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Low Nonfasting Triglycerides and Reduced All-Cause Mortality: A Mendelian Randomization Study

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Guest:
Dr. Børge Nordestgaard is Chief Physician in Clinical Biochemistry at Copenhagen University Hospital, and a Clinical Professor of the University of Copenhagen in Denmark.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I'm Bob Barrett.

Increased nonfasting plasma triglycerides indicating increase amounts of cholesterol in remnant liver proteins and are important risk factors for cardiovascular disease. In the May issue of *Clinical Chemistry*, researchers involved in the Copenhagen City Heart Study found that lower circulating triglyceride concentrations are associated with lower all-cause mortality.

In this podcast, we're joined by the senior author of that paper, Dr. Børge Nordestgaard. He is Chief Physician in Clinical Biochemistry at Copenhagen University Hospital, and a Clinical Professor at the University of Copenhagen in Denmark.

Doctor, let me start by asking you what triglycerides are, and why some people have low or high levels in their blood?

Dr. Nordestgaard: Triglycerides are just common fat that is what you eat. When you eat butter for example or a fatty meat, so the visible fat that is triglycerides. And triglycerides you can eat it, you can have it in your blood and you can have it in your body when you are obese or fat. Why do some people have high or low levels? Well we have, in a different study and the one I talked about today, examined it in about a 100,000 individuals something called the Copenhagen General Population Study and here we can see that about 26% have levels above 2 millimoles per liter, which is about above 180 milligrams per deciliter up until 10 millimoles per liter which is a roughly 900 milligrams per deciliter.

So there's 28% that have, what you would call moderately elevated levels and then, 0.1% have severely elevated levels above 10 millimole per liter or about 900 milligrams per deciliter. And why do they get these levels? Well, the moderately elevated levels between 2 and 10 millimoles per liter. The most common cause for that is simply, people eat too much fat and they become fat and then they have too much fat in the blood. So that is just obesity and overweight. Then some people with diabetes also have

higher levels and then there are genetics factors that can cause it. But there are also some other reasons, there are also if people drink a lot of alcohol, they can also have higher levels. Certain women in pregnancies, there are some other different causes.

In the very special case with really, really high levels are those above 900 milligrams per deciliter, above 10 millimole per liter. The most common cause is severely dysregulated diabetes. Very large alcohol intake and there are some other causes that have been into some rare genetic causes like lipoprotein lipase deficiency and others.

Bob Barrett: When most of us get our triglycerides measured, it's usually in a fasting state, but in your study you examined nonfasting triglycerides. Why is that?

Dr. Nordestgaard: Well, nonfasting is really the normal state for human beings because we define fasting for lipids as you haven't eaten anything for 8 to 12 hours. And if you think of a 24-hour cycle, most individuals would have eaten within the last eight hours, unless just after you get up in the morning for a few hours. So, for the majority of a 24-hour cycle you will be in the nonfasting state. So, we think that is the most natural thing and then it so happen that in our studies, we did that a long time ago when we did the studies.

Because of these types of studies and also some way I published before, it's actually introduced in Denmark now that the standard lipid profile is in the nonfasting state and not as in the fasting state as it is in many places in the world still and has been for many years.

Bob Barrett: We understand that a measurement of triglycerides simply is a measure of the amount of common fat in the blood. Before your study, what did we know about nonfasting triglycerides in relation to all-cause mortality?

Dr. Nordestgaard: I mean there have been some studies over the years but these are all observational studies, they're not causal studies, and one that I myself was first also and published in Germany in 2007. It showed very clearly in the same study, the Copenhagen City Heart Study, that if you measure a single nonfasting triglycerides and follow people for up to maybe 25 years, then the women with levels above 440 milligrams per deciliter versus less than 90 milligrams but they had a four-fold risk of mortality, all-cause mortality and the same value from men was the two-fold risk and this is, in repeated and shown in many other studies.

So those with high triglycerides, nonfasting, they have higher risk of dying early on. But with these types of

studies, you don't know it could be caused by some confounding -- it could be some factors that both cause high triglycerides and the early death or it could maybe even be some sort of this causation when you get close to dying for some reason or another you have high triglycerides. So, observation studies have these problems.

Bob Barrett: Doctor, you use a new type of study design, a so-called Mendelian Randomization Study. Can you explain to us about this study design?

Dr. Nordestgaard: This study is very similar to a randomized clinical intervention trial. In such a trial, if you want to look at -- if something causes a disease, you can recruit individuals or patients into a trial and then you flip a coin and decide whether the individual will have a luck at lowest triglycerides or a placebo. And then the beauty of that design is that, all confounders would be equally distributed between the two groups because of the flipping of the coin and therefore, you can see if you reduce triglycerides and follow a last call or for many years, you can actually determine whether reducing triglycerides reduces mortality.

