Lipid Management, Part 3. Apo-B and Lipoprotein(a) - Transcript

Kendal Williams (Host): Welcome everyone to the Penn Primary Care Podcast. I'm your host Dr. Kendal Williams. So, welcome back to a new year of the Penn Primary Care Podcast. We've set up another round of great experts to come on and talk about the challenges that we face in primary care. I wanted to start the year at a place we've started years in the past and that's something that all of us treat, and that is lipid management because there's been some evolution in the last year.

So, I brought on two of our former guests who were experts on this and brought them in to discuss more of the advances in lipid management that our patients are asking us about. So, I want to welcome back, Dr. Dan Soffer. Dan is an Internist, just like us, who has specialty training in preventive cardiology.

He is a national expert in lipid management and one of the great teachers of this at Penn. Dan, thanks for coming.

Daniel Soffer, MD: Thanks for having me, Kendal. Happy to be here.

Host: And also, welcome back, Dr. Jacoby, Douglas Jacoby, who is the Chief of Cardiology at Pennsylvania Hospital. He is the Medical Director of the Penn Center for Preventive Cardiology and Lipid Management. Doug, thanks for coming back again.

Doug Jacoby, MD: Kendal, thanks for having me. I'm looking forward to the discussion.

Host: So, if you haven't, if you're an audience member and you haven't listened to our previous podcast on lipid management, I urge you to do so. We went over a lot of the basics in both a part one and a part two, so in a sense this is a part three, a year later. Bot I wanted to bring you back. I think, let's start with the alphabet soup, which we actually didn't get into last time.

And, we all know total cholesterol, HDL, LDL but now our patients are coming to us and handing us sheets of paper that say, can you order an ApoB or can you order a lipoprotein little a? I want to see what these are, and then, of course, they're asking us to interpret them when we get them.

So, let's talk about ApoB in particular, but also lipoprotein little a, which is, I think, the newer one. Dan, can you start us off with that, and tell us about what those various tests are?

Daniel Soffer, MD: Sure, it's actually news to me that people are asking about it. I'm thrilled to hear that because ApoB is a very important metric in the management of our patients and I suspect that part of the reason people are asking about ApoB is its popularity raised by one particular podcast that's nationally syndicated or nationally recognized and gets a lot of attention.

ApoB is the main structural protein found on atherogenic lipoproteins. And those lipoproteins include LDL. As a matter of fact, that is the most numerous of the atherogenic lipoproteins. It's also on VLDL, IDL, chylomicrons, and remnant particles of those, as well as something called LPa, which is, which has ApoB as the main structural protein.

The reason people ask about ApoB testing, and the reason that guys like Doug and I order ApoB on a regular basis is because it represents the number of atherogenic lipoproteins, the LDL and all of those other lipoproteins in circulation.

Because there's one ApoB per particle and so instead of looking at the lipid content of those particles, you're looking at the actual number of those particles. And it turns out it represents the risk of that patient much better than the actual cholesterol content in those particles. So, in the 1960s, it was determined, Hey, let's just follow the lipid content of those particles instead of following the protein conte,nt of those particles.

And they actually probably chose wrongly because the protein content predicts the outcomes better than the lipid content. We're stuck with LDL cholesterol as the principal metric for a lot of different reasons. And you can still learn a lot from LDL cholesterol, but ApoB is going to always be a better predictor of cardiovascular risk that's residual in people who are treated, or in people who you're trying to determine should be treated.

Doug Jacoby, MD: So, ApoB isn't just a predictor. It's sort of like the non-HDL that we're used to, only better, which makes it a great therapeutic target. So, when you're looking at truly optimizing risk reduction, an ApoB is a great number to look at to make sure you've adequately reduced the numbers of all the different atherogenic particles within the lipid profile.

Host: If I'm not mistaken, in Canada, it is the basis of lipid management. Is that correct?

Daniel Soffer, MD: Sort of. It depends what province you're in. Certainly, if you're in Quebec and most of Canada, ApoB is covered by the Canadian Health Service, and it is a lot easier to get.

Host: So, how do you use it clinically in the context of the decision making that we all use of ASCVD risk calculator, deciding on lipid therapy? Does it come into the discussion of whether to decide to be on statins? And then, Doug, you suggested that it's also used in terms of whether you're reaching your targets of somebody on statins. How are you using it clinically?

Daniel Soffer, MD: I'm happy to take that. So, you can use ApoB interchangeably with how you would use LDL cholesterol. But, since we're all so accustomed to looking at the LDL cholesterol and we have parameters that are very clear from national guidelines, primarily, I think most of us start with the LDL cholesterol or the non-HDL cholesterol.

ApoB is going to be much more helpful. ApoB, does take a little bit of nuanced training, I think, to get accustomed to using it. But you use it essentially the same way that you would use LDL cholesterol or non-HDL cholesterol. Since the national guidelines in the U. S. primarily focus on LDL cholesterol, though, as at first glance, once you've established that you're treating somebody based upon the LDL cholesterol, and you're looking at the response, if it's clear from the LDL cholesterol that you need to do more, adding the ApoB in that, as part of that decision making, is probably not going to be all that helpful.

