Understanding Cholesterol Guidelines and Implementing Non–statins in High–Risk Populations: Paired Conversations and Case Vignettes

Editor's Note: This is a transcript of an online course released in December 2023. It has been lightly edited for clarity.
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Overview

An interprofessional faculty of primary care and specialty clinicians discuss real-world issues in managing patients with complex and challenging dyslipidemia, including elevated lipoprotein a (Lp(a)). Several paired conversations serve as the foundation for discussions related to recent cholesterol guidelines, patient risk stratification, and recommended goals for patients at risk of atherosclerotic cardiovascular disease. Two case vignettes provide the basis for robust discussion among the faculty, which centers around clinical decision-making and the roles, benefits, and limitations of approved and investigational pharmacologic treatment options. The program fosters critical thinking and the application of key concepts to patient cases, enabling participants to advance their clinical practice.

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Background, Screening and Diagnosis of Lp(a)

Primary Care perspective + Cardiologist perspective

John Anderson, MD: Dr. Bhatt, I was at a conference a few weeks ago and the speaker was really passionate in talking about Lp(a), so I read a few articles about it. Give me your perspective as a cardiologist.

Deepak Bhatt, MD: You're absolutely right. Lp(a) has been an extremely hot topic at recent conferences and I think with good reason. Just to recap, Lp(a) is a genetically-derived LDL–like particle and contains both apoB and apoA. It's about, I'd say, a little over 90% genetically determined. Lifestyle changes probably have a negligible effect on it. Sometimes there's a little bit of variability that can be due to assays that may be due to some environmental influences that haven't been fully characterized. But in general it's believed to be predominately genetically-determined, and multiple studies have shown that it's an independent, linear and causal atherosclerotic cardiovascular disease risk factor, even in the presence of low LDL cholesterols. When LDL cholesterols are high, that's essentially a double whammy. But there have been some genome-wide association analyses, as well as observational data, really supporting these relationships of an independent risk factor, independent, importantly, of LDL. As far as what levels count as being elevated, there's no universal definition. There's some variability, depending on who you ask, but in general Lp(a) levels greater than or equal to 50 mg/dL or 100 to 125 nmol/L are considered to be high. But, as I mentioned before, it is a bit of a linear relationship.

As far as the cardiovascular outcome trials that are ongoing, HORIZON and OCEAN Outcomes, they have different cut-offs for Lp(a). HORIZON is studying an investigational drug, pelacarsen, and OCEAN Outcomes is studying an investigational drug, olpasiran, that lower Lp(a) levels. The cut-off for Lp(a) in HORIZON is greater than or equal to 70 mg/dL, whereas in OCEAN Outcomes it's greater than or equal to 200 nmol/L. Just important to have some sense of the different trials, the different compounds, the different cut-offs, but the bottom line is 2 large cardiovascular outcome trials assessing whether Lp(a) lowering directly decreases cardiovascular risk. That'll be the ultimate test of not only is Lp(a) an independent risk factor for cardiovascular disease, that's pretty clear it is, but can you modify it. That's the really important question that will be answered by these 2 trials. Important to note that all of the major cholesterol guidelines now recognize the role of Lp(a) in atherosclerotic cardiovascular disease and appropriate clinical management. In the ACC/AHA guidelines, for example, Lp(a) is thought of as a risk-enhancing factor and the European guidelines, they recommend measuring Lp(a) at least once in everyone's lifetime.

John Anderson, MD: Dr. Bhatt, you mentioned that Lp(a) contains both apoA and apoB. Is that what plays a role in the mechanisms responsible for the cardiovascular events observed with elevated Lp(a)?

Deepak Bhatt, MD: That's a really good question. Very similar to LDL cholesterol, the apoB within Lp(a) serves as a cholesterol carrier. It leads to foam cells and plaque formation, and so forth, and the overall cholesterol composition of Lp(a) is about 30%. That's much lower than that of LDL cholesterol, but not trivial. It's also worthwhile, I think, to note that Lp(a) is considered a risk factor for aortic valve stenosis. As far as apoA, that's structurally similar to plasminogen, and that is potentially then inhibiting fibrinolysis and predisposing to thrombosis. I must say not all research supports this, but there are some associations that do seem to corroborate that statement. Lp(a) also possesses proinflammatory properties, and that's perhaps related to oxidized phospholipids. There are a number of different pathways. It does seem that Lp(a) can be a bad player.

John Anderson, MD: Help me understand what is the prevalence of elevated Lp(a) and who exactly is at risk?

Deepak Bhatt, MD: Yes, that's really important to know. Elevated Lp(a) is the most common genetic dyslipidemia. It affects about 20% of the population worldwide. I think that counts as common. Certain populations are disproportionately affected, and this includes Black patients, but where elevated Lp(a) remains an independent atherosclerotic cardiovascular disease risk factor across all races. And it's important for clinicians to be suspicious of elevated Lp(a) in patients specifically with a family or personal history of premature ASCVD, and those with familial hypercholesterolemia or severe hypercholesterolemia, for example an LDL cholesterol greater than 190 mg/dL, and in those with unexplainable recurrent or progressive ASCVD. Folks with multiple revascularizations or cardiovascular events, those sorts of high-risk patients.

John Anderson, MD: Dr. Bhatt, you mentioned the recommendations for Lp(a) screening, however I worry about pushback in the primary care community when you say, well, why would I screen when there's really no available therapies that target Lp(a). What are some of the

screening highlights and what do I tell my colleagues when I get that sort of pushback?

Deepak Bhatt, MD: Yes, that's not an unreasonable point to make, actually. Sometimes people do say why test for things if you can treat them. There are 2 ongoing outcome trials. We'll see what they show, but if they end up being positive, well we sort of want to be ready for that and have identified patients who might benefit. Otherwise, let's say you're seeing the patient once a year, the trial comes out tomorrow—it's not going to come out tomorrow, but just for the sake of discussion let's say it comes out tomorrow—then you can't really act on it until you see the patient again a year later. It'd be a good thing on that basis. But beyond that, Lp(a) measurement is considered a component of comprehensive ASCVD risk management. It helps inform individual patients, and possibly family members, of their overall ASCVD risk and certain available therapies, although not formally indicated, do provide modest Lp(a) reduction, such as PCSK9 inhibition, that's really what I'm referring to. And again, there are ongoing randomized clinical trials—I mentioned 2 of the phase 3— some phase 2 trials as well, that are trying to sort out whether therapies specifically lowering Lp(a) also lower cardiovascular risk.

In terms of the cholesterol guidelines, I already alluded to this, but they vary a bit, depending on which side of the Atlantic you're on. In Europe and in Canada, there is a recommendation of universal screening, at least once in adults, because it's believed to be largely genetically-determined. And the ACC/AHA guidelines say Lp(a) testing is reasonable among patients with a personal or family history of premature ASCVD, with familial hypercholesterolemia, that is an LDL cholesterol greater than 190 mg/dL, or for cascade screening of family members with FH and for those with a borderline 10-year ASCVD risk. That means between 5% and 7.5% or so to help risk-stratify and determine therapy.

John Anderson, MD: Dr. Bhatt, this case vignette that we see is an individual that I will typically see in my practice in a primary care clinic, not a lot of them, but some. She's an excellent patient. She adheres to lifestyle modification, heart healthy lifestyle. Her LDL cholesterol is at goal, but she has this significant family history of premature ASCVD, evidence of subclinical disease is worrisome. From our discussion, it would seem that this is a very appropriate patient for those of us in the primary care world to be screening for Lp(a). What are your thoughts?

Deepak Bhatt, MD: This is a terrific case and I'm sure there are different arguments different people would make. I think it's actually quite reasonable in her to measure Lp(a). I always get a bit nervous when I hear about family histories of premature atherosclerosis, and she has that family history. And, on top of that, she has a markedly elevated coronary calcium, CAC score. Evidence of subclinical disease. There are a couple of things that make me nervous about her in terms of her future cardiovascular risk. Just to remind folks, some elements that are suggestive of elevated Lp(a) are exactly that, a family history of premature atherosclerosis, and it's something that I've been measuring for years in people presenting, say, with a premature MI. And I guess more recently I have actually switched to what the European guidelines say to do which is measure it once in everybody since it shouldn't change all that much over lifetime if it indeed is so genetically-determined, as the hard evidence supports, as well in someone who has a really marked CAC score, as she does, and no other obvious cardiovascular risk factors. So that coupling of there's atherosclerosis, but no great reason why in terms of just conventional cardiovascular risk factors, especially if the LDL is well controlled, as it is in her case, then why does she have atherosclerosis at all? I think it's worthwhile to look at Lp(a) and I wouldn't just necessarily stop with her. You might consider screening family members as well. If it turns out that there's just premature atherosclerosis running in the family, good to know not just about the patient but other people that you can potentially help as well. And, in terms of help, that goes back to your prior question, what can you do to help, because there's no actually FDA-approved therapy specifically targeting Lp(a). But, at a minimum, it helps identify that the patient's at elevated risk and then may guide us/her to be more intense about risk factor modification, both with respect to lifestyle modification and medical therapy to reduce cardiovascular risk, in particular LDL cholesterol-lowering therapy, and, as I mentioned, if the LDL is high, there a PCSK9 inhibitor that can be useful, both to lower LDL and to modestly lower the Lp(a) too. There are some things to do while we're waiting to see what the randomized clinical trials of the targeted Lp(a)-lowering agents show us. A lot of reason, I think, to be excited about Lp(a) and, at a minimum, aware of Lp(a).

