Reply to Letters Regarding Article, “Elevated Remnant Cholesterol Causes Both Low-Grade Inflammation and Ischemic Heart Disease, Whereas Elevated Low-Density Lipoprotein Cholesterol Causes Ischemic Heart Disease Without Inflammation”

We thank Dr_Scharnagl and colleagues and Dr Jones and colleagues for their positive comments on our recent article on remnant cholesterol and low-density lipoprotein (LDL) cholesterol as causal risk factors for ischemic heart disease with and without low-grade inflammation. We agree that because of the complexity of the lipoprotein metabolism with many subclasses of lipoproteins and their different lipid contents, our calculation of nonfasting remnant cholesterol as nonfasting total cholesterol minus LDL cholesterol minus high-density lipoprotein cholesterol is a simple way of estimating remnant cholesterol levels. Thus, our calculation of remnant cholesterol cannot answer the question of whether some subclasses of remnants or some lipid fractions of remnants are more atherogenic than others; however, it is exactly the simplicity of our calculation that makes it clinically useful. Clinicians anywhere can use our method to estimate levels of nonfasting remnant cholesterol in patients if they have measured a standard nonfasting lipid profile at, importantly, no extra cost. Although more detailed assays measuring specific subclasses of remnants or lipid contents of these may be very informative, they are not available for clinical purposes everywhere.

We used the Friedewald equation to estimate LDL cholesterol in participants with triglyceride levels ≤4 mmol/L. This means that in these participants nonfasting remnant cholesterol is nonfasting triglyceride levels divided by 2.2. We could have measured LDL cholesterol directly in all participants, not only in those with triglycerides >4 mmol/L. However, correlation studies comparing directly measured LDL cholesterol with calculated LDL cholesterol have found the correlation to be very high when triglycerides are ≤4 mmol/L (r^2 >0.97). Therefore, calculating LDL cholesterol is a valid method and a more economical substitute for direct measurements, especially considering the large number of participants in our study. In our study, we used nonfasting blood samples from participants drawn at random times after a meal. The Friedewald equation for estimating LDL cholesterol was originally defined for fasting lipid levels. However, in a previous study including some of the same participants as the present study, it was shown that lipid profiles are influenced only minimally by normal food intake in the general population and that nonfasting lipid levels are associated with risk of cardiovascular disease. Most people are in the nonfasting state most of the day because fasting implies not eating for at least 8 hours, and for most people in affluent countries, this is the case only early in the morning. This argues for examining the association of remnant cholesterol levels with ischemic heart disease in the nonfasting state, as done in our study.

We acknowledge that from our study we cannot rule out that it might be triglycerides per se, not the cholesterol content of remnants, that are causal for the development of atherosclerosis. However, because most cells can degrade triglycerides but none can degrade cholesterol, it seems more plausible that it is the cholesterol content that eventually causes atherosclerosis by accumulating in the intima of the arterial wall, in the same way as for LDL cholesterol.

After lowering of LDL cholesterol to recommended levels, there is still a substantial residual risk of ischemic heart disease. Elevated remnant cholesterol levels could probably explain some of this residual risk, and our simple way of estimating levels of nonfasting remnant cholesterol makes it possible for clinicians to intervene on these other lipid risk factors besides LDL cholesterol.

Disclosures

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References

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