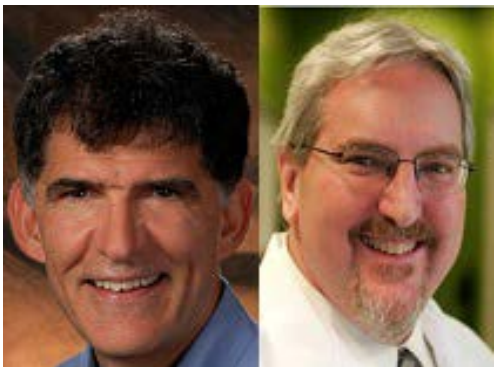
Clinical Chemistry

Beyond LDL-C in assessing cardiovascular risk: ApoB or LDL-P?



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S.R. Master and D.J. Rader
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Guests:
Dr. Daniel Rader from the Department of Medicine at the University of Pennsylvania and Dr. Joseph McConnell from Health Diagnostic Laboratory.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett. Low-density lipoprotein cholesterol, a key cardiovascular biomarker is recommended by National Cholesterol Education Program, Adult Treatment Panel Guidelines, for assessing cardiovascular disease risk and for monitoring lipid-lowering therapy; however, some workers believe that the number of circulating LDL particles rather than LDL cholesterol is a strong indicator of future cardiovascular disease events.

In the May 2013 issue of *Clinical Chemistry*, a special report from the AACC Lipoproteins and Vascular Diseases Division (LVDD) Working Group on Best Practices compared the two diagnostic tests to estimate LDL particle number, namely, concentration of Apolipoprotein B and NMR and their association with outcomes.

One of the authors of that report, Dr. Joseph McConnell from Health Diagnostic Laboratory, joins us today in this podcast. Also joining us is Dr. Daniel Rader, Professor of Medicine in Pharmacology and Chief of the Division of Translational Medicine and Human Genetics in the Department of Medicine at the Perelman School of Medicine at the University of Pennsylvania.

Dr. Rader was an author of an editorial accompanying the report and we'll start with you, Dr. Rader. The current National Cholesterol Education Program Guidelines recommend that LDL cholesterol would be used for cardiovascular disease risk assessment and for monitoring therapy. Now, why was the focus of the report on LDL particle number?

Dr. Daniel Rader: Well, it's true that LDL cholesterol has been the major target of cholesterol lowering therapy for a long time. It's started out because that's something that was relatively easy to measure. In fact, the LDL cholesterol is generally a calculated number that's calculated by a formula from the total cholesterol, the HDL cholesterol and the triglycerides,

and it's true, that's what we have been using as our clinical practice guidelines in terms of the target.

The reason that there has been increasing interest in going beyond LDL cholesterol is basically related to the following: LDL contains cholesterol and the LDL cholesterol measurement or estimate is how much cholesterol is carried within LDL particles, but increasing evidence suggests that it's not the amount of cholesterol carried within LDL, but actually the number of discreet LDL particles that actually is more important in determining cardiovascular risk.

And frankly, LDL can vary. LDL can be relatively small and have only a little amount of cholesterol in it, or it can be large and have quite a bit of cholesterol in it, and having more particles that are smaller is generally much more associated with increased risk of cardiovascular disease. So it's a long way of saying that, a more direct measurement of LDL particle number really is looking like it's a better predictor of cardiovascular risk, than simply measuring or estimating the amount of the LDL cholesterol carried within the LDL particles.

And so LDL particle number, as assessed by the NMR methodology, or ApoB as assessed by immunologic methods that measure the amount of ApoB, the key protein in the LDL particle, both of these are essentially measures of LDL particle number that predict risk of cardiovascular disease, better than LDL cholesterol itself.

Bob Barrett: If there is clinical significance to the number of LDL particles, how are LDL particle numbers measured in the laboratory? Dr. McConnell?

Dr. McConnell: Well, there are actually a couple of different ways that you can measure the LDL particle numbers. Apolipoprotein B or ApoB measurement is one means of assessing the LDL particle number, and the reason is that each particle of LDL has one ApoB molecule. So ApoB measurement indicates the LDL particle number itself. ApoB is also found in chylomicrons and VLDL and IDL and Lp(a) we have to remember that, but the vast majority of ApoB is associated with the LDL particles, about 90%–95%, so a total ApoB measurement really does a good job of reflecting the LDL particle concentration.

Now there are other ways that you can measure LDL particle number. One of the ways that has really been the predominant method is the measurement by Nuclear Magnetic Resonance Spectroscopy. There is another proprietary method for measuring LDL particle concentration which is Ion Mobility Analysis, but we have not really seen a lot of data with regards to this method and before we would

promote the utility of that, we would like to see some more clinical studies and research.

Bob Barrett: Dr. Rader, given the dissimilarities in methodology, how well do the procedures compare in measuring LDL particles as a marker for cardiovascular disease?

Dr. Daniel Rader: Well, interestingly this is a question that has been looked at in several studies, and in a very detailed assessment of the different studies that have looked at LDL particle measurement by NMR compared to ApoB measurement. The conclusions are that these two approaches are relatively similar in terms of their ability to predict future cardiovascular risk.

Not too surprisingly, since they are both essentially measures of LDL particle number, they each predict cardiovascular risk to a similar extent, but both, as I said before, are better than LDL cholesterol itself. So my takeaway from this is that either of these are valid tests that have been subjected now to quite a bit of scrutiny and many studies in terms of their predictive value, and they are comparable top each other, but better then LDL cholesterol, in terms of their ability to predict future cardiovascular events.

Bob Barrett: Non-HDL cholesterol is briefly discussed in the report. Dr. McConnell, did the group believe that non-HDL cholesterol is a superior marker compared with LDL cholesterol?

Dr. McConnell: Non-HDL cholesterol has been shown in many studies to predict cardiovascular events, better than LDL cholesterol, and non-HDL cholesterol is currently a secondary treatment goal in the National Cholesterol Education Program Guidelines. So we fully support the calculation and reporting of non-HDL cholesterol by clinical laboratories. However, we do not feel that it is an adequate substitute for LDL particle or ApoB measurement.

In fact, non-HDL cholesterol is a better marker of cardiovascular risk, not because it includes the cholesterol content of other atherogenic lipoproteins in additional to HDL cholesterol, but really because it is better correlated with LDL particle number. And we can get into the details of why that is the case, but in general, when you have smaller LDL particle numbers, it's related to a number of metabolic abnormalities that can occur, which has been known as the metabolic syndrome. In the metabolic syndrome you tend to have smaller particles, larger number of particles and you also tend to have an elevation of the VLDL particles, which is the factor which affects non-HDL cholesterol.

So in other words, non-HDL cholesterol is really a surrogate measure of LDL particle concentration. If you take a look at all the measures together, the ApoB, the NMR, LDLP, non-HDL cholesterol and LDL cholesterol, we could rank them and the first two would be ApoB and NMR LDL particle concentration. We put ApoB, we would put that before LDLP, mainly because of its availability, its scalability and its relatively lower cost, it doesn't cost as much.

Bob Barrett: Well, finally Dr. McConnell, any final thoughts on LDL relative risk.

Dr. McConnell: Yeah, there are some things that we think are important and one of them is to stop using the term LDL interchangeably with LDL cholesterol. This contributes to the misunderstanding of different biomarkers to characterize LDL related risk. LDL cholesterol is a molecule which is a component of the LDL particle.

Bob Barrett: That was Dr. Joseph McConnell from Health Diagnostic Laboratory. He was joined in today's podcast by Dr. Daniel Rader from the Department of Medicine at the University of Pennsylvania.

I am Bob Barrett, thanks for listening!