Christie M. Ballantyne, MD:

Welcome to this program by CME Outfitters on “Transforming Cardiovascular Care: Uprooting Misperceptions in Therapeutic Inertia in Lipid Management.” This is supported by an independent educational grant from Merck & Company. This activity may include discussions of products or devices that are not currently labeled for use by the US Food and Drug Administration. I'm Christie Ballantyne. I am the chief of cardiovascular research and cardiology at Baylor College of Medicine.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Hi, and I'm Peter Toth. I'm director of preventive cardiology at the CGH Medical Center in Sterling, Illinois, and also I'm faculty at the Ciccarone Center for the Prevention of Cardiovascular Disease at the Johns Hopkins University School of Medicine in Baltimore.

Christie M. Ballantyne, MD:

Well, it's a pleasure to be with you, Peter, today. Our first learning objective is to discuss some of the prevalent misperceptions that impact evidence-based lipid management. And this has been... It's interesting. It's almost gotten to be more of a challenge now than it was, for example, 20 years ago.

Maybe some of the confusion's in some of the guidelines. There've been a lot of different guidelines over time. There was this issue that you didn't need to measure LDL cholesterol, you just only used a statin, I think that was. And then there was this; some thoughts that LDL wasn't even important, and we see that a lot of times on social media.

So we have all these swings back and forth in terms of consensus statements, and then there's multiple choices now. I think it's really important, and I hope that what we're able to accomplish here is to really... The story's pretty simple, don't you think?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

I think it's very simple, very straightforward. It's one of the most highly investigated issues in the entire history of medicine, and it's staggering that it's just not catching on.

Christie M. Ballantyne, MD:

Yes. I mean, it's not that complicated. Lower LDL cholesterol for longer is better.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes. And I think the real buzz line, I think has to be “lower is better, lowest is best, and for longer,” because now we're viewing LDL burden exposure, kind of like we viewed cigarette smoking in PAC years. Now we're looking at it as milligram exposure in terms of number of years. And it really does work. There's a very beautiful linear relationship between the hazard of the magnitude of LDL elevation and the years of exposure and the risk of disease.

Christie M. Ballantyne, MD:

So there's a lot of misperceptions here, and a lot of it unfortunately has to do with lowering LDL that people are saying if you lower LDL, that causes dementia or hemorrhagic stroke malignancies, neuropsychiatric problems. But we have the trials where we were getting LDLs on average down to 30, and we didn't see any of these show up in the studies. Right, Peter?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes. I mean, if you look at recent meta-analyses, you look at recent propensity score matched-case control studies, and most poignantly, you look at the randomized data out of Fourier and Odyssey Outcomes, where in just by way of example, in Fourier, the mean attained LDL was 26 milligrams per deciliter in the combination therapy group, there was no signal for increased risk of hemorrhagic stroke. And then in the EBBINGHAUS subgroup analysis, there was also no augmented risk for dementia based on a very comprehensive evaluation of multiple spheres of cognition.

Christie M. Ballantyne, MD:

About statin intolerance, I mean, how common is that? The other one though we'll get later on is, but are there ways to handle it?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes. Well, statin intolerance is actually not very prevalent. It's over-diagnosed. It's clearly influenced by psychology. We know from the N+1 study, which was probably one of the most insightful studies ever done on this issue, that simply taking a pill, whether it was placebo or statin, correlated with increased risk for myalgia and intolerance. So intolerance is over-diagnosed. And the problem, I think the biggest problem with this is that a patient will say to their physician or their healthcare provider, "Well, I just can't take this statin because my left knee hurts." And then they're told, well, okay, then just stop it. And then there's no evaluation, there's no follow up of this, no re-challenge. And it can be quite catastrophic for the patient, especially if they're in the secondary prevention sphere.

Christie M. Ballantyne, MD:

And there's also some perceptions, for example, women are low-risk. We don't have to treat them. I mean, give us what's the real issue in regards to patient groups that you don't have to treat really old people or women. What's the better approach towards who we should treat? I mean, how do you go into the whole concept of risk, Peter?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes, so actually we know that there are very large disparities between how men and women are treated. Women tend to be under-treated or untreated, unfortunately. They have worse outcomes than men after sustaining acute cardiovascular events. And we don't lower their LDL as well as we do for the men. And this also holds for racial and ethnic minorities. And these are gaps that we simply have to close if we're going to practice good, responsible compassionate medicine.

