doesn't bother me. I think they're meant to be relatively conservative. They're guidelines. They're not mandates for care. And so I think it is a step in the right direction.

**Dr. BHATT:** Yeah, I agree with you, actually. Because I think the incremental benefit of going lower and lower is relatively less. And I think you have a great figure that's a part of a lot of people's talks. I borrowed it, too, with their various blue stick figures. What it refers to really what the dominant mode of residual risk is-- is it LDL related risk? Is that inflammatory risk? Is potentially thrombotic? So lots of axes of prevention potentially is a glycemic related risk, realizing that glycemia, per say, may not be the target. But drugs to lower glucose, such as SGLT2 inhibitors or GLP-1 agonists, reduce cardiovascular outcomes.

So there are a lot of potentially competing therapies. Some are generic, like statins and ezetimibe. Some are somewhat expensive, like the drugs I just mentioned for diabetes. Some are very expensive, like PCSK9 inhibitors. So there's a range of possibilities, in terms of drugs. Their effectiveness on hard outcomes are mortality and their price. So I agree with, I think, as a starting point, LDL less than 70 is good and as a practical point. There are a lot of high risk patients that have LDL's above 100, so--

**Dr. RIDKER:** Right, so we had no trouble finding patients on high intensity status with an LDL above 100. SPIRE-2 was not hard to enroll. And the chunk of FOURIER Outcomes-- I'm sorry, ODYSSEY Outcomes and FOURIER with those values was not that hard to find. So if we can't take care of these highest risk people first, I think we're not going to get there.

**Dr. BHATT:** I totally agree with you.

**Dr. RIDKER:** The other issue here is this idea you raised about these different kinds of patients. Until relatively recently, preventive cardiologist could simply say diet, exercise, smoke cessation, maybe aspirin. And we finally seemed to put that to bed. And then everybody essentially getting a statin, who didn't have a contraindication. And that's very few people.

**Dr. BHATT:** Right.

**Dr. RIDKER:** But the problem is now we have different biologies driving this residual risk. As we been talking about, if apoB and the LDL is the issue, lower it. If the inflammation is the issue, we can possibly lower that. You just presented elegant data about triglycerides just yesterday. That's another bin of what we consider residual remnant risk or triglyceride risk. We're going to see LPA lowering agents being tested soon. That would be residual risk on that basis. And of course, we have the compass data, telling us that there's coagulation issues here and all of the SGLT2 data, which is just extraordinary.

**Dr. BHATT:** It is.

**Dr. RIDKER:** So I think we, as physicians, have to figure out which patient am I going to give the PCSK9 inhibitor to? Which patient I'm going to give the diabetic drug to? Which patient am I going to give the anticoagulant to?

And it's not so easy anymore. And we can't afford to give everybody all of these. So we're going to have to figure out what's the biologic underpinning for my patient in front me's problem. And the only way to do that is to measure it.

**Dr. BHATT:** Yeah, I agree with you. You mentioned the REDUCE-IT trial from yesterday. The hardest thing about getting patients to that trial was the LDL less than 100. So otherwise, we enrolled 43% of the patients we screen. But it was hard to find people whose LDL's were in that range. So yeah, I agree with you. I think shooting for 70 on a population level would be pretty good. And for individual patients, lower certainly could be better if they can tolerate it and afford it.

**Dr. RIDKER:** So one of the most interesting things is yesterday, just after your session, we presented our data from our cardiovascular inflammation reduction trial, where we had an inflammatory [INAUDIBLE] did not work. But relevant to this discussion, that was a trial done only in North America. So it was only US-Canadian sites.

Our baseline LDL was 68 milligrams per deciliter. That's 400 sites across the US and Canada who are just general practice sites. But all of them have worked with us in the past. They all knew, gosh, if I don't have this patient on high intensity statin, Paul's going to [INAUDIBLE] anyway. And it was a largely diabetic metabolic syndrome population. That's telling us something profound. Because these are general practice folks needing an LDL of 68 in a clinical trial-- that's as low as I've ever seen it-- telling us that we are making success here.

**Dr. BHATT:** Yeah, I think so. In REDUCE-IT, our entry median LDL was 75. And yeah, I think that is the lowest [INAUDIBLE] that I've heard of. But it also points to the fact it's relatively hard to get to that level. So I think your core point that the guidelines is starting point for 70 seems quite reasonable.