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A Translational Tool to Facilitate Use of Apolipoprotein B for Clinical Decision-Making

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Guests: Dr. Justine Cole is a research fellow in the Department of Laboratory Medicine at the Clinical Center at the National Institutes of Health. Dr. Alan Remaley is a senior investigator at the National Heart, Lung and Blood Institute and also leads the Special Chemistry Section at the Clinical Center at the National Institutes of Health.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the American Association for Clinical Chemistry. I'm Bob Barrett. Heart disease is the leading cause of death in the United States and an estimated 7% of adults aged 20 and older have coronary artery disease. For years, LDL-cholesterol has been the primary indicator of cardiovascular disease risk and it remains the recommended test to guide lipid-lowering treatments in the United States. However, substantial evidence indicates that apolipoprotein B, or apoB, is a better predictor of risk than LDL-cholesterol in patients prescribed a statin. Furthermore, apoB can be measured quickly and relatively inexpensively using automated test platforms available in most clinical laboratories. Given this information, why hasn't apoB replaced LDL-cholesterol in the assessment of cardiovascular disease risk? What steps can be taken to encourage this transition?

A new research article appearing in the January 2023 issue of *Clinical Chemistry* examines exactly these questions. Two clinical laboratorians with expertise in cardiovascular disease explained the tools currently available to assess cardiovascular disease risk, summarize the reasons why transitioning to apoB may improve patient care, and propose a solution to assist clinicians and laboratorians with this transition. In this podcast, we are pleased to be joined by the authors of this article. Dr. Justine Cole is a research fellow in the Department of Laboratory Medicine at the Clinical Center at the National Institutes of Health. Dr. Alan Remaley is a senior investigator at the National Heart Lung and Blood Institute, where he has worked since 1990 on lipoprotein metabolism and it's linked to cardiovascular disease. He also leads the Special Chemistry Section at the Clinical Center at the National Institutes of Health.

So, Dr. Remaley, let's start with you, just what is apoB and how does it differ from LDL-cholesterol?

Alan Remaley: Well, thank you Bob first, for inviting us to do this podcast, and I'm here, as you know, with Dr. Justine Cole but also this paper was done along with Jim Otvos; unfortunately, he's not

here. So apoB is the main protein that is a structural protein that's on what's called low-density lipoproteins. So low-density lipoproteins are the main driver of atherosclerosis and as you may know, statins are this point, our main therapy for lowering the amount of low-density lipoproteins. But when we measure it in the clinical lab, what we actually are measuring is the cholesterol content on low-density lipoprotein. So it's usually abbreviated LDL-cholesterol. So that's the cargo that's carried by low-density lipoproteins but the apoB is the carrier, so it's a different way of measuring the number of low-density lipoprotein particles and so, that's important to realize there's only one apoB per LDL. So, apoB gives you a sense of how many particles of low-density lipoproteins, and the LDL-cholesterol talks about the cargo, and it's an important distinction because LDL comes in different sizes. So if you're a larger LDL, you're a bigger boat, that's usually higher levels of LDL-cholesterol, but if you're a smaller LDL particle, you have less cholesterol, but it turns out those patients nevertheless have increased risk as you'll hear from Dr. Cole. So they are -- it's a different way of measuring low-density lipoproteins

Bob Barrett: And Dr. Cole, why is apoB measurement preferred over LDL-cholesterol and non-HDL-cholesterol for clinical decision making?

Justine Cole: It has to do with precision medicine, Bob. Simply put, apolipoprotein B is the best choice for the individual patient and we want the best for our patients. Owing to the direct causal relationship between lipoprotein particle number and atherosclerosis, apoB is more sensitive, more specific, and a more accurate marker of cardiovascular risk than is LDL-cholesterol. In addition, apoB measurement is analytically more précised and suffers from lower biological variability than LDL-C and non-HDL-C. So, in caring for a patient at risk of the major cardiovascular event, this is what any doctor would want to offer. No one would want the uncertainty of LDL-C or non-HDL-C when apoB is available.

Bob Barrett: So Dr. Cole, you've mentioned the reason why apoB is preferred over other indicators of cardiovascular risk but there's disagreement on this. What is your response to those who argue against routine measurement of apoB?