I think another factor here is that it's unconscionable to me that when you look at some of these Medicare registries, up to 40% of Medicare enrollees who undergo revascularization following an event, leave the hospital without any statin therapy. Now what is that? We know from other registries, especially from Israel and from Iceland, that actually there's a mortality benefit now up to age 96. So I think we really need to pay attention to this and we need to practice in an equitable way and be very cognizant of the fact that there's really no upper limit on patients we treat, assuming that they are functional and they still want to be treated. And we really need to drill down on practicing better medicine for women as well as racial and ethnic minorities.

Christie M. Ballantyne, MD:

And the other one that comes up in particularly younger people not being treated is the concept that things like heterozygous familial hypercholesterolemia are rare disorders or genetic disorders in lipids are rare. What's the actual like frequency?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes, that's pretty loopy, isn't it, Christie? Because actually heterozygous FH is one of the most commonly occurring genetic metabolic disorders in the world. And over 30 million people worldwide have heterozygous FH. A very sizable number here in the US have it and go untreated, unrecognized, and they're not screened. And if you are looking in the eye of one of the most highly prevalent metabolic disorders in the world, it makes a great deal of sense to screen everyone for it and it's not happening.

Christie M. Ballantyne, MD:

And the other one, which unfortunately I see this for prevention and we see it a lot with lipids and we all see it somewhat with hypertension, put them on a medication statin and you're done. What's the fallacy with that?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Well, the fallacy of that is that every meta-analysis, including that by the cholesterol treatment trial is collaboration. And when you look at the log linear relationship between LDL and the hazard for an acute cardiovascular event, the relationship is a straight line. It is not a line that comes down and then flattens at some arbitrary point. It's a straight line. And the reason being is that there's no lower limit to which there's no incremental benefit from LDL lowering.

And Christie, I don't know what you're feeling about this is, but actually I view LDL particles as a vascular toxin because if you look at the rules of toxicology, whenever you encounter a toxin, the higher the concentration or level of a toxin, the greater the toxicity. And that's exactly what we see with LDL. And the bigger the reduction in LDL, the bigger the risk reduction.

All right. So that takes us to learning objective number two, Christie. And that is to identify the roles of LDL cholesterol and Lp(a) in atherosclerotic disease development and progression.

Let's take a look at a patient case. LT is a 58-year-old Hispanic lady with hypertension. Her current blood pressure on medications is 140 over 80 millimeters of mercury, and her BMI is 29 kilograms per square meter. No prior ASCVD-related events. She's never smoked and her father died of a myocardial infarction at age 54 years. Her lipid panel shows a total cholesterol of 215 milligrams per deciliter. Her LDL is 140, HDL 49, triglycerides 180. Her current medications include lisinopril of 40 milligrams daily and another chlorothiazide of 25 milligrams daily. And her 10-year calculated ASCVD risk is 5% with a fasting blood sugar of 105.

So Christie, give us some insight on how you would approach this lady's lipid management based on her current calculated risk.

Christie M. Ballantyne, MD:

Well, I'm concerned about her with it, although this is, I think that 5% risk doesn't sound very impressive, Peter, but that doesn't include family history, right, in the risk calculator. She's really looks like metabolic syndrome here, impaired fasting glucose, triglycerides are up, BMI is up, hypertension is... I'm not sure if does she really take her medicines the way she said, but I'm very worried with that family history that she's following in the footsteps of her father.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Absolutely. And I agree. For some doggone reason, we have de-emphasized the importance of metabolic syndrome over the course of the last couple of guidelines. But this is a critically important issue because we know that metabolic syndrome in aggregate really is a profound magnifier of risk for both men and women for developing atherosclerotic disease and for propagating it.

So as we look at her lipid profile, clearly her LDL is too high, her HDL is below 50, her triglycerides are elevated at 180 milligrams per deciliter. So as you look at that lipid profile, Christie, what's running through your mind? What are the issues that you've got to drill down into and fix?