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Guidelines, Goals, Evidence-Based Medicine and MIPS

Nurse perspective + Primary Care perspective

Colleen Walsh-Irwin, DNP: Dr. Anderson, in your role as clinic director, I was hoping we could review merit-based incentive programs for the clinics Medicare Part B-covered services. Can you provide some background on your experience with MIPS?

John Anderson, MD: Well, I'd love to, but we're all getting just started with this MIPS reimbursement program. We've just now started to develop the systems to try to address this. We're in a large multispecialty clinic, so we have a lot of resources, I think, that some of the smaller practices are not going to have. But let me just review what MIPS is. First of all, it's a quality program by CMS that's going to determine reimbursement for Medicare fees in those patients on Medicare payment plans. MIPS categories are divided up. There's quality which is about 30%. There is promoting interoperability which counts for about 25% of the payment. There is also improvement activities, 15%. Cost another 30%. And there are links that you can go to to look at all the different categories. And what's funny is that the payment is not going to be an enhanced payment or a decreased payment. The money is the same pool of Medicare dollars that exists today. It's just that, for lack of a better word, there are going to be winners and there are going to be some losers because there's going to be anywhere between a -9% Medicare payment plan to a +4.7% plan for those who do really well. And you'll get your payment scores. I just got my quality MIPS measure back and I was in the 80% green go range. No idea how I got there. But we'll talk a little bit about what goes into that. And so I think, in our office, we're very proactive about this. We talk about scheduling quarterly reviews to track progress, look at deficiencies, identify opportunities, and so there's a lot that goes into this. But, you know, my experience is that we're just getting started with the active mobilization of forces in our offices to try to get this underway.

Colleen Walsh-Irwin, DNP: I think that's where most people probably are too. I think just even learning more about it, being aware that it's there, educating our clinical staff and our clerical administrative staff, setting the goals, and, ultimately, really treating the patients, right? I mean, that's where we really want to focus is not only is it important for MIPS, but it's important for our patients to meet those treatment goals.

John Anderson, MD: That's exactly right and, as we talk about this—and we'll talk about it maybe in just a little more detail—do the right things. Be on point. Make sure your patients are getting guideline- and goal-directed therapy at the appropriate times, and then be sure you're documenting it. And if not document, why not?

Colleen Walsh-Irwin, DNP: Yes, exactly, and again I think if we focus on doing the right thing, like you said, using the resources that we have in our office to ultimately treat our patients to the best of our ability, we're going to meet those MIPS goals.

John Anderson, MD: Yes, and a lot of this is about interoperability, your communication with your patient, communication with other specialists. It's about screening, mammograms, colonoscopy. It's about LDL target goals, we'll talk about statin therapy in particular. It's A1C goals. It's blood pressure goals. And again, it all goes to your point, manage that patient appropriately, and document it, and you should be fine.

Colleen Walsh-Irwin, DNP: I think that there's certainly tools that we can use that can be helpful, such as ASCVD calculators. You know, the ACC/AHA calculator is a good one to make sure that we're getting patients to goals. And then, like you said, making sure that when we have that statin intolerance that is actually true statin intolerance. We know that there's a concern out there amongst our patients about a perceived statin intolerance when we know that only probably somewhere between 5% to 20% actually have true statin intolerance. And knowing now, in this day and age, I think it's great to actually be able to speak so much about hyperlipidemia because we have so many more treatment options than we ever did previously. It used to be, when you got a patient who had statin intolerance, you didn't have a lot of other options and now we do. We need to make sure that our staff are aware, that clinicians are aware of other options for LDL goal therapy so that we can get our patients to target.

John Anderson, MD: To your point, today in clinic I saw a patient with type 2 diabetes who has some subclinical atherosclerosis, has not had a cardiac event, but was talking a little bit about muscle aches and pains and [it] really did not sound like the atorvastatin that they were on, but I said, okay, I'll make a deal. Two weeks off, call me back. If you're not having any improvement in myalgias or whatever you perceive as leg cramps at night, then certainly you're going to take the atorvastatin. It's a disease-altering therapy. If not, we'll find another statin or another lipid-lowering,

evidence-based therapy for you. But I think it's important for our audience here to know that their statin therapy for the prevention and treatment of cardiovascular disease is all about identifying those high-risk individuals and implementing strategies to improve the dyslipidemia for management and patient outcomes. If you've got clinical ASCVD or familial hyperlipidemia and LDL cholesterol greater than or equal to 190 or you have diabetes and you're between 40 and 75 years old, you have goals for that LDL cholesterol lowering. Exceptions, to your point, are statin intolerance, active hepatic disease, end-stage renal disease. One of the things I do want to make a point is if you have fatty liver disease, you are at high risk with diabetes and fatty liver disease, you're at high risk of ASCVD, and that is not a reason to exclude statin therapy. In fact, that's the patient who must be on statin therapy.

The other thing that we found out about MIPS is it's not okay to just say statin intolerance somewhere in the note. There are certain places in the electronic medical record where you need to put that in so it can be captured as a quality measure. If it's in the text of an office note or it's something that's off to the side, you need to make sure it's in a formal place, whether it's allergy and intolerance in that box, to be able to avoid the penalty for the MIPS. Also, if you have a patient who refuses statin therapy, that needs to be officially documented as well. They're going to be looking at key words, like cardiovascular disease, diabetes, myocardial infarction, hypercholesterolemia, throughout your chart, to identify those patients. And again, just be surveillant and make sure you document appropriately.

Colleen Walsh-Irwin, DNP: Yes, and to that point, when we try and get approval for medications beyond statins, one of the things that the approval status includes oftentimes is is it well-documented statin intolerance. You know, that you've tried, which statins you've tried, what were the dosages, what was the intolerance specifically. When we move beyond the statins, we need to make sure that we have well-documented clinical notes that show that statin intolerance or, like you said, other reasons the patients can't be on the statins. And I think we need to be [aware that] the guidelines are getting more aggressive, right? We know that [for] diabetics now, they're looking at targets of 55 for an LDL. Things, you know, we didn't see years ago. I think we need to be much more aggressive about treating our patients to goal because we know that, with that comes reduced cardiac events and ultimately that's the goal.

John Anderson, MD: Yes, isn't that a great conversation to have with your patient? For the last 5 years, you had an LDL target at whether it's less than 100 or 70, and you just told them you're on autopilot, you're on cruise, there's no trouble. You come back in, their LDL cholesterol hadn't change and you go, well, we need to up the dose or we need to intensify therapy. And you have to do the whole sort of guidelines. Evidence has changed, it's a whole different conversation with the patient.

Colleen Walsh-Irwin, DNP: Yes, it's a great time as clinicians, but I think that's also a point that we [should] take with the patients, that research has shown that we can do better. Yes, and I think that's something really important to explain to our patients too, that we're not just pulling this stuff out of the sky, right? We're basing our clinical decisions on research, and we know that targeting LDL will reduce your risk and the more we know about it and the more options we have to treat it, the better off you are in the long term.

Pathophysiology

Pharmacist perspective + Lipidologist perspective

Jim Backes, PharmD: We want to talk about the historical perspective of LDL cholesterol and ASCVD. And we talked a little bit before about the lipid hypothesis and we really both kind of believe that we're beyond the post-lipid hypothesis era because of all the evidence that's accumulated over time. Can you talk a little bit about the connection between LDL cholesterol and ASCVD and just some of the historical milestones that have occurred over the past several decades?

Seth Martin, MD: I mean, I think you and I agree that we are past the hypothesis stage and, in fact, this is an area of medicine where we just have a tremendous amount of evidence over the decades. It's hard to think about other areas in medicine where we have such a wealth of evidence that's been accumulated from various lines of basic to translational to clinical science. It's really been an exciting history.

