Clinical Chemistry

Extreme Nonfasting Remnant Cholesterol vs Extreme LDL Cholesterol as Contributors to Cardiovascular Disease and All-Cause Mortality in 90000 Individuals from the General Population

Article:
A Varbo, J. Freiberg, and B. Nordestgaard.
Extreme Nonfasting Remnant Cholesterol vs Extreme LDL Cholesterol as Contributors to Cardiovascular Disease and All-Cause Mortality in 90000 Individuals from the General Population.
Clin Chem 2015;61:533-543.
http://www.clinchem.org/content/61/3/533.abstract

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

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.

Increased concentrations of non-fasting remnant cholesterol are thought to be atherogenic in the same way as LDL cholesterol, by transport into and accumulation of lipid into the arterial wall.

In the March 2015 issue of *Clinical Chemistry*, researchers involved in the Copenhagen City Heart Study investigated remnant cholesterol concentrations and its association with increased mortality risk and found some interesting results.

In this podcast we are 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's start by just talking about what is remnant cholesterol, and how does it come about in circulation?

Dr. Nordestgaard: Remnant cholesterol is just a cholesterol content in the triglyceride-rich lipoproteins. And I just call it remnant cholesterol because it's much simpler than talking about different fraction of triglyceride-rich protein. So, it's a simple measure of all cholesterol in all triglyceride-rich lipoproteins.

Bob Barrett: Can you tell us who you designed you study and what specific questions you addressed?

Dr. Nordestgaard: First, we tested hypothesis and what we tested was whether extreme concentration of non-fasting remnant cholesterol and LDL cholesterol are equal contributors to risk of ischemic heart disease, myocardial infarction, and all-cause mortality.

What we did was that we really compared stepwise increasing concentrations of non-fasting remnant cholesterol and LDL cholesterol for associating with these three end

points in approximately 90,000 individuals from the Danish Town population. And then we followed these people up to 22 years with complete follow-up; that means in Denmark because of our registers there is not a single person that we lost track of, until in total in this period 4435 participants developed ischemic heart disease, 1722 developed myocardial infarction and 8121 died.

Bob Barrett: Your results seemed to be both interesting and clinically relevant. What do you consider the most novel finding of your study?

Dr. Nordestgaard: Let me first just come a little bit back to sort of like the science, because what we did about this extreme level. So we looked at the people with the highest remnant cholesterol, the top 5% to 6%, which are those remnant cholesterol above 1.5 millimoles per liter. And then we compared that with those with LDL cholesterol in the top similar group above 5 millimole per liter and then we had a medium group and a little lower group and then we compared them all to remnant cholesterol, less than half a millimole and LDL cholesterol less than 3 millimoles.

So, we really looked at the same fractional table with the very highest remnant cholesterol versus the very highest LDL cholesterol, compared to the bottom approximately 30-40%, and then when we looked at that, so you could say, head-to-head comparison of these two atherogenic lipoproteins in plasma.

Then for risk of ischemic heart disease the top group of remnant cholesterol and the top group of LDL cholesterol had approximately the same risk, two and half fold increased risk over these, up to two years of follow up. When we looked at myocardial infarction, again, similar risk but here the LDL was a little bit better, 4.5, 4.7 for LDL cholesterol and 3.4 for remnant cholesterol.

But then very surprisingly, when we looked at all-cause mortality then the top remnant cholesterol group, meaning more than one and a half milimoles per liter versus less than half milimoles per liter had a 1.6-fold increased risk of all-cause mortality, whereas for LDL there was more or less trend toward lower all-cause mortality nothing increased at all.

Bob Barrett: So, why has remnant cholesterol mainly been ignored in the past?

Dr. Nordestgaard: Well, it's a bit of puzzle to me also, but I think it's because when you do a standard lipid profile, you would look at HDL cholesterol, LDL cholesterol, and then triglycerides and triglycerides is just a mark of remnant cholesterol. And then

nobody really thinks that it's triglycerides per se that is causing atherosclotic cardiovascular disease because triglyceride can be degraded by many different cells.

So, people have – by just talking about triglyceride rather than the cholesterol content in these particles, I think they have gone a bit confused and then of course there has been the debate about high triglycerides versus low HDL has also confused us for years.

But I think time has come now that more and more people would take remnant cholesterol much more seriously.

Bob Barrett: When you measure remnant cholesterol, should it be fasting or non-fasting or does it even make a difference?

Dr. Nordestgaard: I think we can do either way, the thing is that the majority of remnant cholesterol, actually when I call it remnant cholesterol of course some experts they think it's a wrong term, because in the fasting state it is really, what we call VLDL cholesterol and IDL cholesterol which is just how you separate them by ultracentrifugation; whereas in the non-fasting state you would have IDL, VLDL and then some chylomicron remnants.