Christie M. Ballantyne, MD:

Well, she's got increased atherogenic lipoproteins with that. And so we look at this, Peter, that triglycerides are going to be carried in VLDL or VLDL remnants, IDL particles. That LDL's increased, but I mean, could some of that be LPA rather than LDL particles? It might be with that family history. We're worried about that. Whenever you see a family history, for sure, we need to look at that LPA.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes, I agree. And here's a situation where I think non-HDL is in fact very important to also take into account or an ApoB, a total ApoB because as you mentioned, the remnant particles, the small VLDLs, the IDLs, which we typically don't look at in a lipid profile in a patient with elevated triglycerides, clearly her metabolism is off. She's going to have high levels of these remnant lipoproteins, and the non-HDL number or the ApoB number is going to capture those and it's going to help you include these ancillary lipoprotein risk factors.

And then a separate LPDL-A determination is actually quite indicated not only because of the family history, but current guidelines now recommend that everyone have at least one LPDL-A measurement performed in their lifetime. Because if it's elevated, even though at the present time we don't have medications that are approved to lower its level, it is a very strong risk enhancer.

LDL, of course, is the most important surrogate marker of circulating atherogenic lipoprotein and the primary biomarker of ASCVD risk because in the average patient, it is the lipoprotein that is available at highest concentration. And when you look back at the clinical trials looking at lipid lowering, LDL is the typical target of therapy.

Major acute coronary events are reduced proportionately to the degree and duration of LDL lowering, as we've already mentioned. And this is critically important to keep in mind as we manage patients, namely earlier is better, lower is better, and LDL is the primary target for lipid-lowering therapies in clinical practice. And it is not representative of the full burden of atherogenic lipoprotein in some patients. And that's why we recommend also looking at non-HDL, particularly when the triglycerides are elevated as they are in this particular patient.

Now non-HDL and ApoB are very important measures of total atherogenic lipoprotein burden in serum. And this is especially true for patients with hypertriglyceridemia, patients who are diabetic, they're insulinresistant, and hence, they typically have elevated serum triglyceride levels because of insulin resistance at the level of visceral adipose tissue. And of course this will also be true of patients who are obese or have metabolic syndrome.

So it is important to consider monitoring non-HDL in ApoB one or the other. I think there is good evidence that ApoB is actually better in a situation of discordance because you're going to get a much more comprehensive and accurate assessment of a patient's risk for developing ASCBD or sustaining acute cardiovascular events. And this of course is also true of high-risk patients and patients with hypertriglyceridemia. Christie, tell us about the impact of LPLA on ASCBD.

Christie M. Ballantyne, MD:

Well, it's LPA, it's a... Peter, you mentioned about non-HDL cholesterol in ApoB and you can sometimes have discordance, but non-HDL cholesterol gives you... the lipid profile gives you a pretty good idea of what non-HDL cholesterol or ApoB elevations will be. You can't predict LPA. The only way you can really tell if someone has a high LPA is to measure it. And it turns out that your levels of lipoprotein(a) are primarily determined by your genetics. Unfortunately, diet and exercise are not going to lower your LPA levels the same way they lower triglycerides, for example. And it's a very important predictor for ASCVD, but also for aortic stenosis, which was really something that we didn't fully appreciate for it.

And there's some association, it's a little weaker with stroke and heart failure, but really having high levels of LPA, this is something we talk about. And FH is a pretty common genetic disorder for monogenic pathogenic variants. But LPA is actually, if you think about it, the most common hereditary factor because almost one in five people have a high level of LPA. Unless it's measured, you have no idea whether you have that or not. So really important, and I think it's something that the momentum is really building up in terms of the data, showing the importance of this for risk assessment. And also, even though we can't currently lower LPA, we do know that there's benefit from overall treatments for risk assessment, particularly lowering LDL seems to be highly beneficial.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Well, and I think what a lot of people do is if a patient does in fact have a marked elevation in their Lp(a), they treat the LDL even more aggressively in an effort to try to offset the excess risk attributable to that elevated Lp(a). What do you think of that?

Christie M. Ballantyne, MD:

Well, I think it makes a lot of sense, is that when we see that someone is very high risk in general, like a calcium score... I don't know about you. I never sent anybody to chelation therapy. I'm not trying to lower the calcium. I'm trying to lower the risk of the patient for having an event. So when you see one of these very high LPAs, it's the same concept, particularly when there's a bad clustering of other things that we need to be treating that patient aggressively. And then all of that also goes to exercise and diet. Even if they're not lowering the LPA, they might be improving metabolic syndrome and insulin resistance. And so treating blood pressure more aggressively, treating LDL more aggressively. So yes, it's a very logical approach and we have some of the data from some of our trials with statins and PCSK9 inhibitors, that the people do have benefit with high LPAs.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

And then I think something else that's very important is that Lp(a) is a significant risk factor for ischemic stroke.