This lipid hypothesis dates back well over 100 years, all the way back to 1910 when cholesterol was first identified in atherosclerotic plaque of human vessels and then, in 1938, familial hypercholesterolemia was described and linked to the early onset, premature onset, of atherosclerotic cardiovascular disease. And then in the 1950s, in 1955, LDL was identified as 1 of the risk factors for atherosclerotic cardiovascular disease. And I think we're going to touch on that a bit more, some of the work that came out of the Framingham Heart Study which has been such an important epidemiologic cohort study in shaping what we

know about lipids and other risk factors in cardiovascular disease, and really serving as a framework for prevention. Fast forward to the 1970s. In 1974, Dr. Brown and Dr. Goldstein discovered the LDL receptor. Of course, for their pioneering work, they went on to receive the Nobel Prize, but this is really critical work because, ultimately, much of the pharmaceutical armamentarium that we now have to lower LDL and lower ASCVD really works through the LDL receptor. This was really critical work. And then, in the 1980s, we had the first approval of a statin therapy in 1987 with lovastatin which, when it was approved by the FDA, really set the stage then for a multitude of additional statins that would become available over the years. And it's interesting, back then when statins were first approved, there were certain requirements due to some concern, for example, around effects that could happen in eyes, particular concern for cataracts. And although I was not practicing at the time, my understanding is that there was quite a bit of concern, based on studies in beagle dogs, for cataracts. And therefore there was the requirement to have slit lamp exams done in patients if they were treated with statins. We, of course, don't require that anymore but it's interesting, in the literature, that this concern for cataracts pops up every now and then even though the highest quality human evidence has really dispelled that concern. But this is some of the early history that led, then, to this dawn of the statin era, and now we're well beyond the statin era with many nonstatin therapies. It's really been a rich and exciting history. Ultimately, this evidence together has really identified atherogenic lipoproteins, particularly low-density lipoprotein, being a central player in atherosclerosis, initiating the process of atherosclerosis when it penetrates into the arterial wall leading to dysfunctional endothelium and inflammatory cascade, ultimately development of plaques in the arterial wall. It does interface with other risk factors, such as hypertension, diabetes, smoking, and so forth, to increase the risk of plaque formation, but LDL is central to that process of plaque formation and ultimately to atherosclerotic cardiovascular disease risk.

Jim Backes, PharmD: That's a great summary and I agree that we both have a great appreciation for this and I think the longer you practice, the more appreciation you have of it. And I think, in 1974, they probably didn't realize then what they truly had discovered and how much drug therapy would come about because of that. Absolutely, regarding some of the pathophysiology, I tell my students LDL really is central, and then if you have the hypertension, if you have the smoking, if you have all the other cardiovascular risk factors, that causes arterial damage allowing the LDL to migrate through and essentially form foam cells and ultimately plaque and cardiovascular events. Absolutely, that's a great summary and a great historical perspective, Dr. Martin.

There's additional evidence. You talked about the wealth of evidence, about the various key points dating back to 1910, 1955, fast food, McDonald's, I believe, was established in 1955. I thought there was kind of a corollary there. But it's beyond that, beyond the lipid hypothesis, and there is talk now about LDL exposure and time of exposure and ASCVD risk. Can you talk about some of this other evidence that has kind of come from some of the other historical markers?

Seth Martin, MD: Yes, absolutely. First of all, just build on some of what we were starting to discuss around the Framingham Heart Study which has been such an important study in the history of lipids and preventive cardiology. Data from Framingham have shown that the LDL level—as you kind of stratify into different groups based on LDL levels—that you can have a small increase in cardiovascular risk, a moderate increase in risk or quite a high risk based on the high LDL levels. Generally speaking, we classify LDL levels of 190 or more as severely elevated and conferring the greatest risk. If we compare the highest LDL vs lower LDL groups, we're looking at a 5-fold or more higher risk of atherosclerotic cardiovascular disease and a 4-fold or higher risk of mortality. And if you were to layer in more detailed information around genetics and identifying someone specifically with familial hypercholesterolemia on top of that very high LDL, we could be looking at 20-fold higher risk of ASCVD. And that really gets into the next, I think, kind of key learning point around cumulative exposure to LDL. If someone's born with a very high LDL, as could be identified quite strongly through a diagnosis at a genetic level of familial hypercholesterolemia, it's no surprise that that's a very much higher risk because of the long-term cumulative exposure to LDL. In addition to the studies of individuals with severe LDL elevations and familial hypercholesterolemia, there's been really nice work by Brian Ference et al looking at the importance of long-term LDL exposure as well as other cohort studies. Some of the other NIH cohort studies, in addition to Framingham, have looked at the importance of long-term exposure to LDL and what it's led us to look at is, at LDL, is not just here's your snapshot LDL level today, it looks high, but thinking about that duration, you can think about it as the pack years of smoking being very similar to what we're thinking about in terms of LDL years. If you just take the milligram per deciliter level of LDL, multiply it by the

number of years that it's been at that elevated level, then we get up to that cumulative, we really get at that framework of cumulative exposure for LDL. For example, if you have an LDL level that's more modestly elevated of 125 but it's been there for 40 years, that's 5,000 mg years of exposure. And so Brian Ference has really shown how that accelerated onset of LDL exposure for folks that are born with higher levels really would lead those individuals to then cross this threshold that can be conceptualized, above which you start to see clinical ASCVD events. It really is an important concept for risk, but then also it's an important concept as we think about treatment—which I know we're going to kind of shift to in a moment—as we think about RCTs, that ultimately clinical trials have tested for 2 years, 3 years, 5 years, maybe a bit beyond that, but that's still a relatively shorter window in the long-term exposure our patients have to LDL and really, as we think about lipid management, prevention, thinking about the long game that we really want to reduce this exposure over the longest possible period of time where we're going to get the greatest benefits from that longer reduction.

Jim Backes, PharmD: Absolutely. I like the analogy of the pack years, the cumulative years of LDL cholesterol and I think that shows just how powerful and how significant LDL cholesterol can be. And anecdotally, I tell the story of Stormie Jones and, for anybody in the audience, Google this because it's worth a 5-minute read, but a young gal that develops homozygous FH with a baseline LDL of 1,000 and, at 6 years of age, she has a couple of heart attacks and requires a heart/liver transplant and passes at the age of 13 because of such significant disease. Obviously, that's anecdotal. That's an N-of-1, but essentially what we're seeing is she had just a majorly concentrated pack-year history of cumulative LDL year history just in her short, short life.

Seth Martin, MD: That can be more exposure in that short life than somebody could have in an entire lifetime if they happen to be born with genes that help lower LDL. It's a function of LDL and time and I think that we need to kind of keep that as a key focus because many patients ask me in clinic, kind of, "Well how long are we going to be continuing therapy for?" Right? And we have to emphasize, like once you get to where you want to be, the benefits are just going to keep accruing year after year after year and that's the key goal of therapy, just to continue it over the long term.

Jim Backes, PharmD: Right, and I think we obviously have safe therapies. We have inexpensive therapies and with prevention being so important, why are we not identifying this earlier and taking care of it and extending the long term? Our understanding is very consistent with how we should be practicing. Now, kind of moving on to the next section, we're going to go into the randomized, controlled trials and meta-analyses.

Seth Martin, MD: Let me ask you, Dr. Backes, we previously covered the basic science milestones, some of the key discoveries as we learned about LDL and ASCVD, but patient outcome data are really critical to close the loop and to shape our clinical practice. Can you give an overview of clinical evidence from RCTs and meta-analyses of lipid-lowering therapies?

Jim Backes, PharmD: Absolutely. And again, just to piggyback off what you had said, we have just a wealth of information. Maybe more importantly, it's very consistent as well. And I think the bottom line for clinicians is generally any time you lower LDL, you reduce your cardiovascular risk. And when we looked at this in randomized, controlled trials, whether it was cholestyramine back in the day from the 1980s from the Lipid Research Clinic trial to obviously statins to now ezetimibe to PCSK9 inhibitors to recently bempedoic acid, you could even argue LDL apheresis lowers cardiovascular events, although it would be unethical to do that in a randomized controlled trial because those people have such high levels. But I like to go back and look at the 4S trial because I think that was very pivotal. That was the early 90s. These were high-risk individuals, mostly men, secondary prevention. Their baseline LDL were nearly exceeded the threshold of 190 that you had talked about. I believe their baseline LDL was 185 and they received simvastatin or placebo. And obviously, in this day and age, it would be unethical not to give someone like that a statin or other lipid-lowering agents, but you saw that simvastatin 40 markedly reduced cardiovascular events and also reduced total mortality.

When they designed the trial, they were smart about it and they chose that very high-risk population and they got great results. And then the statin trials just continued to build and obviously we don't have time to go through all of them, but the Heart Protection Study stands out too. That was a huge trial done in the UK, again involving simvastatin vs placebo, and a lot of secondary prevention patients, if not secondary prevention, high-risk, diabetes with other risk factors. But they intentionally enrolled 25% with diabetes, 25% I believe beyond the age of 70 years of age, and really they showed that regardless of baseline LDL, they reduced cardiovascular events and it works if you have diabetes, but not ASCVD, and they also reduced events in people greater

than 70 years of age. Again, just a wealth of information that was taken from that.

I think another key trial was the PROVE-IT trial. When we were really digging into the data—or having data presented to us—demonstrating that lower is better—and I'm sure you recall that the design of that trial—the investigators, I think, were probably surprised at the results because it was pravastatin vs atorvastatin, so moderate intensity vs high intensity, and lo and behold, the high intensity markedly reduced cardiovascular events among patients that are acute coronary syndrome patients, over a matter of 24 months. So again, that was pretty surprising to the community, but it really showed the importance of reducing, markedly reducing, LDL cholesterol in those high-risk acute coronary syndrome patients.