But I think all these triglyceride lipoproteins in plasma are remnant because as soon as either VLDL produced by the level of chylomicrons produced from the intestines get into the bloodstream lipoprotein lipase would immediately degrade some triglycerides and then you can say they are all remnants.

So in the fasting state still the maturity of the lipoproteins IDL and VLDL, those that come from the liver and chylomicron remnants are in only small fractions, so I think you can use either way. But, there is some evidence now suggesting that when you do it in a non-fasting state, you might actually catch even more of these heterogenic lipoproteins. So in the future, I am hopeful and I think using non-fasting lipid profile including the remnant cholesterol probably will be better.

Bob Barrett: Now when laboratories report lipid profiles you get results for Total, LDL, HDL cholesterol as well as for triglycerides, how does remnant cholesterol relate to these values?

Dr. Nordestgaard: Well, sort of like, when you look at Total cholesterol, and Total cholesterol is HCL cholesterol, LDL cholesterol and then the rest; and the rest is then in my -- how I use the words--is remnant cholesterol. Then of course, there is [06:24], but we won't talk about that right now.

So when we have a triglyceride value it is just a mark of remnant cholesterol, so I would much rather just talk about HDL cholesterol, LDL cholesterol and remnant cholesterol because these three together is the totality of cholesterol in plasma.

Bob Barrett: And how do laboratories measure or calculate remnant cholesterol?

Dr. Nordestgaard: In our studies, and we try to do that because this is the simplest possible way, we just calculate it, so we just take total plasma cholesterol and subtract HCL cholesterol and subtract LDL cholesterol and then the remaining cholesterol is remnant cholesterol. This is really, really simple and its free of charge, it doesn't cost anything, and if you have a laboratory you can just ask your computer to calculate it. So that's what we do.

And then, of course some people say, well, it should be measured much finer because if you, for example calculate LDL cholesterol by the Friedewald equation then you have a certain ratio between triglycerides and cholesterol in the triglyceride lipoproteins; in other words there are some assumptions.

So someone might prefer to make it directly, and then there is of course different options, but none of them are so easy to use in large scale or in clinical practice. Of course, the old fashion or the standard one is the ultracentrifugation. You would simply just use ultracentrifugation and take d less than 0.0 6 g/ml, and that would be the cholesterol and the top fraction would be the remnant cholesterol.

But then you can also use Mass Spec for example, and define the various fractions of cholesterol and lipoproteins that are aren't HDL and LDL and that would be remnant cholesterol.

And there is a need for a direct homogeneous assay. So like what we do today is we use direct homogenous assays formation, HDL cholesterol and LDL cholesterol, and I hope some companies in future will develop a similar direct assay for remnant cholesterol because then it will be automated just like the other lipid fractions.

Bob Barrett: Well, then, should medical laboratories include remnant cholesterol together with LDL and HDL on their reports?

Dr. Nordestgaard: Oh I think so, this would be very good. It's really -- when I try to communicate very simply, I talk about the good, the bad and the ugly cholesterol, and the good cholesterol HDL cholesterol, these days I don't call it good so much anymore but maybe just innocent cholesterol because we don't really

think it protects against atherosclerosis anymore, and then the bad is LDL and then the ugly is remnant cholesterol.

So I would just list HDL cholesterol, LDL cholesterol and remnant cholesterol, and then you can list triglycerides also, which is very similar to remnant cholesterol.

Bob Barrett: Have reference intervals been established for remnant cholesterol, and if these are to be reported to clinicians, at what concentration should values be flagged as abnormally high?

Dr. Nordestgaard: No, they haven't yet. I am working on a consensus paper from European Atherosclerosis Society together with the European Federation for Laboratory Medicine, and we also have several American experts included, and one from Australia, and we talk about there, maybe one should advise something about to flag if it is in the fasting state remnant cholesterol higher than 0.8 milimoles per liter which is corresponding to higher than 30 milligram per deciliter, and if it was in a non-fasting value or sample, it should be greater than 0.9 millimole per liter non-fasting for remnant cholesterol and then in milligram per deciliter more than 35.

Bob Barrett: Finally Doctor, what other research questions need to be addressed with respect to remnant cholesterol?

Dr. Nordestgaard: With respect to remnant cholesterol as well as with triglycerides, what we really need is large randomized intervention trials that specifically recruit people with high remnant cholesterol, meaning also high triglyceride, and try to treat them with some potent block that reduces not only triglycerides but specifically reduces remnant cholesterol to see whether reduction in these lipids will translate into clinical benefit just like LDL reduction has been shown with statin trials.

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

He has been our guest in this podcast from *Clinical Chemistry* on remnant cholesterol in plasma.

I am Bob Barrett. Thanks for listening!