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The Present and Future of Lipid Testing in Cardiovascular Risk Assessment
Clin Chem 2023; 69(5): 456-69. https://doi.org/10.1093/clinchem/hvad012

Guests: Dr. Nicole White-Al Habeeb is a Clinical Biochemist at Dynacare. Dr. Daniel Beriault is Head of Biochemistry at Unity Health Toronto in Toronto, Canada and an Associate Professor in Laboratory Medicine at the University of Toronto.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the American Association for Clinical Chemistry. I'm Bob Barrett. Cardiovascular disease is a leading cause of death worldwide. In the United States, approximately one in every five deaths is attributed to heart disease. For many years, LDL cholesterol has been the primary marker used to estimate risk and guide lipid-lowering therapies but alternative lipoprotein markers have recently shown value for this purpose. Some of these new markers can predict risk more accurately than LDL cholesterol but they have yet to be widely adopted by clinical laboratories despite their recommendation by recent Canadian and European guidelines. What are these markers and in what clinical scenarios are they preferred over LDL cholesterol? If they can predict cardiovascular risk more accurately, what barriers are preventing their implementation and clinical laboratories?

A review article appearing in the May 2023 issue of *Clinical Chemistry* covers this topic in detail by describing the strengths and limitations of LDL cholesterol and summarizing performance characteristics of alternative biomarkers. In this podcast, we are pleased to be joined by two of the authors of that review article. Dr. Nicole White-Al Habeeb is a Clinical Biochemist at Dynacare. She helps oversee routine and special chemistry testing over Dynacare's five laboratories across Canada. Dr. Daniel Beriault is a Clinical Biochemist and Head of Biochemistry at Unity Health in Toronto, Canada. He is also an Associate Professor of Laboratory Medicine at the University of Toronto. So Dr. White-Al Habeeb, let's start with you. How do we currently assess dyslipidemia?

Nicole White-Al Habeeb: So the first-line assessment for dyslipidemia is completed with the basic lipid panel and this includes total cholesterol, high density lipoprotein or HDL cholesterol, and triglycerides, which are measured lipid parameters but in addition we also provide calculated lipid parameters including low-density lipoprotein or LDL cholesterol, and non-HDL cholesterol.

Bob Barrett: So how is the lipid profile translated into an estimation of cardiovascular risk?

Nicole White-Al Habeeb: So one of the main clinical utilities of the lipid assessment is that it is used to estimate atherosclerotic cardiovascular disease risk, which is a leading cause of morbidity and mortality worldwide. However, recommendations on how lipid assessment is used to estimate risk, differs between different societies as they use different risk models. So for example, the American College of Cardiology and the American Heart Association guidelines recommend using the pooled cohort equation in adults 40 to 75 years old with LDL cholesterol between 70 and 190 milligrams per deciliter without diabetes to estimate their cardiovascular risk. Depending on the presence of other risk enhancers, a clinician-patient discussion regarding the reduction of risk factors, and the potential initiation of lipid-lowering therapy if recommended, will be initiated.

The Canadian Cardiovascular Society, on the other hand, recommends treatment approaches based on the patient's 10-year risk of a cardiovascular event and this is estimated using the Framingham risk score or the cardiovascular life expectancy model. Based on the patient's risk and decision thresholds of LDL cholesterol, non-HDL cholesterol, or apolipoprotein B or apoB, discussion of health behavior modification or initiation of statin therapy is discussed.

Finally, the European Society of Cardiology and European Atherosclerosis Society guidelines suggest intervention strategies based on the combination of the total cardiovascular risk, which is estimated using the score or systematic cornering risk estimation, and LDL concentration. Depending on these results, patients are counseled with lifestyle advice or intervention and potentially initiation of lipid lowering therapy.

Bob Barrett: So Dr. Beriault, many laboratories are calculating LDL cholesterol using the new NIH Equation. What advantages does this equation provide over the previous one?

Daniel Beriault: Great question. All right, so let's start with maybe a little background. This new NIH Equation from the National Institute of Health was published in the *JAMA Cardiology* journal in 2020, if you want to check it out. Initially they used 9,000 patients to develop and validate a new equation for VLDL cholesterol, which stands for very low density lipoprotein cholesterol, and then they took that VLDL cholesterol equation to create a more accurate LDL cholesterol equation. They compared their new equation head-to-head to current equations in use for estimating VLDL cholesterol which are the Friedewald Equation, and Martin Equation and found that the NIH Equation was superior. It

was more accurate compared to the gold standard method known as beta-quantification.

So to answer your question, coming full circle, the biggest advantages of this new equation are that it will allow for more accurate calculation of VLDL cholesterol in patients with low LDL cholesterol concentration, so it's very accurate at the low end, as well as in patients with hypertriglyceridemia, which means patients with triglycerides all the way up to 800 micrograms per deciliter or 9 millimoles per liter. Ultimately, this provides us with a more accurate tool for managing patients with cardiovascular disease.

Bob Barrett: So, should all labs move away from the older Friedewald LDL cholesterol equation?

