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The Life and Times of LDL Cholesterol

Narrator:

Welcome to ReachMD. You are listening to "**Lipid Luminations**," produced in partnership with the National Lipid Association and supported by an educational grant from AstraZeneca.

Dr. Bays:

You're listening to ReachMD and this is "Lipid Luminations," produced in partnership with the National Lipid Association. I'm your host. My name is Dr. Harold Bays. We're here at the National Lipid Association in Pittsburgh and with me today is Dr. Alan Remaley from the National Institutes of Health. Dr. Remaley, thanks for being here. Give the folks an idea about what it is you do for a living.

Dr. Remaley:

Very happy to be here. I'm actually originally from Pittsburgh, so I jumped at the excuse to come to this meeting, so I appreciate the invitation. So, I'm at the National Institutes of Health in Washington, D.C. or in Bethesda, Maryland. I have actually two hats. I'm trained as a pathologist, clinical pathologist, and am in charge of part of the clinical laboratory at NIH where we do cardiovascular

biomarkers which we're going to talk about today. I'm also a scientist, a Ph.D. in Biochemistry, and I lead a section of a research lab in the Heart, Lung, and Blood Institute where I'm involved in animal models and also, recently, in clinical trials in terms of new agents for treating lipid disorders.

Dr. Bays:

You know, based upon your qualifications, you're exactly what we're looking for here today and what we're going to talk about biomarkers. I mean, the biomarker we now use most often to assess risk, from a lipid standpoint, is the low-density lipoprotein cholesterol level. That's what most of us are using. Can you give us some insight? I mean, we all just use that term, you know, LDL cholesterol level, but I wonder if everybody knows what all goes into LDL cholesterol and the different ways that it's measured? Help us out.

Dr. Remaley:

Yes, well I think maybe a little bit of history might be useful here.

Dr. Bays:

Sure.

Dr. Remaley:

So, it's hard to believe where we are now, but at the end of the last century we only knew three molecules very well, because you can crystalize them in terms of chemically, so: glucose, uric acid, and cholesterol. So, there was a very famous study feeding rabbits cholesterol. Rabbits hyper-absorb cholesterol and that was the first link; I think was around 1913. So, a little over 100 years ago, we've known that cholesterol has been linked to cardiovascular disease. But in the last hundred years, we've refined it and I would say starting, probably in the '50s it was realized, so for a long time total cholesterol, although it wasn't widely used, it was realized there was a link between total cholesterol -- it wasn't widely measured as a risk marker -- but starting in the '50s, we realized that cholesterol is transported in a wide variety of particles and they are initially separated based on density. So, the so-called low-density lipoprotein particles are large particles of roughly about 20 nanometers in size. They

start out as larger particles as VLDL and the reason we have VLDL is to deliver energy, deliver triglyceride. As they undergo lipolysis they get depleted of triglyceride and you have LDL cholesterol left. Most of the LDL cholesterol goes back to the liver, is taken up by the LDL receptor, but if you have very high levels, it could get deposited into your vessel wall and this is one of the reasons we have atherosclerosis. But starting in the '50s, it was realized there was another class of particles which we will probably talk a little bit about, is HDL cholesterol. The science is still not exactly clear, but the epidemiology is clear that HDL cholesterol is inversely related to cardiovascular risk. So, it became important starting in the '50s to segregate total cholesterol into good cholesterol, HDL, and bad cholesterol, LDL cholesterol. So, for a long time, now to 20, 30, 40 years, we've been measuring LDL cholesterol. Even though we have been doing it for a long time, there are still some issues related to the accurate measurement and the use of LDL cholesterol.

Dr. Bays:

What are those issues? I mean, again, most clinicians they just order these blood tests and so, for most laboratories, exactly how is LDL cholesterol measured? How do we get the values that we see on our laboratory sheets for LDL cholesterol in most laboratories?