Christie M. Ballantyne, MD:

Particularly if you see in children or a very young person, you always should measure LPA.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes, yes. So Christie, now that we've discussed some of the important elements in interpreting risk, what would be your first, and then what would be your second step in managing our lady's lipid-related risk? Given the fact that she has a family history of premature disease, she has hypertension, she has metabolic syndrome, and we really want to reduce her risk substantially.

Christie M. Ballantyne, MD:

So this is someone who needs comprehensive evaluation treatment. But first thing I'd want to do is explain to her 10-year risk is 5%. That sounds pretty low, but you can also calculate the 30-year risk from this risk equation book order. And her 30-year risk is 39%. So she's almost got a 40% chance by the time she's 88, she's going to have an event. That's pretty high. And I think maybe we need to give the numbers. That's basically almost 50% chance you're going to have something that we could prevent.

So I think these 10-year risks can be very misleading and they're not motivating to people. When you give them their actual lifetime risk, and her life expectancy is to be about... we see this more and more now. So she's going to have a high risk for an event. So she should be honest at... and this is somebody who I would like to get... If we take a look at this metabolic syndrome pattern with this, I'd like to get her LDL down.

She certainly has to be, we want to get people's LDL to well below 100. I'd like to get her non-HDL cholesterol below 130 here, and she's about 165 right now. Blood pressure needs some improvement. Lifestyle, we got to talk about diet and exercise. I'd like to get a hemoglobin A1C on this patient. But ideally, and this is the thing that comes up, if someone said, "Well, if it were a relative or someone with..." or just any of my patients say, "Well, where would you think I really should be?" I mean, the guidelines are saying at least under 100, you'd like to have her under 70, right?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

I would most certainly treat her to less than 70 on her LDL and less than 100 on her HDL.

Christie M. Ballantyne, MD:

Non-HDL cholesterol.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes.

Christie M. Ballantyne, MD:

Really, so this is where you really want to have this individual. And the other one that comes up is I would get a calcium score. Yes, it's an out-of-pocket expense. If you shop around, they're pretty inexpensive, a little over 100 bucks. Because you may have a calcium score that's very high, at which point now we're going to get even more aggressive. If she has a calcium score that's three or 400, she's really in the same risk as somebody who has been diagnosed to have coronary disease.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

So here in Sterling, Illinois, we can get a coronary calcium score for $59. And it's fascinating to me that recent data out of the MESA studies showed that any coronary calcium score that is not zero of course heightens risk for future cardiovascular events. But in this new analysis, the majority of first-time events were actually fatal MIs. And so right now, I'd have to say coronary calcium scoring is probably our best crystal ball for identifying patients at risk as early as possible.

Christie M. Ballantyne, MD:

And importantly, you should look at the age and sex percentiles because it turns out that it's a big difference. A 75-year-old man with a calcium score of 100 versus a 58-year-old woman with a calcium score of 100, that that's a very high percentile for 58-year-old woman. So she has a lot more disease than you would predict, and there's frequently some soft plaque in there and things like that. So it's a very useful test, particularly once you're over the age of 35, really over 40 in men or 50 in women. So I would get that for this patient.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes. And Christie, you've shown in studies you've done that actually it appears that patients with metabolic syndrome, whether they're men or women, actually have disproportionate benefit from statin therapy compared to patients who don't have metabolic syndrome. Do you still believe that's the case?

Christie M. Ballantyne, MD:

It's interesting because for so long, we were thinking about for someone like this, maybe your first choice would've been low HDL or high triglyceride of five, eight or niacin or omega-3s. And it's pretty clear your first choice is LDL-lowering statin. And then if you need to add something else, if you're not responding to that, you might add something else. You can add acetamide. We could talk about combination therapy just like we do with blood pressure with that.

We had some problems with adding fibrates. They haven't worked out so well. And we only had one study with the eicosapentaenoic acid (icosapent ethyl) in cancer that showed benefit in regards to the triglycerides. And it looks like it wasn't really a lipid effect. It might've been another effect on there. So I think where you're on really solid ground is to lower the levels of LDL, ApoB, non-HDL cholesterol on this patient. We have ways to do that that are extremely effective, and that would be my first choice on this person. We spent a lot of time chasing triglycerides and HDL, didn't get very far with that. Not yet.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

And I think consistent with the guidelines, given the fact that this patient's LDL cholesterol is around 140 milligrams per deciliter. A high dose, high potency statin such as atorvastatin, rosuvastatin given at 40 to 80 on atorvastatin or 20 to 40 on rosuvastatin would get her LDL to goal. And then you might have to use an adjuvant therapy to get her non-HDL under 100. But clearly, it's very doable in this situation.

