Clinical Chemistry

Quantifying Atherogenic Lipoproteins: Current and Future Challenges in the Era of Personalized Medicine and Very Low Concentrations of LDL Cholesterol. A Consensus Statement from EAS and EFLM

Article:
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Quantifying Atherogenic Lipoproteins: Current and Future Challenges in the Era of Personalized Medicine and Very Low Concentrations of LDL Cholesterol. A Consensus Statement from EAS and EFLM.
Clin Chem 2018;64:1006-1033.
http://clinchem.aaccjnls.org/content/64/7/1006

Guest: Dr. Michel Langlois is a medical specialist in laboratory medicine at the AZ Sint-Jan Hospital in Brugge, and visiting professor at the University of Ghent, Belgium.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Laboratory testing is a key component of models of care for all types of lipid disorders. New therapies demand accuracy of dyslipidemia testing at very low LDL cholesterol concentration ranges. Inaccurate results lead to incorrect diagnosis and therapeutic management, both of which are costly to society and harmful to patients.

External quality assurance programs which structurally evaluate laboratory test performance demonstrate that improvements in the performance of lipid assays are necessary. Even modest improvements in laboratory testing to predict risk of a disease as common as cardiovascular disease could translate into thousands of people benefiting from more appropriate treatment.

In addition, lipid testing has evolved to include a variety of atherogenic lipoproteins. The analytical validity of these markers and their incremental value beyond LDL cholesterol is strongly debated among laboratory professionals and clinicians.

To address these key issues of lipoprotein and apolipoprotein markers and reach consensus on contemporary lipid testing, a multidisciplinary panel was established by the European Federation of Clinical Chemistry and Laboratory Medicine and the European Atherosclerosis Society.

The July 2018 issue of *Clinical Chemistry* includes a special report from this joint consensus initiative. It provides recommendations for improving the use of the lipid profile to assess cardiovascular disease risk conferred by atherogenic lipoproteins.

For this podcast, we are joined by the report's first author, Dr. Michel Langlois. Professor Langlois is a medical

specialist in laboratory medicine working at the AZ Sint-Jan Hospital in Brugge, and the visiting professor at the University of Ghent in Belgium. He is the chair of working group guidelines of the European Federation of Clinical Chemistry and Laboratory Medicine. So doctor, which lipoproteins can cause atherosclerosis and should be measured?

Dr. Michel Langlois: Well, there are three lipoproteins we should address to estimate to the risk of atherosclerosis. So, the first one is very well-known, also to the general public, the LDL cholesterol, so called, "bad cholesterol", because this means low-density lipoprotein cholesterol. And it's known that it can cause atherosclerosis because when they are taken up in the vascular wall of the arteries, they get oxidized and taken out by macrophages and this process causes inflammation and the development of atherosclerotic lesion, and eventually with the complications such as myocardial infarction and so on.

But the other two particles are less known among the healthcare practitioners. The first one is the remnant particles. What are remnant particles? Well, in fact the name says what it is. They are remnants of other particles that are rich in triglycerides, so these triglyceride-rich particles are VLDL, very low-density level proteins, which are produced by the liver. And also, chylomicrons which are present in our blood after, in a postprandial state after taking a meal.

So, this VLDL and these chylomicrons are undergoing some biochemical modifications so these triglycerides are removed in the bloodstream. And the remaining particles, the remnant particles, are also very small like LDL cholesterol and they can enter the vascular walls. And in this way they can also cause atherosclerosis like LDL particles.

And the third one is the Lp(a). It's a kind of genetic risk factor. What is Lp(a)? It's a LDL particle but to this LDL particle is attached a protein which is apolipoprotein(a) and this protein has a genetic variation in its length. You have short apoA but we have very long apoA. And this genetic variation determines the concentration of Lp(a) in the blood. So, there are among people a very wide range of Lp(a) concentration and this gives a kind of genetic risk factor.