Dr. Remaley:

So, let me just again back up; so, the very first measurement is total cholesterol and that was actually a chemical method using the Lieberman–Burchard method, which no one talks about or uses, was a chemical where "inaudible" high dry and you're looking at the hydroxyl group "on the A ring", but starting in the early '70s, people started using enzymes. So we use an enzyme called cholesterol oxidase which oxidizes that hydroxyl "group into A ring and is coupled to a dye." And the total cholesterol assays are rock solid, very reliable, and you're measuring the total cholesterol in your plasma. It then becomes much more challenging when you want to know cholesterol on just one fraction. So, the classic way, and this is how the "inaudible" described as using ultracentrifugation to physically separate and that works well, but it's very tedious and very few labs, except for maybe reference labs, do that technique. What happened, a guy named Burnstein in the '70s discovered that if you use polyanions you can precipitate the B-containing particles, so that's just like dextran sulfate became very popular, and you measured the cholesterol and then supernate it, and if it's a fasting sample where you don't have chylomicrons, that's largely HDL. So, you can measure total cholesterol and then you do a precipitation which is not too hard, but still tedious, and you can measure quite

accurately cholesterol in the supernate. And so, that was the standard method up until about 10-15 years ago. And, as I mentioned, one of my roles at NIH is Laboratory Director and we try to make things as easy as possible, try to make things fully automated, and so, most of these, what are called direct assays, don't physically separate lipoproteins. You kind of shield or consume the cholesterol on the HDL and there is no physical separation and most of those assays were developed in Japan. There are about eight so-called direct assays on the market and initially were direct assays for HDL. Now there are also direct assays for LDL. And I think that one has to be aware that those assays work; they work on normal lipidemic individuals, but there are problems with those assays and one has to be cautious.

Dr. Bays:

If you're just tuning in, you're listening to ReachMD. May name is Dr. Harold Bays and I'm here with Dr. Alan Remaley. Well, let me ask you this, I mean, when a clinician orders a standard, routine lipid profile, that's not a direct measurement, is it? Or is it a calculated?

Dr. Remaley:

Well, until 10 years ago, almost always calculated. And if you're ordering now, this day and age, an HDL cholesterol, looking at the surveys in terms of the assays different laboratories use, good chance it's a direct, probably 90% of labs…

Dr. Bays:

You're talking about HDL cholesterol?

Dr. Remaley:

For HDL cholesterol. Now, in terms of LDL cholesterol, the LDL cholesterol, I guess I neglected to mention this, until recently was a calculated, and it was therefore free. But calculation was assuming certain assumptions. And so, usually a direct measurement could be better, so people then developed so-called direct assays, and that cost money. And so, the uptake or the use of direct LDL was not as much as the direct HDL, because with direct HDL you avoided having to do a precipitation procedure.

So, I haven't looked at the numbers in the last 2-3 years, but I would say, probably your chances are about 50-50, whether you have a direct LDL or a calculated LDL. And there are people now questioning whether it's worth the extra money to get the direct LDL, because there are problems with the calculated LDL, but there are also problems with the direct LDL.

Dr. Bays:

And with regard to issues when you have the calculated LDL cholesterol levels, I mean, we always hear about if the triglycerides are over 400 mg/dL, and I think a lot of people know that, that the…what happens to the Friedewald equation? What happens with the accuracy of that when the triglycerides are over 400 mg/dL? What happens?

Dr. Remaley:

So far we have only briefly mentioned chylomicrons. So, chylomicrons are the other part; they're the lightest particle. They pair mostly in the postprandial state. They mostly carry triglycerides but there are some cholesterol on them. So, unless you adjust, so…if you simply precipitate the LDL and you assume all the HDL is in the supernate you can get an inaccuracy. So, the Friedewald calculation, which was developed by NIH, by Don Fredrickson. It was interesting; Friedewald was actually a student in the lab. This is the lab I now direct and I heard the story. And it was a very small project and Fredrickson is the senior author but it became known as a Friedewald and we actually recently contacted Friedewald and he ended up becoming…he's the actuary in the (inaudible cross talk) Company.

Dr. Bays:

Yes.