Christie M. Ballantyne, MD:

Agree. All right, so let's go to our third objective, incorporating current guidance to optimize lipid management in clinical practice. Another case here, a 59-year-old Black woman who's got well-controlled type 2 diabetes, keeping on an A1C 6.8%. Also has hypertension, never smoked, rarely drinks alcohol, adopted. Family history unknown. No previous AACBD events. Total cholesterol is 200, LDL is 145, HDL is 55, triglycerides 147, LPA 29 milligrams per deciliter. Ten-year AACBD risk is 15.2%.

Now she's on rosuvastatin 20 milligrams daily for three months in 2020. However, she self-discontinued that because of muscle aches. Not an uncommon... If you have a lipid clinic, this is a pretty common case that gets sent in to it.

So let's go back a little bit before we go to this case further. Let's go over the steps. First of all, you got to measure lipids, then you got to assess risk, and then you can manage LDL. And that's because... And let's go about lipid screening. So I think you and I are really firm believers, you should have universal lipid screening. It's going to vary in terms of the reasons for this is you want to screen in children and young adults so you don't miss familial chylomicronemia. We talked about this, right, Peter earlier.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes.

Christie M. Ballantyne, MD:

How important that is. We tend to not be aggressive with drug therapy. The other thing, until if you have FH, you need to treat and you want to treat early with this. You want to start treating at around age of nine to 11 years old, because it's the shielding of exposure to LDL. In adults, then we're measuring lipids, we look at the risk. And depending upon the risk with that, if you've decided to treat someone with lifestyle medications, you need to get follow-up labs, particularly with medications. I like to get around four weeks because I would like to have sooner responses. And if someone's on treatment, you'll want to get measurements annually. So measuring lipids is really important for screening and also responsive therapy.

Now, risk assessment. So one of them ends up is just if you measure lipids, when you see a really high LDL that's over 190, you should be thinking this is a possible genetic disorder. But the other one, Peter, is even if it's not, so let's say if you did genetic testing and your LDL was 210, does that mean you shouldn't treat it?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

No. Oh god, no. Well, plus, I mean unless you're... Okay, so if you did whole gene sequencing for ApoB and for PCSK9 and LDL receptor and et cetera, et cetera, and you found nothing, well, okay, that doesn't mean you don't treat. Of course, you treat an LDL of 210 because the risk for that patient is very, very high long-term. And if you're using a lab that doesn't do whole gene sequencing, keep in mind that they're only looking at some of the most common genetic variants in the genes that give rise to the phenotype of FH. And they're going to be missing a lot of mutations, especially private mutations, founder mutations, mutations that don't occur very frequently. So always, always, always, you treat an LDL of 210, whether you have genetic evidence of FH or not.

Christie M. Ballantyne, MD:

So it's pretty straightforward here, keeping it simple as our goal today. You see a high LDL, it's critical to 190 that you don't need to go into risk assessment, you just treat that.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

You treat-

Christie M. Ballantyne, MD:

You can look at secondary causes. Now that's important. Check their thyroid function, protein urea, looking at secondary factors, but ruling those out, you treat the LDL. All right. What are-

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

And even in primary prevention, you want that patient less than 100.

Christie M. Ballantyne, MD:

Correct.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

And preferably less than 70.

Christie M. Ballantyne, MD:

Well, what about the other groups in terms of risk? So there's a chart that we put together for the National Lipid Association in a publication, putting it all on one page because a lot of our guidelines are, they're 20 or 30 pages long. But basically, if you think of somebody who's had a atherosclerotic event, well, we know those people are in a... that's secondary prevention. And even in secondary prevention, there are some people who have a lot of other risk factors. And so we consider them to be in a very high risk category.

Personally, I try to simplify this almost further, Peter, and I consider almost everybody in secondary prevention to be very high risk.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

I do too.

Christie M. Ballantyne, MD:

I don't know about you.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

I do too. Absolutely.