The last statin trial I think that I'll talk about is one very recent and the last placebo-controlled statin trial probably that we'll have showing cardiovascular outcomes involved pitavastatin in the REPRIEVE trial. These were HIV-positive patients. They were primary prevention. Their ASCVD risk scores were low to moderate, so it was questionable whether that they would really qualify for statin therapy, but we know, with chronic disease, chronic inflammation, with an HIV-positive status, that those are risk factors for vascular events. And pitavastatin showed a nice 35% reduction among this population in major adverse cardiovascular events, among this population that we generally don't view as high risk. But again, it showed a nice reduction. Seeing that they're effective in the very high-risk and now seeing that we can utilize statins in some of these other populations that are perhaps more at risk than what we think, is important. I think other studies, obviously with the PCSK9 monoclonal antibodies, we have the FOURIER and we have the ODYSSEY. So again, you're taking a PCSK9 monoclonal antibody, you're putting it on top of the statin and you're comparing that to placebo and a statin. And again, pretty consistent results. In FOURIER, these individuals had vascular disease and ODYSSEY, they had vascular disease as acute coronary syndrome. And so again, we got the 50+% reduction in LDL and with it, about 15% reduction in ASCVD events. Maybe kind of the exciting thing about this is the lines continue to separate the longer people are on therapy. So that more than likely, the data has supported that that 15% will be more pronounced in subsequent years. Lastly, I should talk about the CLEAR trial, which involved bempedoic acid in statin-intolerant patients. If you look at modern trials, this is the first really modern-day, cholesterol-lowering trial showing that you can reduce cardiovascular events with a nonstatin vs placebo. FOURIER and ODYSSEY, of course, all the subjects were on statin therapy. These were statin-intolerant patients. There was about 20% that were on low-dose statin and so we saw about a 13% reduction in vascular events. Again, it kind of loops back to what you talked about early on that this has been identified for a long time. There's a whole body of literature supporting that we're in the post-lipid hypothesis era and I think, as clinicians and as educators, we really need to get that worked out to identify these patients and treat them aggressively.

Seth Martin, MD: Absolutely. That was a great overview and it's just tremendous, the progress we've made with lowering LDL lower and lower and it's now a wealth of evidence really indicating that lower is better for longer and we can get there in just about any patient. I mean, we now have the tools that the statins and multiple nonstatin therapies from ezetimibe to bempedoic acid, PCSK9 inhibitors that we can get there in just about any patient down to the low LDL levels. And we've not identified a level that's unsafe to get to. I want to emphasize that the safety of low LDL levels, in the FOURIER trial, the average LDL cholesterol was 30 and half the people were below that. Even in individuals who got to LDL levels below 10, it was safe. There was additional reduction in events and there was no increase in any adverse effects. And the data from the cholesterol treatment trials have shown this consistent association of LDL to ASCVD risk, whether using statins or other nonstatin therapies where if you lower LDL by about 1 mmol/L or, in US metrics, about 39 mg/dL reduction in LDL leads to about a 20%/25% relative risk reduction in major adverse cardiac events. Really, the evidence is there and it's up to us, as front-line clinicians, to implement it in partnership with our patients.

Treatment

Cardiologist perspective + Pharmacist perspective

Deepak Bhatt, MD: We're fortunate to have a host of medications that can safely and effectively lower LDL cholesterol, both new and well-established agents. What are some clinical pearls involving the safety and efficacy of the key LDL cholesterol-lowering therapies?

Jim Backes, PharmD: I agree, Dr. Bhatt. We are fortunate to just have a plethora of new and also very well-established agents. I think, first of all, in terms of safety and efficacy, we've got to talk about the statins. These agents are now a few decades old. 1987 is when lovastatin came out, and, of course, we have more common agents that are utilized today, the atorvastatin, the rosuvastatin, and I think a

message to clinicians is, from a pharmacy standpoint, those are probably the agents I would try to utilize in clinic. The rosuvastatin, atorvastatin are high-intensive, high-intensity agents, even if you don't need high intensity. Rosuvastatin is clean in terms of drug-drug interactions, for the most part. And that's where, looking at some safety concerns with the statins, I would be looking at drug-drug interactions. You know, clinicians are most likely to get into trouble with drug-drug interactions with the simvastatins and the lovastatins because of their susceptibility to CYP3A4. Atorvastatin is also metabolized by CYP3A4, but just a small amount compared to lovastatin and simvastatin. I think atorvastatin, rosuvastatin, high-intensity agents, they can lower LDL up to 50% to 60%, even some of the lower doses. We know these agents have a flat dose response, so even the entry level doses with these agents will get you a good 30%/40% reduction.

In terms of side effects, overall these are very safe medications. Patients, though, seem to be concerned about their liver. Is this going to harm my liver is a common question that patients ask. And I think the short answer is no or highly unlikely. These agents, statins, can cause a dose-dependent increase in hepatic transaminases, but I stress dose-dependent. If you do have that patient that reaches the 3-times the upper limit of AST/ALT, you can pull back on therapy because of the dose dependence. But then sometimes it occurs for no reason at all. It's not related to the drug. And it was mentioned in another module, nonalcoholic fatty liver disease, so perhaps the patient at baseline has an elevated liver enzyme. Dose-dependent liver enzymes, simply pull back on the dose. There was talk too about statin-associated diabetes and concerns. And 1 analysis looked at the number needed to harm, which was 250. So I think 250 patients would need to be treated per year in order to see 1 additional case of statin-associated diabetes. The benefit of that outweighs the risk, and there's other calculations, other analyses, that provide numbers as well.

But probably the biggest hang-up with statins is the myalgia or the perceived myalgia. But again, we mentioned in a few other modules, the N-of-1 studies where we take the statin-intolerant patients, we put them in a double-blind study and we see that reported adverse effects are nearly the same. One study said 90% of the reported adverse effects were also observed with placebo, that were with statin therapy. I think the workaround with that is to talk to the patient. The module where we talk about shared decision-making and providing maybe an informed decision-making with actual data instead of some of the stuff that perhaps they've heard from friends or right on the internet. Overall, statins are extremely safe and effective. Clinically, there are some things we do have to work around, particularly the myalgia, but there's a number of alternatives.

Ezetimibe, too, has been around for some time and arguably the safest lipid-lowering drug. You can see an LDL reduction of about 20% and really, there's not a lot that stands out with ezetimibe. Maybe in that patient that has a history of statin-associated myalgia, they might experience or report some muscle soreness and achiness, but just an extremely clean agent. Bempedoic acid is another agent that we need to talk about and this is particularly important because of the CLEAR outcome results that were recently presented. A reduction in LDL cholesterol of 20% resulted in a 13% reduction in major adverse cardiovascular events and this was in a statin-intolerant population. And so I think that's probably where you're going to see this utilized in those individuals that are statin-intolerant, statin-hesitant, perhaps combining it with ezetimibe to get close to a 40% LDL reduction. So that, together, would put you into that moderate-intensity LDL reduction. But there are some noted side effects, small but significant increases in uric acid, gout, cholelithiasis, but not necessarily muscle soreness and achiness and that's probably based on the fact that the drug, the active metabolite is not active in muscle tissue. And then looking at some of the other newer agents, the PCSK9 therapies. Of course, we have the inhibitors, the monoclonal antibodies, alirocumab, evolocumab are well-studied. They're evidence-based. You see a 50% to 60% LDL reduction. You see about a 20%/25% reduction in Lp(a) that we talked about in this program, as well. And again, evidence-based so about a 15% to 20% reduction in major adverse cardiovascular events, among stable ASCVD and also acute coronary syndrome patients, on top of statin therapy.

Maybe the concern that we have with some of the monoclonal antibodies is are we going to see allergic reactions, are we going to see a loss of efficacy, and that's been minimal. And these agents have been out for a number of years now and been well studied and some of [them]—the FOURIER trial, the ODYSSEY trial—have had open-label extensions that have really not shown any signals in terms of long-term effects. Injection site reactions appear to be the most common adverse effect and perhaps another thing that's been discussed and the concern is neurocognition. When you drop the LDL down sometimes to less than 20, I believe in ODYSSEY and FOURIER, the median LDL was between 30 and 40 for both the trials, and

there were no differences in cognitive changes over time. Just good agents.

Inclisiran, too, is being studied in the ORION trial, the ORION-4, and we'll have long-term outcomes with that in about 2026. Doesn't seem to lower LDL quite as much as the monoclonal antibodies, but a nice 50% reduction and then also some reductions in LDL cholesterol as well. That's kind of my thumbnail sketch of the safety and efficacy of the common agents that we utilize today.