Dr. Remaley:

He was very humored by the fact that he was so famous. So, what you do is, you make an estimate of the chylomicrons or actually VLDL. Usually you assume it's a fasting sample so there are no chylomicrons, but you always, always have some VLDL which are like chylomicrons and carry mostly

triglycerides. So, you have a triglyceride divided by 5 is the common estimate. If the units are mixed per dL. So, you're right. So, that is a reasonable approximation but it's an approximation and that approximation falls apart at 400. So, if you read the textbooks they say you should not use calculated after 400, but the reality is, it progressively declines and even after 200 it could be a problem. So, that was one of the impetuses for the direct assays. The other reason people chose to use direct assays is that, it sounds trivial but it's actually, and you see patients so you know this, that it's hard to get people to fast. And for children it's hard to fast. So, the recent guidelines for kids actually recommend that you can at least do a screening on the nonfasting. So, if you're not fasting you have chylomicrons, the calculation doesn't assume that's in there so that's a problem. So, direct assays have the advantage that you don't need to fast.

Dr. Bays:

Well, all right. So what about this? What is the accuracy of an LDL cholesterol measurement, by any method, when you start getting very low levels of LDL cholesterol? What happens then?

Dr. Remaley:

So, that's an important issue, but just to finish up on the triglyceride story, so the direct assays also are affected by high triglycerides, maybe not to the same degree as the calculation, but we did a study where we looked at all the direct assays on the market, we split samples, we sent the samples to the CDC and they did the so-called reference method. And depending on the direct assay, you can have both either positive or negative bias and, unfortunately, many of these assays were developed on normal-lipidemic individuals and if you have any kind of hypertriglyceridemia, many times the direct assays could either give you a positive or negative bias. So, one has to be careful in using that in that setting. And then, now that we have -- and you've been involved in developing some of these drugs -- now that we have drugs that can actually lower LDL cholesterol, although there is a debate now about whether there is a target or a goal and how low it should go, but you know, when the assays were designed, the main LDL cholesterol 20 years ago was 200 or 220 and we never dreamed we'd be trying to measure LDL cholesterols below 50, but that's where we are today and those assays are not very accurate, either the calculate or the direct, then I think, if it turns out to be important to accurately measure LDL cholesterol below 50, I think we have to improve our assays and/or use alternatives which maybe we can talk about such as ApoB or LDL-P.

Dr. Bays:

But again, because the LDL cholesterol level is essentially the gold standard and is what is in the prescribing information as the indicated use for these lipid-altering pharmacotherapies, if you had to give, you know pearls of wisdom to clinicians about how they should be measuring this LDL cholesterol that's so important, I mean, what would you tell them? What would be a simple, you know, maybe one or two things that you would tell a clinician from a very practical standpoint, what they should be doing when measuring this LDL cholesterol?

Dr. Remaley:

Well, I think you first have to understand, you should know what assay you are using and you should ask the lab to make sure that they comply with the proficiency test. So, all laboratories are mandated to have unknowns sent to them, but I think what's not realized is that many times these are made with artificial materials and they're not a serum-based matrix and so they are assessing whether you are operating that assay like your peers. You usually use peer grading. And so, you can have an assay and you can be running it as described by the manufacturer but you can get the wrong answer because you're graded by your peers, not by accuracy. So, this is a hole in our monitoring of clinical laboratory tests. So, this is now recognized and so the College of American Pathology, for example, and I was a part of that committee, that we now produce "proficiency testing which are accuracy based". "Where" actually serum, fresh-frozen serum, and we have an accuracy goal. So, you should probably question your clinical laboratory and make sure that they're offering quality tests.

Dr. Bays:

So, just as you would when purchasing an item for yourself, you'd want to check into the quality before you purchase it. What you're suggesting is, is that clinicians, before they start ordering tests on patients, that they be aware of the quality of the product that they're going to be getting for their patient.

Dr. Remaley:

Yes. I know, it's interesting, when you're close to something you realize all the pitfalls, and I think there are many times physicians have comfort when they see a number and they think it must be correct, but there's a lot goes behind that number, and it makes a difference what test you're doing.

Dr. Bays:

Okay, well thank you very much. I know we spent quite a bit of time on something that's seemingly so simple, but I think after this discussion, maybe it's not so simple, and I think that's something that clinicians need to know. So, thank you very much for being with us here today and again, my name is Dr. Harold Bays, and you've been listening to "Lipid Luminations," produced in partnership with the National Lipid Association on ReachMD. Thank you for listening.

Narrator:

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