A Mendelian Randomization Study is really the same, it's just nature's own randomization, because when you have children, your children gets your genes but it's a flip of a coin whether they get genes from the mother or the father and these genes are completely equally distributed between lifestyle. So if there are some genes that reduces triglycerides like we used in this study, they'll be exactly as many teens that smoke in that group than those that don't give the genotypes and the same, there'll be equal amount of those that are fat and lean and so forth.

So we don't have the proper confounding and for both of these, studied the science, the Mendelian Randomization using the natural genetic variation in population and the randomize intervention trials recruiting patients into a medical trial. In both of these studies, there's no reverse causation. That means, there's no way that death or close to death can change your triglycerides levels because they can't change your genes and they can't change the flip of the coin where you get the placebo or active drug.

Bob Barrett: Well these are fascinating findings and many people are interested in triglycerides, what are the novel findings of you study?

Dr. Nordestgaard: I mean the novel finding is that we show for the first time, that if you have lifelong, some genetic variance, that made you have lower triglycerides than other people, then you simply live longer and you die less. And to give you some simple numbers, when we are in this cohort, compare those

that have lower nonfasting triglycerides like 89 milligrams per deciliter for every lower 89 milligrams per deciliter, then you die 13% less or the half of ratio of 13% less. But the similar things if these lower triglycerides are driven by genetics that means that your life long have lower triglycerides. Then it halves your risk, your half of ratio is only 1.5.

So we can here show using genetics that a life long lower triglycerides leads to much lower all-cause mortality. You could say, "Is this important?" Well, we know that high triglycerides have something to do with cardiovascular disease. So many would argue that, while this, we knew already that if you lower triglycerides maybe have lower cardiovascular disease. However, this is a very important finding because to convince the missions or maybe people that wants to do something seriously about the high triglycerides then, that'll like this is necessary.

For example, for LDL cholesterol which is so well known, it was only after the publication of the so called Forest Fire from Scandinavia in *The Lancet* in 1994 that showed very clearly that if you lower LDL by statins versus placebo, then people simply live longer. And you could say we shown out genetically the same thing for triglycerides.

Bob Barrett: So, the lower your triglycerides the longer you live. How can we understand that mechanistically?

Dr. Nordestgaard: I can't say it for sure but I think the most likely explanation is that when you have low triglycerides, you have low cholesterol content in the triglycerides, which lipoproteins or what I call remnants. So you have lower remnant cholesterol and we have shown in other studies with the first author named Dr. Anette Varbo. She's the second author in this paper here. That those with lifelong high remnant cholesterol, they have more cardiovascular disease and even it seems like that, if you low triglycerides, you have less atherosclerosis and you particularly have less atherosclerosis with inflammation. So, it simply might, low triglycerides, low cholesterol in these particles and less inflammation in the anterior wall and therefore you don't get cardiovascular disease and you live longer.

Bob Barrett: Well, look ahead: is there a need for more studies to even better understand the relationship between nonfasting triglycerides and all-cause mortality?

Dr. Nordestgaard: Yeah, certainly. I mean there's a need for lots of randomized intervention trials like the one I talked about before, where you recruit individuals of patient into getting a triglyceride lowering drugs versus placebo and a very large studies maybe 15,000 or 20,000 individuals followed

for 5 plus years to show that when you reduce triglycerides and cholesterol in the triglycerides, with lipoprotein and then you get less cardiovascular disease and you live longer. These trials are urgently needed.

Bob Barrett: What can people do themselves try and lower their levels of nonfasting triglycerides?

Dr. Nordestgaard: Yeah, it's both very easy and very difficult because what you have to do is that the majority of people now and well, a lot of people in the world and certainly, in the different part of the world, they are overweight and obese and this is the main cause of high triglycerides. You simply had to lose weight; you have to maintain a normal body weight that is the most important thing. Then secondary, if you high triglycerides due to lot of alcohol intake, you should drink a bit less alcohol but losing weight, that's by far the most important.

Bob Barrett: Well, that sounds like work. Do you advise people with high triglycerides to reduce levels using drugs, and if so which drugs?

Dr. Nordestgaard: I mean I much prefer that you lose weight either by eating less or exercising more. But if this is not possible, then of course, you might need to use drugs and the best today is the most potent statins. As long as triglycerides are not higher than 900 milligrams per deciliter or higher than 10 millimoles per liter, then the potent statins, they will reduce not only LDL cholesterol but also triglycerides. If this is not enough or if people can't take statins, that's an intolerant, you can use fibers, niacin or fish oil, tablets which are all effective in reducing triglycerides.

Bob Barrett: Dr. Børge Nordestgaard is Chief Physician in Clinical Biochemistry at Copenhagen University Hospital, and a Clinical Professor of the University of Copenhagen in Denmark. He's been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett, thanks for listening.