Justine Cole: So Bob, these arguments focus on whole population summary matrix, which ignore the impact on individual patients undergoing residual risk assessment. The area under the ROC curve is too crude a metric to evaluate the individual risk attributed to each parameter included in the ASCVD risk score. Also, the fact that the parameters are highly correlated doesn't mean they can't be effectively ranked. Numerous discordant studies have proved beyond doubt that apoB is a superior marker for patient-specific residual risk

assessments than either LDL-C or non-HDL-C and that the choice would affect a large number of individual patients.

The argument that the benefits of apoB do not justify the cost is based on the currently inflated price of an apoB test. The actual cost of the assay is only a fraction of the $21 that is charged, so with sufficient pressure applied by advocates of precision medicine, this argument becomes void.

Bob Barrett: Dr. Cole, the tool you described in your paper translates an apoB measurement to a percentile equivalent LDL-cholesterol value. What is a percentile equivalent?

Justine Cole: A percentile equivalent is the value of one measure that shares a population percentile with a value of an equivalent measure. In this context, the equivalence of the measure refers to the fact that LDL-cholesterol, non-HDL-cholesterol, and apolipoprotein B are all intended to quantify the atherogenic lipoproteins in the blood. So for example, if we have a measurement of apoB that lies on the 95th percentile for apoB, we would provide the LDL-C value that lies on the 95th percentile for LDL-C. In some cases, this will be much higher than the measured LDL-C, owing to the fact that LDL-C is an inaccurate marker of CVD risk in certain patients. Providing the percentile equivalent LDL-C value leverages the power of apoB which is the more accurate marker, while putting it in familiar terms.

Bob Barrett: Well finally, Dr. Remaley, let's put this thing to work. How easy is it for laboratories to implement this tool?

Alan Remaley: Yes, I just want to echo to what Dr. Cole said in terms of familiar terms. I think the best way to think about this is what we describe as basically kind of a Rosetta Stone that allows you to translate what people are more familiar with, LDL-cholesterol, in terms of apoB, which people have less familiarity with. And it's much akin to, you know, how one typically always supplies reference ranges with clinical laboratory tests. The actual right to do it is not too also dissimilar to how one would use any equation in the clinical laboratory. So if you're already using a lipid panel to calculate your LDL by the Friedewald equation or the Sampson equation or Martin equation, you can also easily add another equation where you would translate the LDL or they would be into LDL equivalent units.

And I guess the last thing I'd like to stress is--a positive side is, if you define discordance as more than 10 percentile difference plus-minus, as many as a third of the patients based on non-HDL, you'll have actually a different result either lower or higher risk based apoB and upwards, almost half people are in LDL-cholesterol. So we're actually talking

a large number of people that you may manage differently if you would then translate your apoB into this.

I think the downside however, is that this will of course, cause confusion to clinicians and we're not doing this yet in our laboratory, because I think it's going to take time to educate, it's going to take time for guidelines to maybe recommend this. So it is possible with really not a lot of IT help to actually implement this but I think whether you would do so at this point in time, I think it's an open question and I think it's going to require more studies and certainly more education. But I do think that this is a valuable step forward and it will be a way to bring to the clinical chemistry and the medical community the value of apoB. I guess the last thing I would like to say, this is not that long ago but I remember when, for example, we changed the definition of diabetes. We went from using glucose to hemoglobin A1C, and there wasn't a lot of familiarity with hemoglobin A1C. So, the lab for about a year or two year period reported and estimated -- measured hemoglobin A1C and they reported an estimated glucose until the clinical community was able to understand. So this is what we think will happen to our work, that it probably will have a short term value until there's a point in time that people have enough familiarity with apoB that they just could use it directly without needing to do the translation.

Bob Barrett: That was Dr. Alan Remaley and Dr. Justine Cole from the National Institutes of Health. They developed a tool to translate apoB results into the more familiar LDL-cholesterol values to make it easier for clinicians to use apoB in routine clinical practice. Their work was published in January 2023 issue of *Clinical Chemistry*, and they have been our guests in this podcast on that topic. I'm Bob Barrett, thanks for listening.