Deepak Bhatt, MD: I don't think I've heard a better or more succinct description of all the LDL-lowering therapies out there. That was really beautifully stated and I think you hit all the high points and the practical pearls as well. The statins remain underutilized. I think you're right, especially focusing on atorvastatin and rosuvastatin these days makes sense, though I still see lots of patients out there on simvastatin, occasionally high-dose simvastatin, which is just a recipe for trouble, especially in complex patients on multiple other medicines where interactions may occur. I think ezetimibe can be really useful in that patient that just won't take a statin and when they have muscle aches on ezetimibe, at least then I know probably the muscle aches on the statin were also just a nocebo effect, but if a patient thinks it's a real side effect, then it's a real side effect for all practical purposes. But I do think, for those that want oral medicines and can't tolerate statins, the combination of ezetimibe and bempedoic acid is very useful. And for those that do tolerate injections or are open to it, then the PCSK9 inhibitors really are a major advance, though also remain underutilized, and pricing is part of the reason why. But even as the prices have come down, there's still a lot of underutilization. There's underutilization of generic statins and ezetimibe, but also underutilization of bempedoic acid and PCSK9 inhibitors. Probably that's the biggest problem with respect to LDL lowering, but really great outcome data for the statins, for ezetimibe, for bempedoic acid now, and certainly for the monoclonal antibodies as far as PCSK9 inhibitors go with data that will hopefully be out for inclisiran in the years to come, as you alluded to. Really compelling body of evidence in toto and just, I think, all together supporting the safety and efficacy of LDL reduction in patients who are at cardiovascular risk.

Maybe we can move on now to another interesting topic, managing elevated Lp(a) may be the next frontier in lipid management. What can you tell us about the investigative agents targeting Lp(a) that are currently in phase 2 and 3 trials?

Jim Backes, PharmD: Thank you, Dr. Bhatt. And, as you know, this is an exciting area. We've seen patients for decades—and I'm sure *you've* seen patients for decades—that come in and they're kind of scratching their heads as to why they have heart disease or why they have this elevated calcium score. Lo and behold, you draw their Lp(a) and it's through the roof, and commonly they have the family history. Up until now, there's not a lot that you could really do. You could intensify the therapy. Of course, there's other agents, we've talked about the PCSK9 therapies that can lower Lp(a) and niacin, of course, not a current recommendation. But these Lp(a) agents, mRNA agents, are very exciting because they can really reduce Lp(a) significantly. Reductions anywhere from 70% to 100%.

There's a couple of phase 3 trials. Pelacarsen is an antisense oligonucleotide. It's involved in the HORIZON CVOT clinical trial, and this is an 80 mg, once-monthly, subcutaneous injection. And the results from that trial should be out in a couple of years, so about 2025. Olpasiran, too, inhibits synthesis of apoA in the hepatocytes. It's involved in the OCEAN(a) Outcome trial and this is 225 mg subcu every 12 weeks. And again, both these agents are highly effective and the olpasiran outcomes are expected a little bit later, in about 2026. Even more recently, there was another agent. This was, I believe, a phase 1 trial involving lepidosiren, a small interfering RNA with extended activity. And so this was a one-time injection, and at 48 weeks, it was still lowering Lp(a) by 98%, excuse me, 94% at 48 weeks. This will fill a big gap, but of course we have to wait for the cardiovascular outcome trials to see where this is, to see where they really play out. But again, as somebody that's been involved in lipids for a long time, I think this will hopefully benefit a lot of patients that have gone a long time without therapy.

Deepak Bhatt, MD: It's great science, really going from the bench potentially to the bedside. Of course, we have to see what these clinical trials show, but the science here, I think, is amazing, with mRNA and sRNA. Entering clinical practice in cardiology and other areas, we'll see if it also enters cardiology practice for Lp(a) lowering. These will be very important trials and really just around the corner in the next couple of years. I'm looking forward to the results that could be a big advance. Have to wait and see, but there's a lot of hope here.

Jim Backes, PharmD: Right, a lot to be excited about. I completely agree. Tying everything together, we do have a case, and it involves a very high-risk patient that has 2 words to emphasize, recurrent and progressive ASCVD. The

patient is currently on maximally tolerated statin and ezetimibe, so the staples that we talked about. But LDL cholesterol is not quite optimal and Lp(a) is elevated. What would your treatment approach be, Dr. Bhatt, for this type of patient?

Deepak Bhatt, MD: For this sort of patient, you really throw the kitchen sink at them. I mean, this is someone that is having recurrent and progressive ASCVD despite already being on a maximally tolerated statin and ezetimibe, being adherent to those. There's still lots of residual risk, both because the LDL cholesterol is still not optimal in terms of goals and, on top of that, the Lp(a) is elevated. The clinical situation is concerning, the biomarkers are concerning, everything's concerning. Of course, we want to make sure this patient's doing everything possible in terms of lifestyle modification. That is, the right diet, I'd say a plant-based diet to the extent the patient can do that, regular daily exercise, whatever they can do, and weight control, that is weight loss if they're overweight or obese or maintain a good weight if they're already there. In particular, focusing on the waist circumference and visceral fat. I would emphasize all of that to the extent possible and then make sure that the patient's on all the right medical therapy. Statin/ezetimibe is terrific. Typically, if the patient has hyperlipidemia, atherosclerosis, there are other bad things that travel along with that. Oftentimes, hypertension or diabetes, for example, so we want to treat those risk factors aggressively, not just with lifestyle modification, but typically polypharmacy. And try to make sure the patient's actually adherent to all these different ways of reducing residual cardiovascular risk. But, as far as the biomarkers at hand right now, the LDL being suboptimal and the Lp(a) being elevated, certainly we want more in the way of LDL reduction and options include a bempedoic acid, the PCSK9 inhibitor monoclonal antibodies, alirocumab or evolocumab is what I'm referring to, or inclisiran.

There are a bunch of options and one of them should be used to lower this patient's LDL. Now, bempedoic acid would produce about a 20-ish percent reduction in LDL cholesterol which would certainly be very good. The monoclonal antibodies, the PCSK9 inhibitors, would provide about a 50-ish to 60-ish percent reduction in LDL cholesterol and also about a 25-ish percent reduction in Lp(a). Inclisiran, about a 50-ish percent reduction in LDL cholesterol and about a 25-ish percent reduction in Lp(a). For this patient, I think any of those 3 avenues of reducing LDL cholesterol would be acceptable, and better than just doing nothing or rechecking in 6 months or just saying lose some more weight and check in 6 months. Everything I said about lifestyle modification in this high-risk patient should be done in parallel with escalating pharmacotherapy, not instead of. And here, I think, with the Lp(a), I'd probably favor the PCSK9 inhibitor approach as opposed to just bempedoic acid because I'd like to lower the Lp(a) a bit if I can. Now, it's not clear that PCSK9 inhibitors are providing clinical benefit per se from the Lp(a) reduction in biomarker, but the risk reductions that we've seen in the outcome trials with alirocumab and evolocumab, some proportion of that maybe can be contributed to Lp(a) lowering. It's hard to say. There've been a bunch of fancy statistical analyses done, but what is very clear is that Lp(a) elevation is an independent cardiovascular risk factor and it's a double whammy when the LDL's elevated and the Lp(a) is elevated. Those are very high-risk patients and here we have the clinical scenario to know that the patient's still at high risk in having recurrent events.

Here I think a PCSK9 inhibitor would be the way to go. Which one? Between the monoclonal antibodies, I'd go with whatever's on the formulary, whatever is covered best in terms of insurance coverage for that patient. Choosing between the monoclonal antibodies and inclisiran, well there I think in favor of the monoclonal antibodies is that both alirocumab and evolocumab have cardiovascular outcome trial data, not just LDL lowering data. Inclisiran has a number of trials going on in secondary and primary prevention. We'll see what those trials show. The hope and anticipation is they'll be positive, but you never know until you actually do the outcome trial. As you mentioned, the LDL lowering does seem like it might be a little bit lower with inclisiran than with the monoclonal antibodies. You have to see what they show. Some doctors might say I'm only going to use agents with outcome data. Nothing wrong with that approach. But, on the other hand, 1 potential benefit of inclisiran is that you can give it every 6 months so that dosing frequency vs every 2 to 4 weeks with the monoclonal antibodies, in some patients, could be a really big advantage where you give it in the office and so you know they actually took it because you're giving it to them or your nurse is giving it to them. It is a potential advantage from an adherence perspective. This could be a personalized decision in terms of which one to go with, in part how the doctor interprets the need for cardiovascular outcome trial, in part what patient is best suited for in terms of injection frequency and adherence. And likewise, if they're injection-averse, I'd say well the bempedoic acid is still a good way of lowering the LDL cholesterol. Not as much as a PCSK9 inhibitor, but still better than leaving this patient untreated. And I would also keep an eye on this patient and put him in the back of your mind or on a

spreadsheet, HIPAA-secure of course, or something like that because if the Lp(a)-lowering trials are in fact positive, then this patient perhaps should go on one of those agents, assuming the trials are positive and the agents are FDA-approved. That's how I would tackle this patient who is basically a ticking time bomb.

