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Reevaluating the Role of High-Density Lipoprotein Cholesterol: New Perspectives on Cardiovascular Disease and Alzheimer Disease

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Guest: Dr. Ruth Frikke-Schmidt from the University of Copenhagen, Denmark.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

High-density lipoprotein (HDL) cholesterol has long been described as the 'good cholesterol' based largely on the observation that high concentrations are associated with lower risk of cardiovascular disease. However, recent data have challenged this conventional wisdom as drugs that increase HDL cholesterol have been ineffective in reducing cardiovascular risk. To make matters even more interesting, new studies have shown that high HDL may actually be harmful as it's associated with increased mortality, Alzheimer disease, and other conditions. In light of these new findings should we completely reconsider our view of HDL cholesterol? Is it good or bad? What do we really know about HDL cholesterol, and what additional work is required to bring clarity to this issue?

A perspective article appearing in the December 2023 issue of *Clinical Chemistry* summarizes recent HDL cholesterol studies described this association with various diseases and applies this new information to guide its use in patient care.

In this podcast we are pleased to welcome the senior author of this perspective article. Dr. Ruth Frikke-Schmidt is a Professor of Clinical Biochemistry and Human Genetics at the University of Copenhagen, Denmark. She heads a research group focusing on biomarkers and genomics of common age-related diseases including cardiovascular disease, dementia, diabetes, and age-related macular degeneration.

Dr. Frikke-Schmidt, we have always been told that having a high HDL cholesterol was good, how should we understand the new data questioning this?

Ruth Frikke-Schmidt: It's right that we've known for more than 30 years that high HDL cholesterol was kind of considered good, the good cholesterol, because we have seen during these decades in many population studies that a high concentration of HDL cholesterol is associated with a low risk of cardiovascular disease with atherosclerosis.

But that is only an association; it's not really a proof of the fact that HDL particle in itself is the causal agent. It's just an association like we can see associations between many different things. What requires me to say that HDL cholesterol is the causal agent is, for instance, arranged amongst clinical drug trials.

Bob Barrett: So why do you think the trials of drugs that raise HDL cholesterol have failed to reduce cardiovascular risk?

Ruth Frikke-Schmidt: That's because when you perform a randomized clinical drug trial, if that will be successful, you need to target the molecule, the component that is really the cause of the disease, otherwise, of course, it won't work. We know the bad cholesterol, the LDL cholesterol, that is really a cause of atherosclerosis and cardiovascular disease. It works with LDL cholesterol lowering drugs. Many of us takes that. It works. It reduces your risk of cardiac diseases. Same with blood pressure. Drugs against elevated blood pressure reduces your risk of cardiovascular disease, that's backed because the bad cholesterol, LDL cholesterol and high blood pressure is a cause of cardiovascular disease.

The problem is, with HDL cholesterol, we believe that because it seemed to be good to have a high one, we should elevate it with drugs, but that was again only an association, so when we tried, when drugs were designed to elevate HDL cholesterol, they didn't work, and that was because HDL cholesterol always goes together with another cholesterol type in the inverse direction and that other cholesterol trait was really the causal one.

So, if we only focus on one of two components, on the wrong one, it doesn't work. So, that's one major explanation for why when you only with drugs elevate HDL cholesterol, it doesn't work.

Bob Barrett: Where do you see a mechanistic role for HDL cholesterol?

Ruth Frikke-Schmidt: What is quite interesting now is that in different tissues, not in the cardiovascular disease, but for instance, in the eye and in the brain, those tissues, delicate tissues are very dependent on a local lipid transport. Not in the bloodstream and going into the vessels but across delicate barriers to supply the local tissue vessels in the eye with these nutrients that cholesterol and other lipids and molecules, lipid molecules, cholesterol molecules are, and there the molecule HDL is probably important for that local delivery.

So, if the HDL molecule is too big, for instance, it may not be good for the local tissue as in the eye or in the brain, so we see very interesting findings in these organs for the HDL

cholesterol molecule. So that's a part we are also focusing on.

Bob Barrett: Well, should we still even continue to measure HDL cholesterol?

Ruth Frikke-Schmidt: We should definitely do that because HDL cholesterol measured in the blood, the concentration measured in the blood is a very stable marker of our overall lipid metabolism, lipid cholesterol levels in the blood, and when we take the total measurement of cholesterol, and we subtract the HDL cholesterol, the remaining part, which we call non-HDL cholesterol, is really, really a good measure of your overall bad cholesterol burden, and importantly, that component non-HDL cholesterol is a key component in risk algorithms in the European guidelines.

So, a combination of your risk factors--blood pressure, smoking, non-smoking, and your sex and your cholesterol level, the non-HDL--gives you an overall impression of your risk of a speedy cardiovascular disease and then we know what to focus on. If you're at high risk, we really need to lower your cholesterol, we really need to lower your blood pressure and to know your own risk.

So yes, HDL cholesterol is very important to measure so we can get it into the algorithm and get a measure of the overall bad cholesterol burden.

Bob Barrett: Makes a whole lot of sense. So, let's look ahead. Give us a glimpse of where your future research could be going?

Ruth Frikke-Schmidt: First of all, I think it's important with me to discuss a little bit about cardiovascular disease again. Now we know from randomized clinical trials that high cholesterol or HDL cholesterol is really not a cause in itself. It's due to that it marks the other causal cholesterols. So we see, more and recent data also that for instance, high HDL cholesterol is associated with different diseases, also a cardiovascular disease, but we must also say that the evidence points again that is just associations, it's not causality. It's correct because the disease in itself do something to that.

So it's not a drug target HDL cholesterol in itself anymore for cardiovascular disease, but if we go to the other diseases, eye and brain, especially the eye with local cholesterol transport marked by HDL cholesterol, there may be indications that that could indeed be a course and may be interesting to look further if it could be a drug target for some of the very common eye diseases where lipid cholesterol is also accumulated and causes the disease. So that's an important area of future research.

Bob Barrett: That was Dr. Ruth Frikke-Schmidt from the University of Copenhagen, Denmark. She served as senior author for a perspective article reevaluating the role of HDL cholesterol in the December 2023 issue of *Chemical Chemistry,* and she has been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.