But when you get to a point where you think like, hmm, I think I've done enough. Or, gee, maybe I've even overshot and I've done more than I think I need; that's where an ApoB can help you make that decision, if you're not looking to check it every single time you do a lipid profile, at the edges. And I think, you know, Kendal, I sent you a case earlier today that I think illustrates a bit of that point. And we can talk about that case if you want to, it's something that with some numbers in front of us may be a little bit easier to understand, but the whole basis of having a discrepancy between LDL cholesterol, and ApoB, the other term for that is discordance, is that when you're measuring the number of particles, you get a different perspective than if you're measuring the lipid content of those particles.

And sometimes that perspective is significant. Sometimes that discordance is very significant and we can make bad decisions if we're only relying on LDL

cholesterol when we need to look at other metrics like non-HDL cholesterol or ApoB.

Doug Jacoby, MD: So, when I'm talking to patient, and explaining the different results and explaining the discordance. I roughly estimate that about 20 to 30 percent time we'll find this discordance, meaning the ApoB will give us a different answer than the calculated LDL would have alone. And we see this more in patients with high triglycerides, patients with diabetes, patients with obesity, patients with a lot of the metabolic risk factors that are such a prevalent part of our patient populations.

Those patients very frequently will have an ApoB that's higher than the same percentile of their LDL. And therefore those patients are more likely to benefit from LDL and ApoB lowering therapies, and potentially need higher doses or even second medicines to lower that ApoB all the way down to the therapeutic goal.

Host: So, for, clinical practice, it sounds like a fine tuning tool, I guess. Would that be a good way of describing it?

Daniel Soffer, MD: Yeah, I think so. We also use it in lipid clinic because it's one of the tools that we use to distinguish between inherited lipid disorders. So, it can be the tool that you use at the high end to help you hone in on what's wrong with the patient and what syndrome they may have. And so, I think in general clinical practice, I don't think that that's critical to have that test result.

It's mostly going to help you at the lower end once you're already treating somebody. And you have to put that in the context of knowing that every time you order it, it may not get covered by the health insurance. And so, if you're doing this test, one, you should really know what you're doing and understand how to interpret the result.

And two, make sure you are clear that it's going to help you make a different decision than what you would make if you didn't have the ApoB.

Doug Jacoby, MD: So, if I was going to summarize for our primary care providers that are listening to this. What I would say is if you are seeing a patient and you are on the fence about whether or not to treat them. An ApoB is a valuable test to order to get a better understanding of their lipid profile and the risk contained within it.

And then once you are treating a patient and you think you've optimized everything and you think you're at goal, it's helpful to get an ApoB to find out if you really achieved the goals that you had set out. Those are the two settings where I think it's most valuable in primary care.

Host: What's an ApoB that we should target Doug, just the thresholds that we should keep in our head?

Doug Jacoby, MD: Our thresholds vary based on the person's risk. The higher the risk, the lower the ApoB goal should be. And if you start with an LDL thought process, I would say perfect lDL is 30 and definitely less than 50. Because that's where some clinical atherosclerosis might even regress. So, my highest risk, my extreme risk patients, I'm targeting LDLs in the 30s.

And what I usually do is take my LDL goal and add roughly 10 to it for an ApoB. That's just a rough frame of reference.

Daniel Soffer, MD: I actually wanted to also mention that there are times where you don't need to do that ApoB, that it's not going to change your thought processes. And so, it's nice to check an ApoB in someone who's not treated, compare it to the LDL cholesterol. And Doug was making reference to population norms, and I know I keep a dot phrase for comparison, because I can't keep those numbers in my head.

But if there's good concordance between the LDL cholesterol and the ApoB, once I've established that, I don't need to keep measuring ApoB. I can say, hey, in this case, the LDL cholesterol is giving me a good estimate of what's actually happening. So, when there's good concordance, I don't need to continue to measure ApoB.

And it's the contrary to what Doug described is when it's most important. So, our patients with completely normal triglycerides and HDL cholesterol who don't have any signs of insulin resistance, that's where you get the best concordance between ApoB and LDL cholesterol. So, those people are out there.

Host: So, let's talk about lipoprotein (a) and you can correct me on the terminology of what's popular in expressing that. But Dan, I'm going to just hit you up again with this. Just tell us about this. What does this mean?

Daniel Soffer, MD: So, lipoprotein little a is another lipoprotein. It's in the same density spectrum as LDL and HDL particles. It's composed of an LDL

with an extra tail attached to it. That tail is referred to as apolipoprotein little a. And the apolipoprotein little a is bound. to ApoB on the LDL particle.

Sorry about all these letters. I know it can get a little confusing. As a matter of fact, that protein tail can actually overlap with the binding site for ApoB. And that may be one of the reason why people with high levels of LPA have impaired clearance of these particles. So, in patients who have high levels of LP little a, you can see an entire spectrum of, or an entire range of LPA levels.