Jim Backes, PharmD: I think this would definitely qualify for very high-risk that's been talked about throughout these modules before. Nicely stated, Dr. Bhatt, and I agree. This is an individual that, if we take away all the LDL-lowering therapy, they are likely an FH patient or an LDL above 190 and you had mentioned the double whammy. Yeah, FH along with the elevated Lp(a), so I agree. Throw the kitchen sink at him, don't forget nonpharm therapies that really can help out, not only the LDL but also obviously the other metabolic issues as well. Thank you so much for that insight and it's exciting to have all these therapies for patients such as this.

Deepak Bhatt, MD: Yeah, it's definitely an exciting time in the management of lipid disorders.

Guidelines, Goals, and Evidence-Based Medicine

Cardiologist perspective + Lipidologist perspective

Deepak Bhatt, MD: Data from cardiovascular outcome trials continue to build and recommendations from recent cholesterol guidelines reflect these findings. As a lipidologist, what are some important recommendations for clinicians from the recent 2022 ACC Expert Consensus Decision Pathway on the role of nonstatin therapies?

Seth Martin, MD: Yeah, this is a great question. Thank you, Dr. Bhatt. Overall, the new guidelines provide a chance to tailor or personalize therapy for our patients. In the secondary prevention setting, they define criteria for very high risk ASCVD. This builds on the 2018 AHA/ACC guidelines by carrying forth this definition of very high risk. That's a way to stratify the ASCVD patients. There is a group that's called not very high risk. That doesn't mean that that other group is not at high risk; they're just not in the top echelon of risk that we call very high risk. How do we define very high risk ASCVD? It's either having multiple ASCVD events or 1 ASCVD event plus multiple high-risk conditions. Major ASCVD events include a recent acute coronary syndrome, a history of MI or ischemic stroke or symptomatic PAD. Those all qualify as ASCVD events. You can have multiple of those or you can have 1 event and you have a high-risk condition. The high-risk conditions include age over 65, a diagnosis of heterozygous familial hypercholesterolemia, a history of CABG, a history of diabetes, hypertension, chronic kidney disease, smoking, heart failure, persistently elevated LDL of 100 or more despite max-tolerated statin therapy or ezetimibe also qualifies as a high-risk condition. If you have 2 or more of those high-risk conditions on top of an ASCVD event, you're considered very high risk. This, again, is a chance to further personalize and intensify lipid-lowering therapy, including the use of nonstatin therapies, such as PCSK9 inhibitors.

I'll just briefly mention, in the primary prevention setting, there's also a chance to further tailor decision-making using risk-enhancing factors. If you have an individual who's in an intermediate risk category and you're kind of on the fence around whether to start a statin or not to start a statin, these risk-enhancing factors could push you over the threshold to then start a statin therapy. This includes family history of premature ASCVD, metabolic syndrome, chronic kidney disease, chronic inflammation such as with rheumatoid arthritis or HIV, premature menopause or preeclampsia. We see some of the factors commonly used in women's health clinics being more prominently integrated into the guidelines. Increasingly measured is Lp(a). If you have an elevated Lp(a) level, above 125 nmol/L, that would qualify as a risk-enhancing factor and push you towards statin therapy. And then, in terms of lipid targets, I just wanted to highlight that we now have even more aggressive targets in the 2022 ACC, the ACC Expert Consensus Pathway. In that very high-risk group with multiple ASCVD events or 1 ASCVD event with multiple high-risk conditions, we want to lower LDL by 50% or more and get the LDL to absolute concentration below 55 mg/dL. You also can look to get the nonHDL below 85. And this is supported by multiple high-quality cardiovascular outcomes trials, including the IMPROVE-IT trial which tested the addition of ezetimibe on top of simvastatin in the secondary prevention population, the FOURIER trial which tested the addition of evolocumab on top of max-tolerated statin therapy in patients with ASCVD, and the ODYSSEY Outcomes trial which was an ACS population that had the addition of alirocumab to max-tolerated statin therapy and those trials had some use of ezetimibe as well. These trials have taught us that going lower is better and that we, the guidelines have taken the data and helped provide this risk stratification scheme to really identify those that are most likely to benefit from additional lipid therapy.

Dr. Bhatt, I wanted to see if you wanted to add any thoughts on before I ask you a question.

Understanding Cholesterol Guidelines and Implementing Non–statins in High–Risk Populations: Paired Conversations and Case Vignettes

Deepak Bhatt, MD: No, I think those were a really great summary of the highlights. I think that you hit upon all the major points.

Seth Martin, MD: Thank you, thank you. Let me ask you, given your extensive background and expertise in the world of cardiology, what stood out to you from the 2022 ACC Expert Consensus Decision Pathway?

Deepak Bhatt, MD: I thought for folks with clinical ASCVD, but not very high risk, such as stable ASCVD not meeting the above criteria for very high risk, for those sorts of folks the lipid targets for this not very high-risk cohort are an LDL cholesterol greater than or equal to 50% reduction and less than 70 mg/dL or nonHDL less than 100. But for high-risk primary prevention with or without diabetes and a 10-year ASCVD risk score greater than 20%, their lipid targets again are LDL cholesterol greater than or equal to 50% reduction and less than 70 mg/dL for LDL or 100 for nonHDL. I thought that those were good and appropriately aggressive targets for lipid lowering. But I think it's also important, beyond just the numbers and guidelines and targets and that sort of thing, to focus on the fundamentals and to utilize our colleagues and available tools and to emphasize adherence to guidelines and medications and other cardiovascular risk factor control. It's not all about just lipids. Prevention, of course, is much broader than that. And adherence is a really critical part of any sort of medical therapy or lifestyle recommendations. If the patient doesn't actually do it, you don't get the benefit and, for sure, in the lipid-lowering field, there's a lot that's been written about how patients, even really high-risk patients, are off their lipid-lowering therapy by a year. MI patients, for example, half of them are not taking statins in many registries. It's something we have to keep emphasizing with patients, working with them to try to keep them on their medicines. And if they're going off their medicines, understanding what is it, is it a side effect, a perceived side effect, is there anything we can do, is there an alternative therapy we can utilize? I think sometimes, in terms of lifestyle modification, it can be useful to not just try to do everything in the office, but to refer to a nutritionist or dietician, that can go a long way in terms of making actual changes in a person's diet oftentimes involving their spouse or partner just to make sure that things really change at home. For challenging cases, it's not a bad idea to refer to a lipid specialist. Sometimes, things can get really complex, especially in patients with multiple intolerances and, finally, I'd say use technology. There's different things, lipid manager apps, for example, determining the ASCVD risk score, statin intolerance and just using some of the latest and greatest technology to aid efforts in prevention.

Seth Martin, MD: Great, yeah, that was a fantastic overview and I love that you brought up the importance of once you get the lipids under control, make sure we don't lose sight of other CV risk factors and use the team-based approach and technology to help support it.

Individualized Treatment Plans for Persistently-Elevated LDL-C

Pharmacist perspective + Lipidologist perspective

Jim Backes, PharmD: Another good topic to discuss regarding care approach is individualized treatment plans for persistently elevated LDL cholesterol and, again, we're very fortunate to have multiple pharmacologic therapies to lower LDL cholesterol. I'll throw it out to the faculty, how do we individualize treatment plans for patients that have persistently elevated LDL cholesterol?

Seth Martin, MD: That's a great question, Dr. Backes. The 2022 ACC Consensus Pathway really gives more flexibility to individualize or personalize treatment plans, and we are starting generally with a foundation of healthy lifestyle habits and then maximizing statin therapy. Then, as we go from there, we have a number of options with nonstatin therapy. But, even with lifestyle habits, the diet, of course, it's going to look very different for one patient to another based on what kind of diet they're starting with and what kind of foods they like and, emphasizing a point that was made in other discussion, this is an opportunity for team-based care to refer someone to a dietician, if possible, to help individualize their diet. If it's somebody in the secondary prevention setting, they might be learning diet as well as exercise habits through a cardiac rehabilitation program and that's very much an individualized treatment plan where the exercise prescription is adjusted based on where they're starting and what the goal would be that would be achievable in that individual patient. And then, with statin therapy, we generally want to be on maximal statin therapy. In the secondary prevention setting, we're talking about being on a higher dose of rosuvastatin or atorvastatin, on high-intensity statin therapy. But, of course, many patients—particularly coming into a lipid clinic—will have had some prior issues taking statin therapy and we'll need to individualize the statin treatment plan, if that's the case. If patients have had difficulty with statins in the past, sometimes a lower dose of a higher-potency statin can be a good way to go to get some early success because most of the effect of the statin is happening at the lower dose and

with each doubling of the statin dose, there's about a 6% additional lowering that occurs. These are some of the ways we can individualize the statin and lipid-lowering plan by working with our patients, understanding what their prior treatment has looked like and how they responded to it. But for many patients, they'll have done perfectly fine without any side effects with statin therapy, but yet the LDL cholesterol level, despite that statin therapy and lifestyle, is still above where we want it to be. We've talked about how, for example, in the secondary prevention setting, a very high-risk patient, the LDL, we really want to see levels below 55. If we're at that threshold of 55 or above, we should be considering nonstatin therapies and we now have a multitude of options, including oral therapies that previously was ezetimibe and more recently we have the addition of bempedoic acid as oral therapy and they even come together in a fixed-dose combination pill. And then we have the option of adding PCSK9 monoclonal antibody therapy and more recently, there's been the addition of sRNA therapy, inclisiran, for PCSK9 inhibitors.

