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Genetically Low Triglycerides and Mortality: Further Support for "the Earlier the Better"?

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S.S. Martin and M.J. Blaha.
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Guest:
Dr. Seth Martin is a cardiology fellow in the Division of Cardiology and the Ciccarone Prevention Center at the Johns Hopkins Hospital in Baltimore.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I'm Bob Barrett. In the May issue of *Clinical Chemistry*, researchers involved in the Copenhagen City Heart Study found that lower nonfasting, circulating triglyceride concentrations are associated with lower all-cause mortality.

We were joined by one of the authors of that paper in another podcast. This work at the intersection of lipidology and preventive cardiology was accompanied by an editorial in the same issue by Drs. Seth Martin and Michael Blaha from the Division of Cardiology at Johns Hopkins Hospital in Baltimore. Dr. Martin joins us in this podcast. And Doctor, there were some very interesting findings there. What are the strengths of this study?

Dr. Seth Martin: I think there are three major strengths to the study. The first strength is that the follow-up in the study was excellent for important clinical outcomes. The study had a long duration of follow-ups spanning over two decades, and all of the patients were accounted for. And this latter point is really an advantage of conducting research in Denmark, where they have the Danish Central Person Register that keeps very close tabs on the population. So I think that's the first major strength of the study, the follow-up for outcomes and the completeness of that follow-up.

The second major advantage, I think, is the modern epi technique that they used, Mendelian randomization. This is really an exciting technique that's been used in many recent high-profile studies. And it can be thought of as a randomized trial of biomarkers, the randomization occurring naturally at the genetic level, and that genetic information is linked with biomarker levels and, ultimately, clinical outcomes. And this Mendelian randomization technique is really thought to limit much of the bias in traditional EPI approaches and allow for causal inference.

And then I think the third and final major strength, in my view, is the nonfasting measurement of the circulating triglyceride levels in this study. You and I and the listeners, we spend most of our lives in a nonfasting state. And so, in

a way, it could be viewed a little funny that we've often measured triglycerides for the last several decades in the fasting state, but it's really the nonfasting state that we're living in.

So this study measured nonfasting triglycerides and found that, consistent with prior studies, there is an important association with the clinical outcomes. And it has previously been found that nonfasting triglyceride levels have a stronger association with incident cardiovascular events. In this study, we're looking at the other flip side of the coin in terms of very low triglyceride levels and outcomes.

Bob Barrett: Well, where there are strengths, there are limitations. What do you feel were the limitations of this study?

Dr. Seth Martin: I think the main limitation that I would point out -- and this was primarily just because of the way the data has been gathered not only in this study, but in many other studies -- is the measurements that we've had.

Ultimately, as the authors very rightly point out, triglycerides are serving likely as a marker of remnant lipoproteins, triglyceride-rich remnant lipoproteins. And so, the direct measurement of those lipoproteins wasn't available in this particular study. So we're using the triglycerides as a marker for that as the group has done in their prior study suggesting causality of remnant lipoproteins in ischemic heart disease.

And so, while this is a very exciting study, and certainly points to the importance in clinical outcomes of triglyceride-rich remnant lipoproteins, we really need to directly measure those in a future study with a similar Mendelian randomization design.

Bob Barrett: So what's the bottom line? Does this mean that earlier is better for lipid-lowering treatment for the prevention of cardiovascular disease?

Dr. Seth Martin: I think this is another piece of evidence pointing to the concept, that "earlier is better." That's why my colleague, Dr. Blaha, and I highlighted that in our title of the editorial accompanying this article, stating further support for "the earlier the better." This is really an exciting concept and something that, on a conceptual level, makes a whole lot of sense with several lines of evidence supporting it -- and I'll get into that some -- but then, from practical standpoint, poses more of a challenge. But I think this is talking about it at a conceptual level.

It makes a lot of sense that, as the study shows, if someone has long-standing low triglycerides, then that could confer

more protection than treating triglycerides later in life when plaque development may be more advanced.