So, the normal range, if you use mass measurements, is between, is less than 30 milligrams per deciliter. Maybe as high as 50 milligrams per deciliter to the point where risk for cardiovascular disease starts to go up. And so, above 50 milligrams per deciliter, that's where you start to see higher risks for atherosclerotic cardiovascular disease and aortic valve stenosis.

And the higher the level, the higher the risk. These particles are highly atherogenic. Not only do they contain this LDL portion, but they tend to carry these highly oxidizable phospholipids that seems to promote atherosclerosis as well. And the protein tail that composes apolipoprotein little a, has genetic and structural homology with plasminogen.

And the consequence of that is that it interferes with fibrinolysis. So, in a way, having high levels of this is like a pro coagulant. It disables the fibrinolytic cascade to some degree. So, it's not only more atherogenic than LDL particles, it's also pro coagulant. And this combination makes it pretty dastardly, not just for the development of atherosclerosis, but for atherosclerotic cardiovascular disease.

So, that's the bad news. The good news is that even when it's found in high levels, the predominant particle in the circulation is still LDL particles. So, even people with very high levels of LP little a have the predominant particles LDL. And so, our therapeutic strategy right now is still focused primarily at lowering LDL, not so much at focusing on targeting LP little a.

However, as new science develops, we may find ways to lower LPA that reduce cardiovascular event rates. And the science is progressing rapidly towards that now. And I think that's part of the reason why people are talking about LPA more.

Doug Jacoby, MD: To add to what you were just saying, one thing I want to make sure everyone knows is to be careful about the units. You mentioned the units and upper limit of normal when it's reported in the milligram category

with the upper limit of normal of 30. But labs use different reporting values and sometimes it comes out in nanomolars, where the upper limit of normal is 75. LPa is essentially a genetic marker of risk. It's incredibly stable over time and changes very little. So, sometimes you'll see patients come in, they've had their LPA checked at one lab, and then they repeated it for some unknown reason at another lab, and they think, oh my god, it's gone up 2, 3, 4 times as high.

But the only thing that changed is the units. So, when you interpret LPa, you have to be really careful that you know what units you're dealing with. And as a rough rule of thumb, cardiovascular risk really goes up when you're about two and a half to three times upper limit of normal. So, that's usually how I interpret it.

If it's only a touch above normal, I wouldn't worry about it, if it's basically more than two times upper limit of normal; that's when I start talking to the patient about genetic risk and suggesting that they do cascade screening of their family members because family members might have high LPa too.

LPa, because it's genetic, you can't really guess by looking at the rest of the lipid profile. You really have to just order it and look at it separately. So, it's worth looking at in patients who have a family history of heart disease or have premature disease, or have aortic stenosis because this is a risk for aortic stenosis, or maybe even unexplained stroke, or quite frankly, some would argue that we should just check it in everyone.

But the point is, if you have any concerns about a patient's genetics, you have to check this, and you won't get this information anywhere else.

Host: And as you noted, to be clear, we don't have specific therapy for Lipoprotein a, although I understand there are some drugs in development and so forth, but Doug, let me point this back to you. So, how are you using it clinically? You, mentioned it as identifying people at genetic risk because it's highly stable and it's predictive, but how else do you use it clinically?

Doug Jacoby, MD: So, the major role of LPa right now is to help better understand a patient's risk. And when an LPa is markedly elevated and upticks them into a higher risk category, which therefore makes me more aggressive in my interventions to lower their risk. I'm going to push lifestyle even harder, but I'm probably actually going to add on more medicines and lower their LDL goal as an example.

Now it's only partially true that we don't have ways to lower LPa right now. We actually have some. PCSK9 inhibitors lower lipoprotein little a, a little bit. Although not enough that we order PCSK9 inhibitors just for the purposes of lowering LPa, but it is an added bonus. For patients that have had premature disease and have extremely elevated lipoprotein little a's, we can actually do apheresis and filter off their LPa.

They do this more in Europe, especially in Germany. And we do it occasionally here. So, Dan and I both have patients that we will actually send to apheresis to lower their LPa's. You get hooked up about once every two weeks, and it's almost like a mini dialysis style session where you're filtering it. But that really is the exception to the rule.

Drugs that will lower LPa are in clinical trials. So, I think if we come back and do this podcast in a couple of years, we'll have a very different answer for you. But right now, the main benefit of LPa is just understanding the person's risk. Because we really treat people trying to come up with the best crystal ball we can to figure out the future.

And if you have high LPa, your lifetime risk has gone up. So, we should be more aggressive with prevention.

Host: So, can lipoprotein a explain some disconnects that I see? So, a typical patient may be somebody who's been walking around for five decades with an LDL over 190, but they've never, decided to go on therapy and most of them, maybe they've been resistant. And in my discussions with them, I check a coronary calcium score and it comes back zero, right?

Would a lipoprotein a help me understand that disconnect? Or the opposite might be true, where I do a coronary calcium score in somebody that I think is relatively low risk or in an intermediate range and it comes back much higher than I expected. Is that potentially explained by lipoprotein a?