We have this multitude of options. Previously, the guidelines had suggested statin, ezetimibe, then PCSK9 inhibitors and, as the evidence has accumulated and the ACC Consensus Pathway kind of digested this evidence, there's a bit more flexibility where you might go to ezetimibe after the statin, but you might also go directly to the PCSK9 monoclonal antibody therapy, particularly if you need a high magnitude of LDL cholesterol lowering. For example, if you have a patient who's very high risk and let's say their LDL cholesterol level is now around 90 or 100 and ezetimibe would tend to give you a 20% lowering on top of their current therapy and maybe get you down into the 70s or 80s, that's not going to be where you want to be for a very high-risk ASCVD patient. In that case, you may use a PCSK9 monoclonal antibody on top of statin and ezetimibe or you might directly go to the PCSK9 monoclonal antibody on top of the statin to get down to an optimal LDL level below 55. That's just an example in the very high-risk secondary prevention setting where that very high-risk stratification is helping individualize therapy because that leads us to go for an LDL below 55, rather than below 70. But we also have more flexibility in which nonstatin agent we kind of move to next in such patients and some folks may end up on 2 therapies, some may end up on multiple, 3 or more therapies. But then, we do pay a lot of attention to the expected LDL reduction.

Now, each patient will not have that exact LDL reduction from the population, that would be expected based on a population average effect and so that really speaks to the importance of following up a lipid panel 4 to 12 weeks after adjusting therapy to see where we end up with absolute LDL concentration and then further individualize therapy based on the guideline thresholds. I mentioned the 55 threshold, but in other patient groups, the threshold will be 50, it will be 70 or 100. And I'll just also mention that in particularly complex cases where the therapy, the existing statin and nonstatin therapies are not getting the job done, there might also be an option for LDL apheresis which is a procedure to remove LDL from the blood, kind of like a dialysis machine but removing it, removing the lipoproteins typically every 2 weeks, sometimes less frequent than that, but that one would be an option for somebody with familial hypercholesterolemia or with coronary artery disease with an LDL that still can't be brought under control with existing therapies. That would be something needed by a smaller number of patients and generally conducted in a lipid center.

Jim Backes, PharmD: Very well-stated and I think, just to kind of piggyback on some of your points and referring back to our previous discussion, I'm a big fan of the focused care. A dietician, a nutritionist was mentioned and you're not going to get a 50% LDL reduction, but you may get some LDL reduction. And that very high-risk patient is likely to also have hypertension, they probably have some degree of glucose intolerance, so a good diet can go a long way. They may physically feel better with a better diet as well. And then I'm a big fan of the 2022 ACC Nonstatin Guidelines and they nicely lay out the algorithm and just, to your point, we have options now. If somebody can tolerate, fully tolerate a statin, use the maximally-tolerated statin. Ezetimibe is an easy second medication to pull from, so both inexpensive medications, effective medications. You can get a 60%, perhaps a 70% LDL reduction. But you're right, in the more complicated patients that occur with the statin intolerance or maybe the FH patient who may have a baseline LDL of 300, you now have therapies where, even if they can't tolerate a statin, you have the PCSK9 monoclonal antibodies. You have the bempedoic acid. You have the siRNA, inclisiran, PCSK9 therapy and so you can really kind of mix and match and individualize therapy. And while I think a lot of people are not perhaps as needle-phobic as they were because the injection devices are pretty user-friendly, inclisiran is a nice option for those individuals or, obviously, adherence is a major, major factor. That's where you can really kind of pick and choose and really individualize the therapy. I agree wholeheartedly with everything that's been said.

Understanding Cholesterol Guidelines and Implementing Non–statins in High–Risk Populations: Paired Conversations and Case Vignettes

Seth Martin, MD: Well said! That is important to consider that as we individualize patient treatment plans, the patient preference around oral vs injectable therapies. Bempedoic acid, ezetimibe are oral therapies. PCSK9 monoclonal antibodies and sRNA therapy, the evolocumab, alirocumab, inclisiran, are injectable therapies. Inclisiran has an initial starting dose and then it's 3 months later and then every 6 months thereafter, administered in the healthcare setting, whereas evolocumab and alirocumab are home-based injectable therapies every 2 weeks. And so that, as you said, many patients are okay with that and they do well with the injectable therapy, but it's important to kind of consider the frequency of those injectables, whereas some patients just have a strong preference for oral therapy, and the good news is we also have nice options there. Ezetimibe and bempedoic acid each lower LDL about 20%, together they can lower it about 40%, whereas we get, with high-intensity statin therapy, above a 50% reduction. With PCSK9 monoclonal antibody therapy, a 60%, 45% to 60% reduction, depending on what dose we're looking at. But we can get robust LDL reductions with these therapies, particularly when used in combination, and really allow for some combination of therapy to get our patients to where they need to be.

Patient Education and Shared Decision-Making

Pharmacist perspective + Nurse perspective

Jim Backes, PharmD: Welcome back. It's good to have Dr. Walsh-Irwin and Dr. Anderson here. And the topic that we're going to talk about now is patient education and shared decision-making. And I think we all know the importance of engaging the patient and that providing evidence-based information is very critical to patient care. What are some of your tips to share with our audience for patient buy-in? I think I'll start it off and then you guys can fill in if you want. But what we deal with a lot is statin intolerance, statin hesitancy and probably this is even a bigger umbrella of just a hesitancy towards cholesterol medications. Interviewing the patient and taking down and asking what is their concern. Is it what they read on the internet? Is it, are they concerned about their liver? Or are they concerned about the muscle soreness that they perceive they may receive? That's how I guess I get buy-in is I dig down, tell us why you're concerned, what your concerns are, where are these concerns coming from. And then I share the evidence with them and I think what's really been helpful over the course of the past few years are the N-of-1 trials that talk about statin intolerance and how these N-of-1 trials have enrolled statin-intolerant patients and, lo and behold, they have almost comparable muscle soreness, achiness when they're on placebo as they do statins. Being a good ambassador and kind of breaking the ice with the patient with some of that information. But what about you, Dr. Anderson? What are some of your insights?

John Anderson, MD: It's everything you said, you summarized it really nicely. I mean, the first thing you do is actively listen. I try not to be judgmental. What are your concerns? From whence comes this sort of stuff? Is this a family member? Did you have a mother-in-law who will never take that medication again because she heard something negative about it or there was a family member who started that medicine and had a bad event? But you're right, calmly going over the evidence, calmly addressing and hopefully, especially in the primary care setting, they have your trust. They're there because usually you have a longitudinal relationship with them and you can build that trust over time. And you can sit them down and say, here's the evidence, right? We get this a lot too, Jim, with the diabetes thing. You know, the statins are going to cause diabetes or, with all the diabetics, they're going to worsen my glycemic control. You have to go through that too. The other thing I would tell a clinician and a physician is you may not get it that visit. Be persistent. When they're back in 4 months for their diabetes visit, let's have this conversation all over again. You don't necessarily have to win that battle the very first time.

Colleen Walsh-Irwin, DNP: I think a lot of the common themes is, yes, statins have a bad rep, right? They need better PR from the beginning because everyone comes in like immediately the hair raises on their neck when you mention a statin, at least in a lot of my patients. I think, like you and Dr. Anderson said, making sure that you acknowledge their concerns. I also try to show them that research has shown that far fewer people have statin intolerance than originally thought and then I engage them in conversations about their risk and when I show them a risk calculator and can print out, showing them that, by lowering their cholesterol by 38 points, we can reduce their risk of heart disease by nearly 25%. Is it worth trying the statin? And sometimes, like Dr. Anderson said, it's a little bargaining. You know, like yes, ideally I would like to get you on that moderate-intensity statin to start, but maybe, if you're agreeable to even starting at a lower dose and we can work our way up to the goal, that's better. That's the long game is get them to goal eventually rather than have them completely hesitant to start. And then offering them reassurance that they can call me if they have a problem and don't wait until you come back in 3 months to tell me that you didn't take it. I'd much rather hear from you now

than to find out in 3 months that the day you took it you thought you had a cramp, and now you've waited to come back for 3 months to tell me that. We've already lost 3 months to getting you towards goal. Encouraging them to call me and then I think we also know that, for those patients who do come in and have concerns about statin intolerance, again having that conversation repeatedly, getting their trust that we need to either restart at a lower dose, we definitely have ways to get them to goal even once they're concerned about that statin intolerance, every-other-day dosing, adding ezetimibe, etc.