So, there are three particles, three lipoproteins, LDL, remnants, and Lp(a), and they should be measured if you have to estimate the risk of atherosclerosis.

Bob Barrett: Well, what are the major challenges in measuring LDL cholesterol?

Dr. Michel Langlois: Well, the number one challenge during the last year is a new challenge that affects the novel therapies. We are attaining very low LDL cholesterol concentrations of 20 milligram per deciliter or even lower. But the methods developed for measuring the LDL have not been validated for use in these very low concentration ranges which are now attained with these novel therapies.

Another issue that's among the different manufacturers that produce methods for measuring the LDL and the clinical laboratories, all these methods agree very poorly, so with one method you can guess you have a low LDL cholesterol but with another method you have can have a high LDL cholesterol. So, the commercial methods available in the clinical laboratories agree very poorly.

And also, with the increasing prevalence of obesity and diabetes and so on, you have a number of hyperlipidemias in which LDL has not increased for instance in diabetes patients and a high number of small LDL particles, but they are small because their cholesterol in these particles is very low. So, you underestimate the measurement of LDL cholesterol. So, that's another challenge mostly for patients with obesity and diabetes.

And another challenge that, again, with the genetic risk factor of Lp(a). Lp(a) is included in the measurement of LDL cholesterol but with people with very high Lp(a), you overestimate LDL cholesterol because this particle is included in the measurement.

So to summarize the challenges, so with novel therapies, you've got very low LDL cholesterol for which the methods have not been validated; you have the interference of Lp(a), the poor agreement between the different methods, and in patients with diabetes, the small LDL particles which give rise to underestimated LDL cholesterol.

Bob Barrett: Doctor, if you could talk about, if there are any alternative measures that can be taken, and can they replace LDL cholesterol measurements?

Dr. Michel Langlois: Yes. There are two major alternatives which have been also proposed by the international guidelines. The first one is a calculated measurement that is non-HDL Cholesterol. And it's a very simple measurement, just total cholesterol minus HDL cholesterol. And it affects a simple calculation with no additional costs. Just measure two parameters, total cholesterol and HDL and you subtract to this. And what does this mean is -- HDL is the so-called "good cholesterol." So, if you take this off the total cholesterol, all that is left you have the so-called "bad cholesterol", so the atherogenic

cholesterol particles. So, not only the LDL but also the VLDL and the Lp(a) and the remnants.

So, non-HDL cholesterol, the simple calculation in effect captures all the atherogenic particles which can cause atherosclerosis. It's more than LDL, so it also includes these remnant cholesterol particles.

And another measure, but this is adding additional cost because it's with immunoassay, is to measure apoB. And what is apoB is, this is a protein which is present on all atherogenic particles, so not only on LDL but also on remnants and Lp(a). They all carry one apoB molecule. So in fact, apoB -- there's a simple standardized measurement that has good agreement between the methods and that's apoB. In fact, you measure the total number of all of these atherogenic particles regardless of the cholesterol content.

So, there is a technical advantage of this. But also, for non-HDL cholesterol, the calculation or the measurement of apoB, you don't need to do a fasting blood measurement, blood sampling, because fasting does not influence the calculation of measurements.

And from a clinical point of view, non-HDL or apoB in large clinical studies and observational studies, they are on average comparable to LDL cholesterol to predict risk. And in some studies, they are even more performant. But then, a subset of patients, about 75% of the population, when you have the discordant values, for instance, if your LDL is normal but your non-HDL cholesterol is increased or your apoB is increased, despite normal LDL you have an added risk prediction value.

So, if you only measure LDL in these 25% of the population, your risk will be underestimated. So, by discordance analysis, non-HDL versus LDL or apoB versus LDL, you can predict an additional risk which is not recognized by just measuring LDL cholesterol. And this is important for treatment because it's known if people with high LDL cholesterol are treated for instance, with statins, when they attain the LDL cholesterol value, there is still a residual risk unexplained. So, with non-HDL cholesterol or with apoB, you can predict in part at least this residual risk among these treated patients.