Doug Jacoby, MD: Yeah, I think that the second example you gave, where someone has a beautifully normal LDL, but a markedly elevated lipoprotein little a, that's a great explanation for premature disease, both premature subclinical disease by a calcium score or premature clinical disease coming in with a myocardial infarction or an ischemic stroke at a young age.

So, lipoprotein little a can easily explain that. In terms of the reverse, where you have someone with a very high LDL and a zero calcium score, I have a couple of thoughts for you. The first is... think LPa, a normal LPa contributes, but it's

not sufficient. I think that LDL alone is not a great predictor of a person's future risk, unless it's extremely, extremely elevated.

There's so many different factors that go into building up atherosclerotic disease. So, of course, if you have FH, familial hypercholesterolemia, with markedly elevated LDLs, many people will develop disease. But at the lower LDLs, you need a much more complete picture than just that LDL to predict risk.

And, in fact, we're trying to understand the genetics more and more. So, what Dan and I are both ordering in our clinic new this year, is actually polygenic risk scores. They're sort of in their infancy, but they look at 1.9 million genes for small variation. And we're starting to use those to understand risk that we otherwise couldn't explain by traditional risk factors or LPa or inflammation. So, cardiology and lipidology is moving in that direction, but we're just getting started.

Daniel Soffer, MD: I think that's well said, Doug. I'll tell you, when I see my patients, I talk to them about these four pillars that established their atherosclerotic cardiovascular disease risk. And first and foremost, we talk about their own personal medical history and their family's medical history because that influences how we think about things.

The second pillar is their metabolic status, and that would include their lipid and lipoprotein analysis, including ApoB and LPa as along with the other things, you know, that we normally measure, their glucose levels, their kidney function, their thyroid function, all of the other metabolic parameters. At that point, you have a good sense already of what their atherosclerotic risk is, and you have enough to use a risk calculator if that's can give you an answer in a direction, but oftentimes you still want to have a sense of what their atherosclerosis burden is. And so, you're looking at the third pillar, and that is imaging.

And the imaging tool that we use more than anything else is coronary artery calcification score. And that tool is the single best predictor of atherosclerosis burden in primary prevention in adult patients, typically over the age of 40, but can be used even in younger patients, and maybe we can talk about that too, and can be used in older patients to help stratify risk even in our older patients.

So, now we have those three pillars set up. We have almost all of the explanation for their cardiovascular risk. But then that fourth pillar speaks to what Doug was just mentioning, that we have a genetic predisposition. And that

family history, which I mentioned as part of the first pillar, can point us in the right direction.

But, we all know from being in clinic that family history is hard to get a reliable description. Oftentimes families are disjointed, they don't have all of the adequate information, or somebody says that their family member has heart disease and that's the only information you get, or they died suddenly.

And it was assumed to be from their heart, but you still don't know yet whether it's due to atherosclerosis. So, family history is very, is really inadequate. And looking at the genetic profiles that predispose people to atherosclerosis, I think are, the wave of the future that we're already sort of diving into. It's never going to take the place of the other three pillars, but it's another way to augment our understanding of the direction and the trajectory of atherosclerosis in our patients. And I think it's a useful to think about it in those four pillars. I think that's how we make all of our decision making in primary prevention is taking a look at all four of those pillars for care.

Host: Dan, could you say those pillars again?

Daniel Soffer, MD: Sure. So, we have the medical and family history as the first, we have metabolic parameters, and then we have imaging. And finally genetics.

Host: Family history is separate from genetics?

Daniel Soffer, MD: I think it is because that's something that you don't need any special testing for and it gives you the context for understanding the person's medical history.

Host: Circling back to ApoB and lipoprotein a, I want to close the door on this discussion. So, my understanding of what you said is that ApoB should largely track with LDL but can be a fine-tuning mechanism. Lipoprotein a, however, is a completely separate independent and fairly potent risk factor that we have not been measuring, that is somewhat treated by the strategies we're employing, but is a separate thing that won't necessarily track with LDL. Is that right?

Daniel Soffer, MD: That was very well said. I like the way you described that. Yeah. I have a few other comments that I'd like to say about LPa too because I think they're going to come up in the near future. One is that there's going to be a widespread call for universal LPa testing to make sure that everybody just knows their LPa as a one-time test and I'm pretty sure there's going to be a big

pushback against doing so because clinicians are going to be upset that they're getting a test result that they can't manage directly because we don't have an LPa lowering therapy specifically. But I think that the response to that is that we are going to describe LPa as a risk marker that probably contributes to atherosclerosis directly, that if you have a high level, increases your risk.

Similar to calcium scoring, right? We do calcium scoring, but we don't have a direct treatment for coronary artery calcification. We treat atherosclerosis when we see somebody has a high calcium score. So, in this case, if you have a high LPa, we're not going to target LPa unless we have drugs for that. And we don't yet, but we do target atherosclerosis in our patients with high LPa.