This study fits really nicely with the PCSK9 study, showing that genetic variation conferring very low levels of LDL cholesterol over time are protective against cardiovascular disease. And it's been found that the extent or the magnitude of protection is beyond what we see with introduction of drug therapies, particularly statins later in life. The percentage reduction is that much greater and it may have to do with the earlier reduction in levels of the atherogenic lipoproteins and in the long-term exposure to those low levels.

So it really points at this concept, "the earlier the better." And it fits with other basic lines of evidence suggesting that we may be less able to reduce plaques once they're at more advanced stages. And I think this is a really exciting concept and could be the next frontier for preventive cardiology. I really would also point listeners to a fabulous editorial by Dr. Grundy and Dr. Steinberg in the *Journal of the American College of Cardiology* where they really summarized a lot of this evidence for the concept of "the earlier the better." This is an exciting potential avenue that we could really help patients and prevent a whole lot more cardiovascular events.

The practical challenge is when we're talking about treating the patients earlier in life. We'd really want to be sure that they are going to have a high likelihood of benefit, and it may not be enough to simply know their lipoprotein profile. There certainly may be a very large role for directly measuring the presence of plaque, likely through atherosclerosis imaging, such as a coronary artery calcium scan. And so, our group at Hopkins really thinks that that consideration of the development of plaque itself really could play a key role in decision-making.

And there's likely a sweet spot where someone is developing plaque but it hasn't gotten too advanced where the time may be to intervene, that may be the sweet spot. We certainly don't want to be treating huge segments of the population, even if they have some abnormalities in lipids but don't have any presence of plaque whatsoever. It could be hard to justify that because the probability of events is so low.

So we think that this could really help sort out the types of patients and really help with the practical application of this concept, of "the earlier the better." But certainly, the signals in the literature pointing us that way, we just have to figure out how to do it.

Bob Barrett: Well, finally, Doctor, let's look ahead. Can you give us a look at where the research in this field is going?

Dr. Seth Martin: Yeah, I think the research in this field, first of all, is just incredibly exciting. I think, from so many different vantage points, prevention is really coming into the focus everywhere from the very big picture policy levels, to the clinical research level, including very exciting big data concepts and studies, to the translational and basic science level, that I think it's really coming to focus. And this is an incredibly exciting field for us all to be a part of. But some very basic fundamental concepts need to be kept in focus, which includes the measurement of lipoproteins, the accurate measurement of lipoproteins.

So I think from the standpoint of this particular study by the Copenhagen Group, they've really helped move us forward. And now, the next step for this plan of research is to move beyond the traditional measure of triglycerides and really directly measure what we think is the causal element in cardiovascular disease, the remnant lipoproteins. I think that will be a big next step in this field to do that, and then dealing in randomization, studying maps to directly measure remnants. That will be huge.

I think we also as a research community need to work together to really make sure we're using consistent definitions of remnant lipoproteins in our studies so that we can best compare our studies and build a cohesive literature, and ultimately translate those timings to the bedside so that we can take care of patients.

And it hopefully will be able to show the added value of this higher resolution lipoprotein quantification and how we'll integrate that into our risk assessments and follow-ups with patients who are on lipid therapies to better treat people and better understand the timing of treatment, at what point treatment should be made.

I think we'll also have to be very careful, as the study was, to whether we're looking at fasting or nonfasting triglycerides or remnant lipoproteins; because if we don't, that could add to some confusion in the literature. But those are all sort of the thoughts off the top of my head. But I think the next major step will be to do a similar study to this great study that the Copenhagen Group has done, just with the one change that directly measured remnants are used instead of triglycerides.

Bob Barrett: Dr. Seth Martin is a cardiology fellow in the Division of Cardiology and the Ciccarone Prevention Center at the Johns Hopkins Hospital in Baltimore. He's been our guest in this

podcast from *Clinical Chemistry*. I'm Bob Barrett, thanks for listening.