Christie M. Ballantyne, MD:

So it's no problem. If you want to just count them all as very high risk, I think that's okay. But then we look at the issues in terms of in primary prevention, we already talked about one. Over 190, I've already know what to do here. Type 2 diabetes, what about that, Peter?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Oh, absolutely. And this is a rhetorical statement, Christie, because I know that you know this, but if one was to sit down and look at the enormous range of pro atherogenic phenomena that insulin resistance regulates, it is absolutely incredible. You could probably count 30 or 35 influences just attributable to insulin resistance. So a patient who's a type 2 diabetic off the bat has off the charts risk of developing premature multi-vessel disease and I, to be honest with you, I treat them all very aggressively, very aggressively.

Christie M. Ballantyne, MD:

So we have the couple categories there. The other one as you mentioned calcium scores, if they're over 100 or the 75%, if someone's primary prevention with a 10-year risk, over 20%, that's really high. So an LDL, this is people we're trying to get LDLs under 70. Now you've got other people who have a lower risk, but they're going to be... This was saying 7.5 to 10%. We talked about a case where it was 5%, 10-year risk, but they had a lot of other factors. And 30-year risk was high, family history.

I am a little more lenient than this, and I'll go... We know that the five to 7.5% could benefit, but that's a joint decision making on that. On the lower-risk patients, go less than 100. But when someone asks you for everyone, the ultimate LDL is less than 100, So this was kind of a simple algorithm, but trying to make it a little easier for people to check a box and figure out what to do with somebody. Because these very high risk patients, Peter, the consensus now is we ought to be getting to less than 55, that top part in the pink there.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes, actually it's very interesting because I think NCEP ATP-III first noted that an optimal LDL would be less than 100 for anybody. But I strongly disagree with that because if you look at the log linear relationship between LDL and the hazard for a ischemic heart disease related event, the Y intercept of one, meaning no excess risk occurs at an LDL of 40 or one millivolt per liter. So less than 100 just doesn't cut it. And for my highest risk patients, I really target less than 40.

Christie M. Ballantyne, MD:

And these are, there are guidelines in other places that are saying, because we have someone who's had recurrent PCIs and MIs less than forties, even lower would be better. We talked about lower for longer is better with this. But this is a fairly simple statement that has been put out that I think it'd be helpful for people.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

It is helpful.

Christie M. Ballantyne, MD:

Now, in terms of starting there, Peter, you've already talked about when it's a high-intensity statin, what that. Then so that's going to be rosu with 20 to 40 or ato for 40 to 80, and then we have a lot of options for moderate intensity.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes, yes we do. And I wouldn't emphasize low- and moderate-intensity statin in older patients too much because we really want patients to be titrated to an appropriate LDL based on their overall risk. To me, one of the biggest problems we see in daily practice is patients are started at a low dose on a statin out of caution, and they're parked there, and they're left there and the statin winds up not being titrated even with prompts in the EHR. Studies have shown that the statin winds up not being titrated, the patient does not wind up at goal. And hence, I typically start with high-dose, high-intensity statin as appropriate because starting low really makes no sense given what the data have shown us.

I'll tell you, Christie, my approach here, especially since it's an African-American lady who's diabetic and has hypertension, I'm going to be really aggressive here because number one, compared to any other group, Black women have the highest level of disparity in terms of inadequate lipid lowering efficacy and poor, poor goal attainment. And second, they have the highest rate of reinfarction and doing poorly after having an incident event.

This is a case where this is a group particularly impacted by healthcare disparities, and this is where we have to drill down. And not only does the healthcare provider have to do their job, but they have to help educate the patient so that the patient understands that they share in the responsibility of their care and decisions have to be made very carefully. And if they're going to do well and have successful outcomes, they need to take their medication as prescribed. They need to understand what their medications are doing and why they're important. If there's any issue with transportation, with the financials of getting the medication, et cetera, they need to be made known.

So be that as it may, here we see that her LDL is 145. HDL is not bad, but we know that HDL probably has reduced functionality in the setting of insulin resistance, diabetes, but there's nothing we're going to do about that. The triglycerides are 147, less than 150, so that's good. And her kidney function is actually good, but that may be a false normal because we know that in diabetic patients, their GFR can actually be increasing due to abnormal changes in their glomeruli, and then suddenly their glomerular function can decrease rapidly.