The other thing I wanted to say about LPa is that even though it's a highly genetically determined, level, the level itself is not determinative for the development of atherosclerosis, just like LDL cholesterol is not. You mentioned that patient who has a LDL cholesterol of 190 milligrams per deciliter, but doesn't seem to have atherosclerosis.

Well, you can have LPa levels that are 10 times the upper limit of normal and not have atherosclerosis. So, having a high level doesn't mean you have atherosclerosis. We think that long term exposure to that high level will increase your risk for atherosclerosis and ultimately maybe should be targeted as a part of the therapy for atherosclerosis. But this is an evolving science.

Host: I want to circle back with what Doug said real quick and emphasize it. Doug, you had said that two and a half times the upper limit of normal is what makes you really pay attention. No matter what scale you're using. I just want to emphasize that point. I found that very valuable.

Doug Jacoby, MD: That's correct. People can just remember two and a half or three times upper limit of normal is really where the cardiovascular risk goes up enough that I would manage the person more aggressively than I otherwise would have.

Host: We're focused on sort of labs now, and I want to get to lab measurement in a minute, but triglycerides is something that we all know of. We have patients who are on maybe a high dose, high potency statin. Their numbers look great, but their triglycerides remain high, and they'll come in and they'll say, everything looks good, but you know, doc, my triglycerides are high. Can you talk about triglycerides themselves as particles we need to be concerned about?

Daniel Soffer, MD: Yeah, I could do that for hours, Kendal. But I'll keep it as brief as possible. So, of course, triglycerides like cholesterol are carried in lipoproteins. LDL and HDL particles tend to carry minimal amount of triglyceride. So, if you have high triglycerides as defined by a triglyceride level greater than or equal to 150 milligrams per deciliter, then that means that you have other lipoproteins in circulation in a fasting state that are also atherogenic.

And those are the so-called triglyceride rich lipoproteins. And just like LDL, there's one ApoB per triglyceride rich lipoprotein. Now, unlike LDL, as LDL cholesterol goes up, the ApoB level tends to go up proportional to that. Triglyceride rich lipoproteins, you can have increases in triglycerides, but the ApoB level does not necessarily go up directly one-to-one, proportional to that because the particles can be, can contain a lot of triglycerides and have a ratio of triglyceride, the cholesterol of like five to one.

So, having big increases in triglyceride doesn't necessarily mean you have a lot more particles in circulation. They may just carry more triglyceride. And this is where the nuances of this actually get pretty interesting. And it's important to think about it in these terms, at least for me to think about it in these terms, because if I see bumps in changes in triglycerides, as long as the non-HDL cholesterol, or ApoB, is staying pretty steady, I'm not terribly concerned that I need to focus too much on the lipid and lipoproteins as a target.

But rather, think about the triglycerides merely as a reflection of the metabolic status of the patient because triglycerides are going to fluctuate considerably with indiscretions with diet, changes in physical activity, other medical and metabolic abnormalities that are going on. And it will make me pay attention to those things a lot more closely.

And so, I'm not going to be targeting triglycerides if the non-HDL cholesterol and ApoB are under good control. I'm going to be using that triglyceride level to tell me Hey, there's something going on here that's putting this person at risk, but we don't have to focus on the lipoproteins as the target of therapy.

It doesn't mean they need more cholesterol lowering drug, necessarily. They need more attention to their metabolic

Host: So, you had described HDL before in our previous podcast as a marker of good metabolic health. And, you know, I was reading today in prepping for the podcast that the triglycerides is sort of the mirror image of that. So, the flip side of that, and we know you can raise your HDL to some degree through exercise and good practices and lifestyle practices and so forth. And I guess you're

saying, Dan, that you can do the same with triglycerides, that it, gives you a sense, not what the medications are doing, but what the patient's lifestyle factors are doing.

Daniel Soffer, MD: To be clear, it's actually the triglycerides that are much more sensitive to lifestyle modification and other metabolic interventions, and that the HDL cholesterol level responds to the changes in triglyceride. There's a mechanism we don't have to get into, but it's mediated through an enzyme called CETP, which regulates the transfer of cholesterol and triglyceride between lipoprotein.

So, as triglycerides go up, HDL cholesterol goes down as a consequence of that. And that's why the most important cause of reductions in HDL cholesterol are actually high triglycerides.

Doug Jacoby, MD: Yeah. And Kendal, what I just want to add to this discussion, and I think one of the reasons that triglycerides are so confusing to people is that they're actually different types of triglycerides from a management perspective that all get reported out the same way in a lipid profile that a primary care clinician sees. So, there's the extremely elevated triglycerides, more than a thousand.

And when you get very, very high triglycerides, these are the ones that can cause pancreatitis. Those are actually chylomicrons. They're incredibly large particles. They're rare, and they usually reflect an extreme underlying genetic condition, frequently with a little bit of lifestyle exacerbation. And those are frequently fat driven particles, often controlled through the gut.

What Dan's been talking about and summarizing so beautifully for everyone is focused a little bit more on the metabolic form of the triglycerides that are often in VLDL. And those are the ones that are actually cardiovascular risk factors more firmly. And those are the ones that we usually see in our patients that might be overweight or obese, have prediabetes or diabetes, relying too much on carbs.