Daniel Beriault: So, I would say absolutely. There are only advantages to switching, there are no disadvantages to switching to this new equation. At my institution, we independently validated this new equation in the Canadian population and adopted it for clinical use last year. There are also guidelines out, one from the Canadian Society of Clinical Chemists recommending the adoption of this new NIH Equation. So, highly recommend switching.

Bob Barrett: Okay, Dr. White-Al Habeeb, apoB and non-HDL cholesterol are alternate biomarkers for LDL cholesterol. When should these alternatives be measured instead of LDL cholesterol?

Nicole White-Al Habeeb: Yes, so LDL cholesterol has been the long-standing lipid parameter used for clinical decision making. However, when triglycerides are elevated, triglyceride replacement on LDL cholesterol occurs and the LDL cholesterol estimates may actually underrepresent the number of atherogenic particles. So when triglycerides are greater than 133 milligrams per deciliter or 1.5 milimoles per liter, LDL cholesterol levels do not reliably indicate LDL particle number, and for this reason, when triglycerides are greater than 133 milligrams per deciliter or 1.5 millimoles per liter, it is recommended to use non-HDL or apoB as alternate targets, and these are not affected by eating or by triglyceride levels.

Additionally, there is now some evidence to support that apoB is actually superior to both LDL cholesterol and non-HDL cholesterol as a marker of residual atherosclerotic cardiovascular disease risk in statin treated patients. So previous discordant studies show that cardiovascular risk was more accurately associated with apoB than LDL cholesterol and in this manner the use of apoB can really provide some downstream benefits because patients would receive more appropriate treatment.

Bob Barrett: Well given the advantages of apoB and non-HDL cholesterol, why don't labs offer apoB instead of LDL cholesterol?

Nicole White-Al Habeeb: Yeah, so this is a really good question. So although we do know that there are several benefits to using apoB, LDL cholesterol is still widely used. And one of the potential barriers on the uptake of apoB is that many of the clinical studies examining cardiovascular risk have used LDL cholesterol as the primary marker and clinicians have been using LDL cholesterol for years and are much more familiar with LDL cholesterol targets and thresholds. However, they generally do remain unfamiliar with how to apply apoB test results. Additionally, the cost of offering apoB may also contribute, so in Canada for example, publicly-funded hospitals need to absorb the cost of apoB. So providing a calculated lipid parameter rather than a test is certainly more cost-effective.

So you know, the question is, how will labs be willing to switch? So fundamentally, the use of apoB has to be included in the clinical guidelines before adoption of this marker will take off. The latest Canadian and European guidelines do provide apoB and non-HDL targets as alternatives to LDL cholesterol. The U.S. guidelines on the other hand acknowledge apoB and non-HCL are superior to LDL cholesterol however, they do not recommend specific risk-based targets or thresholds for these markers.

Bob Barrett: Well finally, Dr. Beriault, lipoprotein(a) concentration has been shown to be an independent genetically determined causal risk factor for cardiovascular disease. How is lipoprotein(a) used to help estimate patient risk?

Daniel Beriault: Right. So, for any of the listeners that don't know this biomarker, lipoprotein A is an LDL-like particle. It has been shown to have both prothrombotic and pro-atherosclerotic effects. And like you mentioned, Lp(a) is an independent risk factor for cardiovascular disease. This biomarker is used for risk stratification. The higher the concentration, the higher the risk of cardiovascular disease.

And because blood concentrations of Lp(a) are genetically determined, measurement is required only once in adulthood, at least for now.

In the clinical lab, this biomarker has really taken off lately, with both Canadian and European guidelines recommending population-wide screening for Lp(a). Specifically, Canadian guidelines recommend testing in primary prevention. Patients with Lp(a) greater than 50 micrograms per deciliter or greater than 100 nanomoles per liter should receive earlier and more intensive cardiovascular management such as

healthcare behavior modification, like diet or exercise, or drug therapy as needed. European guidelines recommended a cutoff of greater than 180 micrograms per deciliter or greater than 430 nanomoles per liter, and use this cut off to identify individuals with high risk, lifetime risk of atherosclerotic cardiovascular disease, which is equivalent to the risk associate with some having a heterozygous familial hypercholesterolemia. So really that high level risk type individual, and that is why the cutoff is also much higher.

The American guidelines recommend measuring Lp(a) in patients with a family history of premature atherosclerotic cardiovascular disease and indicate cutoff of greater than 50 micrograms per deciliter or greater than 125 nanomoles per liter to identify higher risk individuals. At this time though, the American guidelines do not recommend population-wide screening, and all that being said, no matter what clinical guideline you look at, routine monitoring of Lp(a) is not recommended at this time until targeted Lp(a) therapies have been proven clinically.

Bob Barrett: That was Dr. Daniel Beriault from Unity Health Toronto and Dr. Nicole White-Al Habeeb from Dynacare. They wrote a review article summarizing the current approach to cardiovascular risk assessment and describing the advantages of new clinical laboratory tools that may become standard-of-care in the future. They publish their article in the May 2023 issue of *Clinical Chemistry*. I'm Bob Barrett, thanks for listening.