So her 10-year ASCBD risk is 15.2%. Truth be told here, I would be very aggressive in this situation and I would drop her LDL to less than 55 to give her every benefit possible. And I would make doggone sure that if she stopped her statin in the past, I would investigate that fully. I would find out where exactly she was having muscle pain discomfort, whether or not it was accompanied by weakness. I would fully investigate that.

Christie M. Ballantyne, MD:

So, Peter, one thing in terms of some of the patients, particularly if there was some issue of a CK elevation, do you like to restart and re-measure just getting their... for safety issues and convincing them. If they complained of my allergies and there was a high CK in the past, do you like to get a repeat measurement of CK before starting the statin again, and also ALT/AST?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes, that's very interesting because it's unusual to see an elevation in skeletal muscle creatine kinase in patients who complain of statin-induced myalgias. So if she did in fact have an elevation in her creatine kinase, and especially if it was greater than five or 10 times that of a normal, then I would repeat it when I re-challenged her with a statin. The ALT/AST in her situation because she's diabetic, she has insulin resistance, the odds are pretty good that they're going to oscillate because of augmented intrahepatic inflammatory tone, a touch of underlying hepatic steatosis. In those patients, it can vary test to test. And if her transaminases were elevated, I would definitely see if she had evidence of hepatic steatosis. And actually, there's absolutely no reason why not to give her a statin if she has hepatic steatosis.

Christie M. Ballantyne, MD:

Still we use it. And one thing you said, the lab norms for CK were based mostly upon European ancestry, but we see individuals who are Black that basically higher CKs are common. And it also, it's not reflective of any pathology. I have a number of patients, their baseline CKs are always about twice normal. So useful to say, "Look, this is your number not being on any statin, and it's a little bit high so we can repeat it, but if it's elevated, it's always elevated, so we're not going to stop the medication."

And the other one you mentioned is the lower dose. What's your experience where even these kind of alternate day? If someone won't take it every day, have you had a good success with some of these things where you're using even five of rosuv Monday, Wednesday, Friday plus ezetimibe.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Sure. Sometimes, we have to reach for any LDL reduction that we can, and that's been looked at. There have been a number of papers published on this, and yes, it can work for some patients who really have difficulty tolerating a statin, but this has also been looked at. There are papers that have come out of Cleveland Clinic as well as from Hopkins. And when you look at patients who have a history of statin intolerance and then carefully counsel them and evaluate them and really re-challenge them in a systematic way, those two papers showed that 89 and 91% of re-challenged patients do just fine with appropriate counseling and guidance. So truly, statin intolerance is over-diagnosed, and the biggest problem with it is patients wind up not being re-challenged and their lipids go untreated, and it's really terrible.

Christie M. Ballantyne, MD:

Peter, it looks like in my experience, PCSK9s have been very, very successful for giving robust reductions and also very few side effects. It's been a whole challenge sometimes getting them approved, but that has improved somewhat.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

But I would, in this situation, start her at a lower dose of a statin to provide her with reassurance that I care about her past symptoms, but I would titrate them pretty rapidly, making sure that we understood one another very clearly at every patient visit. And I would track her lipids at every patient visit so that she understands where we are and where we still need to go.

Christie M. Ballantyne, MD:

Now she appears specifically, she's on combination therapy for blood pressure and combination therapy for her diabetes. Now, you mentioned about this, and I agree with this, lower dose of statin initially. So statin intolerance. First of all, the patient needs to understand that you did hear them and then you look at, was there other things? I always check a TSH and going to other things here, but then we had this other possibility about what about combination therapy? If she's tolerating that lower dose of statin, instead of going up adding a non-statin such as ezetimibe.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes. I think it's perfectly reasonable to... well, especially ezetimibe, since it's generic, it's cheaper. Bempedoic acid would also be a possibility, a PCSK9 monoclonal antibody. The PCSK9s, they provide equal efficacy in terms of capacity to reduce LDL, another 61, 62% over and above statin, and then silencing messenger RNA therapy with a drug like inclisiran. So we have lots of options, thank goodness. We have a good healthy toolbox to use. So, yes,, if we hit a roadblock because the next titration step caused an issue, then we do have to reach in and go for a second drug.

Christie M. Ballantyne, MD:

So we'd like to get her LDL cluster ulcer in less than 70 here. There's a lot of arguments that you could bill that if she has a high counseling score, which reasonably good chance that she does have, that we need to go lower than that. I mean, in terms of optimal... And this question is optimal as per a guideline or optimal as per your medical opinion. And with all the evidence that we have in some of the trials here with it here.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

As I tell people, guidelines aren't laws, they're not rules, they're guideposts. And if I lower this patient's LDL to less than 55, am I acting in her best interest? And I would argue, I sure as heck am.