Those are the far more common ones. It's these sort-of mild to moderate elevations. And so, when we see elevated triglycerides, if anyone ever calls Dan or calls me and says, what should we do about it? One of the first questions Dan and I are going to ask is we need the rest of the lipid profile. We need to know the total cholesterol.

We need to figure out the non-HDL and we'd love to have an ApoB if possible, because that helps us figure out what type of triglyceride problem we're dealing with. And that dramatically affects the clinical advice we would give in terms of diet interventions, as well as the medications.

Host: That's really helpful. I mean, these things come up a lot, and most of us aren't treating triglycerides directly now. There hasn't been a lot of success doing that, I think, from cardiovascular risk reduction perspective. Is that right, Doug?

Doug Jacoby, MD: Well, for the very high triglycerides, the rare case of the chylomicrons for pancreatitis, we usually focus more on avoiding pancreatitis risk. For the more common metabolically elevated triglyceride rich lipoproteins, those actually do correlate with cardiovascular risk, and we do want to control it. It's just, they're not our primary target. Our primary target is that non-HDL ApoB. And it turns out, with using our standard LDL lowering medications, we can drop LDL, non-HDL, and ApoB remarkably well by stacking our LDL lowering meds, especially statins. So, that's usually where we focus. Now, we do sometimes add on agents just to target the triglycerides for people with moderate elevations.

I'm sure you know the REDUCER data where they looked at a cosapent ethyl fish oil and omega 3s, lowered triglycerides by about 30 to 50 percent. And the, REDUCER trial using an EPA only fish oil in addition to lowering the triglycerides, also reduced cardiovascular event rates by about 25 percent. So, there is some data that lowering triglycerides with the right agents will give you cardiovascular protection. But it's still a secondary goal. Our primary goals are still focused more on the LDL and ApoB.

Host: So, everything I said was wrong actually, that actually it should be something that we pay attention to if it's above 150 and it's not because they weren't fasting or some other aspect of measurement, right?

Daniel Soffer, MD: Well, as a risk marker, having elevated triglycerides is a risk enhancing factor according to the 2018 guidelines. And so, even just knowing that your triglycerides are elevated tells you that you have more risk than if your triglycerides were normal. So, it's worth knowing the triglycerides if for no other reason to know that.

Host: So, if you have a patient comes in, sees you and their LDL is, I don't know, 54. And you're very comfortable with that. And then their triglycerides

on a fasting sample are 196. Are you then turning around and saying, okay, I'm going to put them on fish oil. I'm going to do these things?

Doug Jacoby, MD: Well, there are two aspects to that. First of all, I actually am offering them fish oil, especially icosapent ethyl. That's the first thing. The second thing is I'm pushing their lifestyle because that tells me that they probably have room to go from a metabolic perspective in terms of decreasing their carb intake, maybe exercising more and maybe losing some weight.

And the last component is with that triglyceride elevation, this patient is more likely to have the discordance that Dan mentioned earlier. So, that's a patient where I think their LDL is 54, but if I looked at it more accurately, their LDL could be 100 and they might not be at goal. So, that's a patient where doing something like checking their ApoB is particularly valuable to make sure you've reduced the risk as much as you wanted to.

Daniel Soffer, MD: Kendal, I'd like to just add a little clarification that when you are using icosapent ethyl for a patient you're specifically using that in patients who have atherosclerotic cardiovascular disease or are adult diabetics who have elevated triglycerides and other risk factors for heart disease.

That's the group for whom it's indicated. It's not just for anyone who walks through the door who has high triglycerides. You can use it probably off label, but that's how it's labeled for use, is to reduce cardiovascular event rates in those two types of patients. And it's specific to icosapent ethyl at full dose, two capsules, twice a day, with food.

The same type of intervention with a non-selective fish oil that has EPA and DHA has not been shown to reduce cardiovascular event rates, nor has the use of fibrates when added to statins. And so again, you're not targeting the triglyceride, you're using medicine that lowers atherosclerotic cardiovascular event rates in people at risk for disease and events, and you're using the triglycerides to target them to say, oh, this person may benefit from Icosapent ethyl because he has the same features of the people who were in the large, randomized, placebo controlled trial where benefit was seen. So, it's very specific to icosapendethyl, and it's very specific to the type of population who was in that clinical trial. It's possible it has benefit beyond that, but that's where the evidence is. And so, I really reserve that therapy for that group of patients.

Host: So, you said known atherosclerosis and patients with diabetes and metabolic risk factors?

Daniel Soffer, MD: Yeah, who have high triglycerides.

Host: Who have had triglycerides. Yeah. That's very helpful. So, we've been talking about measurement a bit, and Dan, you had mentioned in sort of our pre discussion before the podcast that Penn is going to shift to a different way of reporting lipids, and let's just dig into that now. How is that change going to affect what we do?