So these are the two alternative measurements, non-HDL and apoB. And there's not enough clinical evidence yet to replace them by LDL cholesterol because there is no evidence in clinical practice that you will reduce healthcare-related costs related to cardiovascular disease. But from an analytical point of view in the laboratories, they are more robust measurements, more accurate measurements.

But we need more clinical evidence in order to say that they can replace LDL cholesterol.

Bob Barrett: Well, you may have already partially answered this question, but what are the takeaway messages of this for clinical practice?

Dr. Michel Langlois: Well, for clinical practice, there are two takeaway messages that we proposed from our consensus group. First, for the clinician, you must take into account if you measure LDL to follow up your patient on treatment so patients are followed and monitored by their LDL cholesterol. It should take into account that methods agree poorly.

So, what the clinician has to do is, he must send his samples always to the same laboratory, or at least recognize that all the methods are the same methods. Otherwise, if he follows his patients with different methods, because all these methods agree poorly, his measurements will be confounded, and so he will give some rise to unexplained values.

So, follow up for the patients will be done with the same methods and preferably in collaboration with the same laboratory to eliminate disagreement between the different methods. And also LDL cholesterol is a primary target of lipid lowering therapy, there is no doubt about it. There's a strong evidence for this. But then people with diabetes or with hypertriglyceridemia or obesity, they have another kind of dyslipidemia like I previously said, that they have small LDL particles. So, dyslipidemia is missed by just measuring LDL cholesterol and they have a residual risk, so they have to address this residual risk. They should choose a secondary target, non-LDL cholesterol or apoB.

So, the primary target should be LDL cholesterol when you get your LDL cholesterol value, right? Then, you should target a secondary parameter that is non-LDL cholesterol. Just simply calculate, and then either increase the therapy or add another therapy to address non-LDL cholesterol or apoB. But apoB comes with extra costs. Non-LDL cholesterol is calculated with no additional costs. So, this is very cost-efficient.

And you should also follow up the patient in a non-fasting sample because otherwise if you use fasting sample you might underestimate the risk due to the remnant particles. So, these are the takeaway messages for the clinicians in fact.

Bob Barrett: Well, let's go full circle and head back to the lab. Finally, what's the takeaway message for laboratories?

Dr. Michel Langlois: Well, laboratories should do more efforts to assist the clinicians in order to get a good management of dyslipidemia treatment. So, what laboratories should do in the first place is to calculate the non-LDL cholesterol. It costs nothing, just a simple calculation on all the labs report, on the lipid profiles. So, on the lipid profile is there should be calculated on non-LDL cholesterol value in order to educate the clinicians and also assist them to make them more easy and to follow up for their patients.

Also, the laboratories, when the patients come to the lab for blood sampling, they should also promote non-fasting samples. So, it makes no sense to send the patient back to home if he is non-fasting. It can be done in a non-fasting sample. There is one exception, if your triglycerides are very high, above 400, then you should use a fasting blood sample. But this is very rare. It's less than 5% of the population. So, the majority of the blood sampling can be done in non-fasting. And also, the third takeaway message that Lp(a) as is should be more available in laboratories because this parameter is not very well-known among clinicians. But like I said, it can overestimate your LDL, so you have to correct your LDL cholesterol value according to Lp(a).

And also, if there is often a case of unexplained cardiovascular event, certainly at young age before 50 years, and then genetic risk factor. So, basis for the strong family history of cardiovascular disease, Lp(a) measurement should be more available in order to consider these measurements more frequently. So, these are the takeaway messages for the laboratories.

Bob Barrett: Dr. Michel Langlois is a medical specialist in laboratory medicine working at AZ Sint-Jan Hospital in Brugge and a visiting professor at the University of Ghent in Belgium. He's been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.