Remnant Cholesterol and Triglyceride-Rich Lipoproteins in Atherosclerosis Progression and Cardiovascular Disease

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In this issue of the journal, Puri et al[1] examines the association of on-treatment concentrations of non–high-density lipoprotein (non-HDL) cholesterol and triglycerides with coronary atheroma progression and clinical events. They used data from 9 clinical trials, originally designed to examine effects of different medical therapies on regression of coronary atheroma burden, assessed by intravascular ultrasound. The main finding was that achieved concentrations of non-HDL cholesterol and achieved concentrations of triglycerides were closely associated with coronary atheroma progression and regression, irrespective of achieved concentrations of low-density lipoprotein (LDL) cholesterol, C-reactive protein concentration, and diabetes mellitus status.

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Non-HDL cholesterol is a combined measure of the cholesterol content of LDL, lipoprotein(a), and triglyceride-rich lipoproteins, the latter also known as remnants (Figure). Remnants are here a combined term for intermediate-density lipoproteins, very-low-density lipoproteins, and chylomicron remnants. These lipoproteins likely are atherogenic by penetrating the arterial wall, leading to accumulation of cholesterol in the intimal space, foam cell formation, and atherosclerosis[2–5] (Figure). Triglycerides are primarily carried by remnants, and concentrations of triglycerides are highly correlated with the cholesterol content of remnants, that is, remnant cholesterol.[6] It is most likely that the cholesterol content of remnants, and not triglycerides, causes atherosclerosis because most cells can degrade triglycerides but not cholesterol[2,5] and because cholesterol, and not triglycerides, accumulates in the intima.[7]

The findings of Puri et al[1] are in line with previous studies by us and others showing associations between concentrations of remnant cholesterol (or the highly correlated triglycerides) and increased risk of cardiovascular disease, both in observational[8–16] and genetic studies,[6,17–19] indicating remnant cholesterol as a causal risk factor for cardiovascular disease. It was therefore a limitation to the study, and a missed opportunity, that Puri et al[1] did not report on the direct association between remnant cholesterol and coronary atheroma regression, because this could have added to the understanding of the relative importance of the different parts of cholesterol in non-HDL, that is, LDL cholesterol and remnant cholesterol. But perhaps, a head-to-head comparison of remnant cholesterol with LDL cholesterol can be reported on in a follow-up publication, similar to what we have reported previously for individuals in the general population[15] and in patients with ischemic heart disease.[20] Nevertheless, Puri et al[1] found a stronger association between achieved non-HDL cholesterol concentrations and atheroma progression compared with achieved LDL cholesterol concentrations, indirectly indicating that additional predictive information lies in the remnant cholesterol part of non-HDL cholesterol. This is important for the design of future lipid-lowering studies to most effectively reduce the residual risk of cardiovascular disease seen after LDL cholesterol lowering.

There is strong evidence suggesting that high concentrations of remnant cholesterol cause atherosclerosis and ischemic heart disease, with important differences in how remnants cause atherosclerosis compared with LDL. Remnants pass into the arterial wall[3,4] and are taken up by macrophages and smooth muscle cells without modification, which is unlike LDL, that needs to be modified before uptake.[21] Also, remnant particles are larger than LDL and carry ≤40 times as much cholesterol per particle, perhaps making them even more atherogenic than LDL.[7] Also, we have previously found that high remnant cholesterol concentrations were associated with low-grade inflammation and with ischemic heart disease, whereas LDL cholesterol concentrations were not associated with low-grade inflammation, despite an association with ischemic heart disease.[22] This indicates that remnant cholesterol causes atherosclerosis with an inflammatory component, whereas LDL cholesterol causes atherosclerosis without. These differences in mechanism make it interesting to examine remnant cholesterol and LDL cholesterol separately.

Unfortunately, among some lipid experts, there is resistance toward using the easily calculated remnant cholesterol, determined as total cholesterol minus HDL cholesterol minus LDL cholesterol, as we have done previously.[5,6,10,15,20,22–24] Remnant cholesterol can be calculated from a standard lipid profile without additional cost and can probably add to the risk evaluation of cardiovascular disease in an individual. Arguments against using calculated remnant cholesterol are mainly that it is in fact calculated; however, LDL cholesterol is also calculated often, and non-HDL cholesterol likewise, and there is no doubt that lowering LDL cholesterol is beneficial, despite the fact that some of the evidence is based on calculated LDL cholesterol.