Daniel Soffer, MD: Well, it really comes down to believe it or not, the math behind looking at LDL cholesterol. So, just remember, when you get a lipid profile, the total cholesterol is directly measured, the HDL cholesterol is directly measured, and the triglycerides are directly measured. The LDL cholesterol is calculated using a formula that was derived at the NIH in the 1960s called the Friedenwald formula. The formula calculates LDL cholesterol as the difference after you've removed HDL from the total cholesterol and the VLDL component. And they use the VLDL component to be triglycerides divided by 5. You probably all have memorized that for some test at some point, but that's what that Friedenwald formula is.

So, the LDL cholesterol that the Penn Lab reports is the Friedenwald formula calculated LDL cholesterol. And it works by and large for the most part for a large population, especially when the triglycerides are normal. But in these patients who have high triglycerides, that formula fails because the triglyceride to cholesterol ratio of five to one, is no longer accurate. As a matter of fact, the range of true ratio can be anywhere as low as 3 to 1 to as high as 8 or 9 to 1. And so, a couple groups have tried to find a better way to calculate the true LDL cholesterol without having to spend any extra money, like ordering other tests like ApoB. And there's two different methodologies that are used for this that are in common usage now.

Quest Laboratory uses the so-called Martin Hopkins table, where they looked at a very large database of lipids and lipoproteins. And they saw what the LDL cholesterol would be based upon the cholesterol, the triglycerides and the HDL cholesterol. And they created a table that will give you a much more accurate assessment of LDL cholesterol.

So, if you send your patients to Quest Lab, you're actually getting the Martin Hopkins version of LDL cholesterol, not the Friedenwald formula. At the NIH, currently, at the Sampson NIH formula was derived and they’re, they updated the old Friedenwald formula using a much more sophisticated model for this that gives you a much more accurate LDL cholesterol level.

And so, for example, I think you and I had talked about a patient who had a triglyceride level roughly 300, and an LDL cholesterol that was being reported as 60 milligrams per based on the Friedenwald formula. When plugging in those numbers into the Martin Hopkins table, the LDL cholesterol comes out to be more like 90 milligrams per deciliter.

That's a big difference. So, if you get the report back and it says 60, you think you're done, you've lowered the LDL cholesterol far enough. You may a little upset to see the triglycerides are high, but you know, maybe you're like, oh, well it's an LDL cholesterol world. I'm only going to pay attention to that.

Whereas if you get the report back and it says 90, you may think to yourself, wow, those triglycerides are high. The LDL cholesterol is not good enough. I think I need to do more. And that's where you, going to intensify the plan. And so, when the hopes are that Penn Lab is going to transition away from the Friedewald formula, like we see it now, to the Sampson NIH formula because it fits in nicely to the EMR. It's a mathematical formula rather than a table. And we are in the process right now of putting all of our ducks in a row to make that happen. And you'll, you can look for an email from the health system that explains this in greater detail and has some references if you want to look into it.

But you're going to see that some of our patients who are down at the borderline, who are on therapy, whose LDL cholesterol looked like it was good enough, are no longer good enough. Now that we have a different test, you're going to see they go from 60 to 80 or 60 to 90. And you're going to need to do more.

So, this is in response to a changing formula. I don't have a timeline for when that's going to happen, and I can't even promise that it's going to happen, but all roads point to that actually happening. And I've gotten good buy in from the laboratory, good buy in from the cardiology and primary care community so far, and endocrinology.

So, it looks like it's going forward. I just, I can't tell you when that's going to happen.

Doug Jacoby, MD: And when this change does happen, to be clear, it's still going to be the same LDL and the management strategy is still going to be the same. It's just, it's going to be a more accurate LDL, which is going to be better for patients. And there'll be a brief period during the transition where someone's LDL might jump that you can't explain. And it's just because the calculation is

giving you a better, more accurate LDL. But once we restabilize in the new calculation and the new metrics, it's really going to be business as usual. It's not going to change the way you should think about the LDL at all.

Host: That's great information. Understanding these things on a deeper level is extremely valuable, so there's two remaining issues I wanted to address, and that is, and Doug, you referenced this earlier, that is, you guys are really enthusiastic about getting those LDL targets down. I mean, Doug, you were talking about 30s for some of your patients, are these going to get lower and lower, Doug?

Doug Jacoby, MD: I think the general shift over time, if you look in the last decade or two, is that our goals for LDL keep getting lower and lower and we keep getting more aggressive. And the reason is as we keep studying additional pharmacologic agents that are more potent like the PCSK9 inhibitors, we've achieved lower LDLs than we used to and we've seen benefit both at a subclinical imaging level, as well as a cardiovascular outcomes level.

So, as I said before, I think we can now say that a perfect LDL is 30. Absolutely, you don't need to get everyone to an LDL of 30, but for your highest risk people, that's a reasonable place to try to get the LDL. And I would view it as a continuum. So, my general approach would be, figure out how high the person's risk is. If they've had a clinical event and they're very young, or they've had recurrent clinical events, you really want to be able to get their LDL below 50 because that is our best category. And in Europe there are actually guidelines for extreme risk that get LDL goals below 40. So, in terms of getting there, for a while, we were just focused on statins and there was a little bit of a belief that if you just put someone on a statin and you got them on a high potency statin, you are really lowering the risk in every way you were supposed to.