John Anderson, MD: And it's interesting because Colleen heard me talk about this earlier in a module, I had a patient come in today with type 2 diabetes, extremely well controlled, subclinical ASCVD, on atorvastatin at a moderate dose. You know, Dr. Anderson, my wife who's sort of in the medical profession but not a clinician, said you need to ask about this, because I come home every night and I have leg cramps and things and it takes me a while to walk them off. It's not waking me up at night, but it's kind of a bother. Do I really need the statin? I go, well, you've been on this statin for a long time. This is not something we just initiated, so I find it highly unlikely that that's the case, but let's make mom happy at home, let's make you happy. We're going to stop the atorvastatin for 2 full weeks. If it completely, 100%, eliminates any leg cramps, then we're talking about another statin, not nonstatin therapy. And to her point, I'm not waiting another 3 or 4 months. He's going to call me in 2 weeks. He has his homework assignment.

Colleen Walsh-Irwin, DNP: Yes, and John, to make that point also, a lot of times when I ask patients, well gee, you know, it's the summertime and you're telling me you've been more active, have you been drinking enough water during the day? Because oftentimes they're getting a little of dehydrated leg cramps, not really true statin intolerance.

Jim Backes, MD: Right, now as a pharmacist, I can say that the statins are not side effect-free, but they also get blamed for a lot of side effects that they have nothing to do with as well. Dr. Anderson, Dr. Walsh-Irwin, thank you for your insight and I think we all make valid points. Listen to the patient, communicate with the patient, build that relationship, be persistent. To mention something that you brought up, Dr. Walsh-Irwin, the objective information that you can provide with a risk calculator or having that calcium score, showing them what that is or measuring the carotid intima media thickness. When they can see the disease, then that can oftentimes trigger some buy-in as well.

Multidisciplinary and Interprofessional Care

Lipidologist perspective + Primary Care perspective

Seth Martin, MD: Dr. Anderson, Dr. Walsh-Irwin, I think it's a great time now to talk about the multidisciplinary and interprofessional care aspects of our discussion, particularly for the complex patient. Patients are living longer with ASCVD. They have a bunch of comorbidities and this, of course, is what we want for people to live longer with the advancements in the standard of care, however with more cardiovascular therapies and procedures comes an increase in management and patient complexities. I wanted to think through together how each member of our faculty approaches the complex ASCVD patient, whether it's from team-based approach to care, how you kind of stagger things across visits, how you prioritize, successes and pitfalls. Maybe we can start with you, Dr. Anderson, and then we'll move to Dr. Walsh-Irwin.

John Anderson, MD: This is a great question in the current setting where we have multiple therapies that cross different therapeutic sort of targets and cross from nephrology to cardiology to endocrinology to primary care. And so it starts with collaboration. I mean, I tend to think, as a primary care physician, that I own sort of the navigation for that patient through the healthcare system, but for the complex patient that has cardiovascular disease, there's no question that there's going to be collaboration with me and a cardiologist. Sometimes it's a cardiologist and a heart failure specialist. Sometimes it's a cardiologist and an EP specialist because they all have afib, right? It's about identifying, during that visit, where the gaps are. Is this someone who has diabetes and should be on a GLP-1 receptor agonist? Is this someone who has heart failure and should be on an SGLT-2 inhibitor? Or conversely, the cardiologist sees them upstairs and says, I'm not comfortable prescribing SGLT-2 inhibitors, but they need one, how comfortable are you with doses, formulary, do you have samples in your office. Whoever sees that patient, take the responsibility for identifying the gaps in care and then maybe not just put it in the medical record. I say, pick up the phone and call. Have a direct communication to identify, at that particular time, what's the patient not getting that they should be getting.

Colleen Walsh-Irwin, DNP: And I think, as providers, it's not just a provider-specific target for getting the patients to goal. I think we can also pull in our pharmDs, our registered dieticians, our RNs in the office. As a nurse practitioner, I know our RNs are up to helping with the call-backs and the follow-ups, etc. We really need, in this day and age, to utilize

everyone on the team as much as we can to get the patients to goal. And then having that relationship with primary care and our other specialists so that we're all repeating the same things over and over again to the patient, so they're hearing it from multiple people, primary care, cardiology, the registered dietician. We want to make sure that we all have the same endgame in mind.

Seth Martin, MD: Absolutely. It's really easy for care to become fragmented and for there to be communication breakdowns and so I think really coming together as a team, just making sure we're kind of communicating from clinician to clinician. And the more education that the patient gets and has bought into their care, the more they can also be a good kind of common denominator as they go from appointment to appointment to make sure each clinician is kind of fully updated. But yeah, I could not do what I do without my staff and a team-based approach. When it comes to patients with complex advanced lipid disorders who we're starting on a PCSK9 therapy or other nonstatin therapy that requires prior authorization, I heavily rely on our specialty pharmacy to help fill out the initial paperwork, manage the reauthorizations a year from that point and help educate our patients. Our specialty pharmacy has a pharmacist who connects with each of our patients to make sure they're comfortable with the injection technique and see if they have questions. This team-based approach is really critical. And then it's such a common thing that I've referred someone with high lipids, but their blood pressure's out of whack or they have obesity and their diabetes is not under great control, so it does become a challenge sometimes in prioritization. I definitely try to extend my reach in the lipid clinic beyond just the lipids, but I also try to work with my patients' other physicians, with their primary care provider. We also have a cardiometabolic clinic and really just do whatever we can to provide a holistic approach for the patient.

John Anderson, MD: I completely agree and I think it's, again, in my purview, that the cardiologists are all on the same electronic medical records, but our nephrology colleagues are not. It's okay to send an ankle to an orthopedist without a comprehensive note, but to our staff, they understand when we are making a nephrology referral, they need data, they need A1Cs, they need laboratory, they need UACRs, they need the progression of EGFR over time, they need medication lists, they need to understand why that patient's arriving so that they can have an effective first visit with an individual rather than wasting 30 minutes trying to gather data.

Colleen Walsh-Irwin, DNP: I was just going to add that in addition to the patient, I think when we engage the family also, sometimes that can be helpful. And then especially not forgetting family members of those patients who have the familial hypercholesterolemias, that we start targeting them early. Even if they're children, in the pediatric population, making sure that they're getting lipids done so that we can rule them out for having familial hypercholesterolemias.

John Anderson, MD: The key thing here is we have to break down silos. The cardiologist is no longer just in charge of atherosclerosis and that management. The primary care/endocrinologist is not just in charge of glucose. That we have to break down all our previous silos where I'm only in charge of this and understand the patient more as a cardio-renal-metabolic risk as a whole.

Seth Martin, MD: Right. I mean, Dr. Anderson, when you say it's fair that we probably shouldn't worry too much about stepping on each other's toes, but more so each doing what we can to advance care forward and then, when the patient sees the next part of their team, continue to try to move the ball forward. I've yet to have someone say, hey, why did you do that? I wanted to do that, right? I think we appreciate when each [of us] are helping advance the patient's care and then when we, if there's something that falls outside the context of our clinic, getting the patient referred to where they can go.

John Anderson, MD: I think that's absolutely true. I would never get on anyone who's trying to take care of my patient. And again, frequently, the cardiologist will send them down to start a GLP-1 receptor agonist because I'm better at teaching the technique, my nurse is better at teaching the device. We have samples in our office they may not have. But no, if you've got an idea or you want to initiate therapy, you're not going to find people who care for that patient sort of worried about whose foot is being stomped on.

Seth Martin, MD: I often see patients who get to my clinic, but they have just not established care with a primary care professional and so I'll, if their blood pressure's out of whack, I'll start getting the blood pressure therapy going, but then highly encourage them to get in to a local PCP who can help continue to move that forward because my clinic's not necessarily convenient to them because of distance or set up to do that as well as a PCP office could do. But it's very much a team-based approach.

Colleen Walsh-Irwin, DNP: Yeah, I mean, a lot of times you're seeing patients, their first entry into the medical

office is after they've had an MI because they had undiagnosed hypercholesterolemia, or a young person in their family went undiagnosed and then they ended up having an MI or is at high risk of one. Again, sometimes we are the first ones to see them in cardiology.

Seth Martin, MD: Right, right. And you bring up a really good point too around familial hypercholesterolemia, thinking about the family, working on cascade testing to find other family members and that's one of the really satisfying aspects of caring for a patient with familial hypercholesterolemia that you can help them, but then you can help the rest of the family. There's that cascading effect. And they can each kind of learn together and help each other achieve their best outcomes.

Colleen Walsh-Irwin, MD: Plus we actually now have medications that can target that. You know, before we just had the statins. You were doing the best you could, but now we actually have medications and we're learning so much more about it. We have more options now than ever.

Seth Martin, MD: Right. Now we have a robust armamentarium to get that LDL not even just under reasonable control, but to a really optimal low level.