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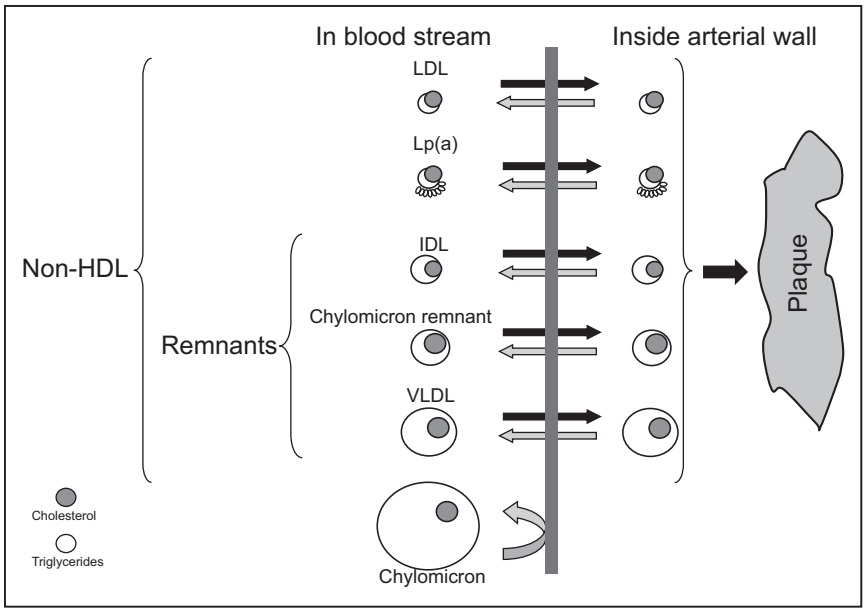

Figure. Definition of lipoprotein categories and proposed mechanism of how lipoproteins cause atherosclerosis in the arterial wall. Low-density lipoproteins, lipoprotein (a), and remnants are small enough to enter the arterial wall, get trapped, and cause plaque formation. Chylomicrons are too large to enter the arterial wall[27,28] until they are hydrolyzed by lipoprotein lipase and become remnants, which is a process that in most individuals happens rapidly, and therefore, large chylomicrons normally are only present in plasma in minute amounts. HDL indicates high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); and VLDL, very low-density lipoprotein.

There is an urgent need for future randomized clinical intervention trials examining whether lowering remnant cholesterol and triglycerides in those with high concentrations can reduce the risk of cardiovascular disease. Previous studies with triglyceride-lowering drugs have had conflicting results[5]; however, this can partly be explained by the way participants were recruited. No study to date have selectively recruited individuals with mild to moderately elevated or high concentrations of triglycerides, and the present study from Puri et al[1] showed that atheroma progression was only associated with triglycerides >200 mg/dL (2.27 mmol/L). This is in line with previous post hoc analyses of triglyceride-lowering studies, showing that in the subgroup of individuals with high baseline triglycerides, the risk of cardiovascular disease was reduced after triglyceride lowering.[5,13,25] Fortunately, 2 randomized, placebo-controlled trials of triglyceride-lowering therapy added to statin therapy in individuals with elevated triglyceride concentrations with the aim of reducing cardiovascular disease are ongoing (NCT01492361 and NCT02104817), and one is planned to start relatively soon.[26]

The findings of Puri et al[1] contribute valuable information about non-HDL cholesterol, triglycerides, and atherosclerosis. In Kaplan–Meier sensitivity analyses, the study also demonstrated greater major adverse cardiovascular event rates in those with higher versus lower non-HDL cholesterol and triglycerides, with earlier separation for the non-HDL cholesterol curve compared with the LDL cholesterol curve. Their interesting, well-performed, and timely study warrants future studies examining whether lowering of non-HDL cholesterol, triglycerides, and remnant cholesterol can reduce the considerable residual risk of cardiovascular disease seen after lowering of LDL cholesterol with statins.

Disclosures

B.G. Nordestgaard has received lecture and/or consultancy honoraria from AstraZeneca, Merck, Omthera, Sanofi, Regeneron, IONIS, Aegerion, Dezima, Amgen, Kowa, and Denka Seiken. The other author reports no conflicts.