And I'd really like to change that mindset. Because what Dan and I both do, is we're very much guided by the percentage of LDL reduction, and the LDL achieved, and the ApoB achieved. So, I'd rather people think about it more like blood pressure. The victory is not getting someone on one blood pressure medicine and saying you've adequately treated their hypertension.

The victory is deciding what the blood pressure goal was and stacking medicines until you get to that goal. Most people with high blood pressure need, as you know, almost three medicines at good doses to get there. I think we have a similar philosophy towards cholesterol at this point. It is very reasonable for people to need to stack medicines and need non statin agents to be added to the statins to truly optimize the risk reduction from a cholesterol standpoint.

Daniel Soffer, MD: You know, if you don't mind to indulge me a little bit, I want to tell a little backstory of something that's going on relevant to this. And that is the push by several associations around the country to get CMS to think about changing their quality metric related to lipid management. So, you may recall that in 2013, when the guidelines were published, that the evidence at the time was only for statin therapy and that there were no clinical trials that showed that adding anything to statins reduced atherosclerotic cardiovascular event rates.

And so, at the time it was take a statin, take a high potency, high intensity statin for people at higher risk. You could use a moderate intensity statin for people at lower risk. Or don't take a statin. Those were the options and shortly after that was published, new clinical trial data started to roll in, including that with ezetimibe and then with PCSK9 monoclonal antibodies.

And then after that with bempedoic acid. Even before that data rolled in, CMS decided to change their quality metric for all of us to, did you prescribe a statin or didn't you prescribe a statin for high risk patients? And they got rid of the LDL cholesterol goal attainment. The consequence of that is that clinicians all around the country stopped monitoring LDL cholesterol, or let alone ApoB and LPa.

Of course, those weren't monitored, but not even monitoring LDL cholesterol because they weren't getting paid to do so. They were getting reinforcement from CMS that said they prescribed a statin. As a matter of fact, there was no special reimbursement to determine whether or not your patient was actually taking the statin that was prescribed.

You just needed to prescribe it. And if you don't measure it, they're probably not going to be taking it. And it actually led to worsening cardiovascular outcomes since that time. Now, getting CMS to change is difficult. It is a very difficult thing. It's like turning an ocean liner. It takes a long time.

It takes years to make it happen and it's going to take a big push. The National Lipid Association and other associations are banding together to establish lobbying to CMS to ask them to change their quality metric from a process measurement of prescribing a statin to an outcome measurement of achieving an LDL cholesterol level.

The devil's in the details, of course, so which LDL cholesterol to choose so that clinicians are optimizing care for their patients; that's going to be another

challenge, but first things first from a national health care perspective is trying to move away from that process to an outcome measurement.

And we think that's actually really important for achieving best outcomes for all of our patients. And how you get there, whether it's with statin or statin plus ezetimibe or statin plus a monoclonal antibody or monoclonal antibody plus ezetimibe, that's probably less, far less important. As long as you're using evidence-based therapies that we know reduce cardiovascular event rates.

Host: And the takeaway for us as primary care physicians is that we should not be just putting patients on statins and saying, well, that's great. We should be actively managing to target a certain LDL. I like Doug's example of blood pressure regimens. We're actually trying to achieve a goal.

Daniel Soffer, MD: And I would add that while 30 to 50 is perfect, our lower risk patients, we're not adding more and more therapy to get them to that. That 30 to 50 is what we target when we are treating our highest risk patients. And we can be a lot more liberal and allow higher LDL cholesterol levels in our lower risk patients comfortably.

Host: So, Dan, I understand you know a lot about this because now you're the president of the National Lipid Association. Is that correct?

Daniel Soffer, MD: That's right. It's a one-year term, and we are the main organization that's spearheading this effort to CMS, but we are not the only organization. I won't go through the whole alphabet soup of associations. But this is really my principal task for this one year is to get the ball rolling in this process. And it's truly a team effort and it's going to be it's going to be a marathon. It's going to take a long time to get CMS to go back to the metric they were using prior to when they changed in 2015.

Host: So, I really appreciate having both of you on. You know, we're all very confused about these things. And we know we can send our patients to you, but they come to us with these results often or wanting these results and it's helpful for us to just be able to at least dialogue with them about them in a meaningful way.

So, this is really helpful to understand these newer tests and some of the older tests we're not using. So, I'm sure this is going to result in more questions that will result in another podcast somewhere down the line, but Dan and Doug, thank you so much for coming.

Daniel Soffer, MD: Thank you so much for having us.

Doug Jacoby, MD: Thanks for leading a good discussion.

Host: And thank you to the audience. Please join us again next time for the Penn Primary Care Podcast.

Disclaimer: Please note that this podcast is for educational purposes only. For specific questions, please contact your physician. And if an emergency, please call 911 or go to the nearest emergency department.