Christie M. Ballantyne, MD:

We have these cardiology, endocrinology, primary care, nurse practitioners, dieticians. So there is a lot of communication that's necessary in terms of really optimizing care for these types, like this last patient, right?

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes. Oh, yes. And it's extremely important that each member of the team provide an integrative approach so that everybody knows what is happening and that the care is focused and effective. So, yes, it can be very helpful, especially have pharmacists, nurse practitioner, et cetera, but we have to make sure we're executing and communicating with each other.

Christie M. Ballantyne, MD:

Okay. So we got lots going on, lot on the pipeline. There's still a lot of things happening, and there's going to be things that are pretty far along phase 3 studies for LDL, and then we've got a whole 'nother batch of things in terms of LPA and triglycerides. But let's talk a bit about things going on for LDL.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

Yes, so lipids are never boring. It's amazing how many new medications are in development, how many drug classes are in development, injectables, orals. Lipids, if you think about it, are at the front line of everything, because one of the very first monoclonals to be used widely in practice was actually the PCSK9 monoclonals. Inclisiranintroduced a tidal wave of silencing messenger RNA type approaches. So really, and now when you're looking at newer oral medications and the approach is to modeling how a small molecule can interact with the active site of an enzyme or how it neutralizes the effect of another molecule, it's really quite remarkable.

I mean, look at obicetrapib, the entire class of CETP inhibitors, cholesterol ester transfer protein inhibitors really collapsed because they found that HDL cholesterol raising in serum with that drug class really did not provide much incremental benefit. But anacetrapib had a outsized impact on LDL cholesterol, and that is the only CETP inhibitor at the time that I actually provided incremental risk reduction over and above a statin.

And obicetrapib comes along and provides even larger LDL and non-HDL reductions. And so it is now being developed not as an HDL raising agent, but as an LDL ApoB and non-HDL lowering agents. So very exciting. And then you've got newer drugs that will be impacting LDL non-HDL Lp(a). And the Lp(a) drugs encompass not just monoclonal antibodies or silencing RNA, there are also oral medications that are being developed. So very exciting time.

We don't have anything yet, but hopefully by next year, at least one of the Lp(a) lowering medications will show us what stuff it has and whether or not it impacts risk for future cardiovascular events over and above a statin.

Christie M. Ballantyne, MD:

So yes, it's interesting. So we have phase 3 of an oral PCSK9, which is interesting, the macrocyclic peptide. This is elicitide. And then the rodalzibep, which is a adnectin scaffold instead of a monoclonal antibody. So the technology keeps moving. We'll see. It looks like we're going to have more options. These are still, these are not FDA approved agents, but they're investigational, but it's just giving a glimpse ahead of what's coming down the pipeline and stay tuned.

Peter P. Toth, MD, PhD, FCCP, FESC, FAHA, FACC:

All right. So let's talk a little bit about SMART goal, so specific, measurable, attainable, relevant, and timely. So put information into action, consider the following goals and set a timeframe that fits with your work environment in a reasonable improvement target that aligns with your patient population.

So it is very, very important to discuss common misperceptions in lipid management with both colleagues and patients. Lipids do tend to be undertreated, no question about it. Increased attention to the identification of management of FH and clinical settings. You don't want to miss a patient with FH. It's easy to catch. And once you find a patient with FH, you can initiate cascade screening to identify first-degree members of family who also have FH and can be treated in a timely fashion. Incorporate comprehensive risk assessments including LDL and Lp(a) measurements for patients at risk of cardiovascular disease.

And yes, it's true, we don't have means for lowering Lp(a) but please keep in mind that an elevated Lp(a) is a risk-enhancing feature and magnifies risk and can place patients in a higher level of risk, which means they need a lower LDL. Enhance the use of appropriate lipid-lowering therapies and support patient adherence to treatment plans. Remember, about 50% of patients still stop their statin after just six months, and it's incredible that among very high-risk patients, still only 18 to 25% reach an LDL target of less than 55. You and I need to make a difference and change this. Use shared decision-making to address barriers to effective therapy, including considering escalating statin dose and adding on non-statin options when appropriate.

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