References

1. Puri R, Nissen SE, Shao M, Elshazly MB, Kataoka Y, Kapadia SR, Tuzcu EM, Nicholls SJ. Non-HDL cholesterol and triglycerides: implications for coronary atheroma progression and clinical events. *Arterioscler Thromb Vasc Biol*. 2016;36:2220–2228. doi: 10.1161/ATVBAHA.116.307601.
2. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. *Circ Res*. 2016;118:547–563. doi: 10.1161/CIRCRESAHA.115.306249.
3. Shaikh M, Wootton R, Nordestgaard BG, Baskerville P, Lumley JS, La Ville AE, Quiney J, Lewis B. Quantitative studies of transfer in vivo of low density, Sf 12-60, and Sf 60-400 lipoproteins between plasma and arterial intima in humans. *Arterioscler Thromb*. 1991;11:569–577.
4. Nordestgaard BG, Wootton R, Lewis B. Selective retention of VLDL, IDL, and LDL in the arterial intima of genetically hyperlipidemic rabbits in vivo. Molecular size as a determinant of fractional loss from the intima-inner media. *Arterioscler Thromb Vasc Biol*. 1995;15:534–542.
5. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet*. 2014;384:626–635. doi: 10.1016/S0140-6736(14)61177-6.
6. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol*. 2013;61:427–436. doi: 10.1016/j.jacc.2012.08.1026.
7. Borén J, Williams KJ. The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity. *Curr Opin Lipidol*. 2016;27:473–483. doi: 10.1097/MOL.0000000000000330.
8. Austin MA. Plasma triglyceride and coronary heart disease. *Arterioscler Thromb*. 1991;11:2–14.
9. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213–219.
10. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298:299–308. doi: 10.1001/jama.298.3.299.
11. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. 2008;300:2142–2152. doi: 10.1001/jama.2008.621.
12. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000.
13. Chapman MJ, Ginsberg HN, Amarenco P, et al; European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*. 2011;32:1345–1361. doi: 10.1093/eurheartj/ehr112.

14. Varbo A, Nordestgaard BG, Tybjaerg-Hansen A, Schnohr P, Jensen GB, Benn M. Nonfasting triglycerides, cholesterol, and ischemic stroke in the general population. *Ann Neurol*. 2011;69:628–634. doi: 10.1002/ana.22384.
15. Varbo A, Freiberg JJ, Nordestgaard BG. 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. doi: 10.1373/clinchem.2014.234146.
16. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*. 2007;298:309–316. doi: 10.1001/jama.298.3.309.
17. Do R, Willer CJ, Schmidt EM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet*. 2013;45:1345–1352. doi: 10.1038/ng.2795.
18. Thomsen M, Varbo A, Tybjærg-Hansen A, Nordestgaard BG. Low nonfasting triglycerides and reduced all-cause mortality: a mendelian randomization study. *Clin Chem*. 2014;60:737–746. doi: 10.1373/clinchem.2013.219881.
19. Helgadottir A, Gretarsdottir S, Thorleifsson G, et al. Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease. *Nat Genet*. 2016;48:634–639. doi: 10.1038/ng.3561.
20. Jepsen AM, Langsted A, Varbo A, Bang LE, Kamstrup PR, Nordestgaard BG. Increased remnant cholesterol explains part of residual risk of all-cause mortality in 5414 patients with ischemic heart disease. *Clin Chem*. 2016;62:593–604. doi: 10.1373/clinchem.2015.253757.
21. Nakajima K, Nakano T, Tanaka A. The oxidative modification hypothesis of atherosclerosis: the comparison of atherogenic effects on oxidized LDL and remnant lipoproteins in plasma. *Clin Chim Acta*. 2006;367:36–47. doi: 10.1016/j.cca.2005.12.013.
22. Varbo A, Benn M, Tybjærg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. *Circulation*. 2013;128:1298–1309. doi: 10.1161/CIRCULATIONAHA.113.003008.
23. Jørgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjærg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J*. 2013;34:1826–1833. doi: 10.1093/eurheartj/ehs431.
24. Varbo A, Benn M, Smith GD, Timpson NJ, Tybjaerg-Hansen A, Nordestgaard BG. Remnant cholesterol, low-density lipoprotein cholesterol, and blood pressure as mediators from obesity to ischemic heart disease. *Circ Res*. 2015;116:665–673. doi: 10.1161/CIRCRESAHA.116.304846.
25. Sacks FM, Carey VJ, Fruchart JC. Combination lipid therapy in type 2 diabetes. *N Engl J Med*. 2010;363:692–694; author reply 694.
26. Landmark Trial Entitled "PROMINENT" To Explore The Prevention Of Heart Disease In Diabetic Patients With High Triglycerides And Low HDL-C. http://www.pharmiweb.com/pressreleases/pressrel.asp?ROW_ID=146981. Accessed January 12, 2016.
27. Nordestgaard BG, Stender S, Kjeldsen K. Reduced atherogenesis in cholesterol-fed diabetic rabbits. Giant lipoproteins do not enter the arterial wall. *Arteriosclerosis*. 1988;8:421–428.
28. Nordestgaard BG, Zilversmit DB. Large lipoproteins are excluded from the arterial wall in diabetic cholesterol-fed rabbits. *J Lipid Res*. 1988;29:1491–1500.