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Comparing Measures of HDL: On the Right Path with the Wrong Map

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Guest: Dr. Jeffrey Meeusen is Co-Director of Cardiovascular Laboratory Medicine and is a consultant in the Division of Clinical Core Laboratory Services in the Department of Laboratory and Medicine and Pathology at the Mayo Clinic.

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.

High-density lipoprotein, or HDL, cholesterol is often referred to as the "good" cholesterol due to its involvement in transport of cholesterol from peripheral tissues back to the liver during reverse cholesterol transport. However, some studies have demonstrated that the size and composition of HTL particles may influence the mechanism and capacity for this cholesterol efflux and other possible protective activities. So, some researchers believe that measurement of HTL particles, size, and composition may provide an indication of HTL protective activity.

The March 2018 issue of *Clinical Chemistry* published a report comparing five different procedures for HDL particle measurement. In the same issue an editorial by Dr. Jeffrey Meeusen appeared titled "Comparing Measures of HDL: On the Right Path with the Wrong Map." Dr. Meeusen is Co-Director of Cardiovascular Laboratory Medicine at the Mayo Clinic in Rochester, Minnesota, and is a consultant in the Division of Clinic Core Laboratory Services in the Department of Laboratory Medicine and Pathology, and he is our guest in this podcast.

First of all, Dr. Meeusen, can you tell us something about the paper that your editorial addresses. Method comparison studies are often relatively easy to perform; a lab uses two or methods and compares the results. Sounds pretty simple, but I guess that's not the case with HDL particle measurements. What were some of the novel features of this paper?

Jeffrey Meeusen: That's a great question and it really gets to the heart of the issue. Just to start off with a little background, so we all know cholesterol is the bad guy that we look out for when it comes to heart disease. Well, that was the original test, and then after some time it turned out not all cholesterol is bad, some of it was good, that's when we started to distinguish HDL cholesterol from the rest.

Well, now we know that cholesterol itself isn't necessarily good or bad, but it's the lipoproteins that are carrying it that are good or bad. And think of lipoproteins like grease bubbles that allow these real polar fats to be transported within our aqueous blood. So, the study we're discussing compared different measures of HDL size, so that's the size of these lipoproteins that are circulating in our blood stream. The problem is each of the commercially available tests actually measured an entirely different aspect of HDL. One of them measured how much cholesterol was in the large, medium, and small. One of the measured how many particles were large, medium, or small; another measured how many HDL proteins were in the large or the medium or the small – so you see what we're saying here--they are actually each measuring a different thing.

And then to confuse it even further each of these methods actually defines large, medium, and small in completely different ways. Some separate them based on size, some based on charge, some on density, and even those that separated by the same manner? They didn't actually define small or large using the same cut offs.

So, the authors really had their work cut out for them. And I do think it was a very important and worthwhile task to get after. And they came up with something clever, what they did to get around this confusion was normalize each test, and compare the relative amount of either large, medium or small HDL reported as a percentage of the total HDL measure.

Bob Barrett: Often method comparisons use a so called "gold standard" procedure. What's the current gold standard method of measuring HDL subfractions?

Jeffrey Meeusen: Well, truly is there isn't one. The closest that we might come to having a gold standard for these subfractions would be density grading and ultracentrifugation. And some of the methods, such as the NMR method, were actually standardized to this method when they were first developed. However, this ultracentrifugation is a very tricky, labor-intensive, time-consuming process and it's not available clinically, or it is not widely available at all, actually.

Bob Barrett: So, in the absence of a gold standard, is there any consensus on how HDL subfractions should be defined?

Jeffrey Meeusen: Yeah, actually in 2011 *Clinical Chemistry* published a consensus statement – with an extra panel that included some of the authors from the paper at hand, as well as other experts in the other methods that were compared. And the statement proposed nomenclature as well as

specific definitions for what should be small, medium or large HDL.

Bob Barrett: Can you comment on the methods currently available and whether they follow these recommendations?

Jeffrey Meeusen: Unfortunately, none of them do. For instance, according to this consensus document, medium HDL would have a density between 1.11 and 1.13 grams per liter, and it would have a diameter between 8.8, 8.2 nanometers. Well, looking at test that were compared, the VAP test, the HDL mapping, and the IR Gradient, all would classify a particle of that size as a small HDL.

The only that would correctly classify it as medium was actually NMR. So, all of the tests have unique classifications that really don't necessarily even follow the consensus statement.

Bob Barrett: Then, how do all these methods compare with each other?

Jeffrey Meeusen: Unfortunately, the biggest conclusion that we came away with in this study is that they don't compare well to each other. They're not going to call the same amount of large HDL versus small HDL even within the same person.

Bob Barrett: But HDL is HDL, so why shouldn't we expect the various methods to be comparable with each other?

Jeffrey Meeusen: Well, this gets right back to the heart of the matter, each of these methods is measuring something unique, and when you measure different things in different ways, you're going to get different answers. So, we don't necessarily want them to compare. For instance, a very large HDL particle, again imagine these are just grease bubbles in the blood, a large particle can hold a lot of cholesterol so it might mean that we have more large cholesterol, but fewer large actual particles because you don't need more particles to hold that much more cholesterol. The same might be true for proteins. A very small particle can only accommodate one protein so you need to have lots of small lipoproteins in order to have lots of small protein. So, we don't expect them to compare with one another just because what we're measuring is different aspects and then we're throwing in the confusion of the size, and then once more just to say, even the sizes weren't necessarily defined in the same manner.

Bob Barrett: Well, you are right there, it does sound confusing. What's the take-home message regarding HDL subfraction analysis?

Jeffrey Meeusen: We're in the early stage of this science. I think there is some very useful things to be gleaned from HDL

subfractions and even this method paper, but at this stage, what we need to looked at is which of these methods has data that supports actionable clinical interventions, which of these methods says that if you have elevations and large, medium, or small that is then something your doctor can talk to you about and take an intervention on. And to date, I don't know whether we have any of that for any of these, but that's really going to be the point to where we need to go moving forward.

Bob Barrett: That was Dr. Jeffrey Meeusen, Co-Director of Cardiovascular Laboratory Medicine and a consultant in the Division of Clinical Core Laboratory Services in the Department of Laboratory and Medicine and Pathology at the Mayo Clinic. He has been our guest in this podcast on HDL particle measurements. I'm Bob Barrett, thanks for listening.