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Remnant cholesterol as a cause of ischemic heart disease: Evidence, definition, measurement, atherogenicity, high risk patients, and present and future treatment

Anette Varbo [a,b,c], Marianne Benn [b,c,d], Børge G. Nordestgaard [a,b,c,e,*]

[a] Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Denmark
[b] The Copenhagen General Population Study, Herlev Hospital, Copenhagen University Hospital, Denmark
[c] Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[d] Department of Clinical Biochemistry, Gentofte Hospital, Copenhagen University Hospital, Denmark
[e] The Copenhagen City Heart Study, Frederiksberg Hospital, Copenhagen University Hospital, Denmark

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ABSTRACT

This review focuses on remnant cholesterol as a causal risk factor for ischemic heart disease (IHD), on its definition, measurement, atherogenicity, and levels in high risk patient groups; in addition, present and future pharmacological approaches to lowering remnant cholesterol levels are considered.
Observational studies show association between elevated levels of remnant cholesterol and increased risk of cardiovascular disease, even when remnant cholesterol levels are defined, measured, or calculated in different ways. In-vitro and animal studies also support the contention that elevated levels of remnant cholesterol may cause atherosclerosis same way as elevated levels of low-density lipoprotein (LDL) cholesterol, by cholesterol accumulation in the arterial wall. Genetic studies of variants associated with elevated remnant cholesterol levels show that an increment of 1 mmol/L (39 mg/dL) in levels of nonfasting remnant cholesterol associates with a 2.8-fold increased risk of IHD, independently of high-density lipoprotein cholesterol levels. Results from genetic studies also show that elevated levels of remnant cholesterol are causally associated with both low-grade inflammation and IHD. However, elevated levels of LDL cholesterol are associated with IHD, but not with low-grade inflammation. Such results indicate that elevated LDL cholesterol levels cause atherosclerosis without a major inflammatory component, whereas an inflammatory component of atherosclerosis is driven by elevated remnant cholesterol levels.
Post-hoc subgroup analyses of randomized trials using fibrates in individuals with elevated triglyceride levels, elevated remnant cholesterol levels, show a benefit of lowering triglycerides or remnant cholesterol levels; however, large randomized trials with the primary target of lowering remnant cholesterol levels are still missing.
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Abbreviations: HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; LRP, LDL receptor-related protein; VLDL, very-low-density lipoprotein.

* Corresponding author at: Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark. Tel.: +45 3 868 3297; fax: +45 3 868 3311.
E-mail address: Boerge.Nordestgaard@regionh.dk (B.G. Nordestgaard).

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1. Introduction including definition

Ischemic heart disease (IHD) is a leading cause of morbidity and mortality worldwide. An important risk factor for IHD is elevated levels of low-density lipoprotein (LDL) cholesterol, but even after lowering of LDL cholesterol to recommended levels, there is a considerable residual risk of IHD. Some of this residual risk may be explained by elevated remnant cholesterol levels (Chapman et al., 2011).

Lipoproteins transport water-insoluble triglycerides and cholesterol between tissues and organs in the body (Havel & Kane, 2001). They consist of a core of hydrophobic cholesterol esters and triglycerides surrounded by a hydrophilic mono-layer of phospholipids, free cholesterol, and apolipoproteins. The different classes of lipoproteins, i.e. chylomicrons, chylomicron remnants, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, lipoprotein(a) and high-density lipoprotein (HDL), are different in density as a result of the amount of triglycerides and cholesterol they contain, and have different apolipoproteins on their surface. Chylomicrons, chylomicron remnants, VLDL, and IDL are rich in both triglycerides and cholesterol and have relatively low densities, whereas LDL, lipoprotein(a), and HDL mainly contain cholesterol and have a higher density. Lipoproteins are produced by two pathways: 1) the endogenous pathway in which VLDL are assembled in hepatocytes and are converted to IDL and LDL by triglyceride lipolysis in plasma (on the luminal surface of endothelial cells lining the capillaries or in the lumen of vessels) and by exchange of lipids and apolipoproteins with other lipoproteins, and 2) the exogenous pathway in which chylomicrons are produced by enterocytes, and are converted to chylomicron remnants by triglyceride lipolysis in plasma (Havel & Kane, 2001). Finally, lipoprotein(a) is an LDL particle with an additional apolipoprotein(a) attached, and levels of this lipoprotein is mainly genetically determined (Nordestgaard et al., 2010; Kronenberg & Utermann, 2013).

After secretion of chylomicrons from the intestine and VLDL from the liver, both types of lipoproteins are enriched in apolipoprotein E during their degradation to remnants. Apolipoprotein E is important for the uptake of remnants by the liver, because it, like apolipoprotein B, functions as a ligand for hepatic receptors, i.e. the LDL and LRP (LDL receptor-related protein) receptors (Havel, 2010; Ramasamy, 2013). Consequently, mutations in the *APOE* gene can cause increased plasma levels of cholesterol and triglycerides (Frikke-Schmidt et al., 2000). However, hepatic uptake of remnants is complex and not fully understood, and mechanisms other than uptake via the LDL and LRP receptors have been proposed, such as internalization after binding to heparan sulfate proteoglycans (MacArthur et al., 2007).

We define remnant cholesterol as the cholesterol content of a subset of the triglyceride-rich lipoproteins called remnants, i.e. chylomicron remnants, VLDL, and IDL in the nonfasting state, and VLDL and IDL in the fasting state; in most individuals chylomicrons are not present in plasma as these particles are degraded to chylomicron remnants very fast due to rapid triglyceride hydrolysis by lipoprotein lipase. Remnant cholesterol levels are therefore highly correlated with triglyceride levels (Varbo et al., 2013a). In plasma, triglycerides and cholesterol are exchanged between HDL and remnants, and levels of HDL cholesterol and remnant cholesterol are inversely correlated. This has previously made it difficult to determine if it is low levels of HDL cholesterol per se or the concurrent high levels of remnant cholesterol and triglycerides per se that is the cause of the increased risk of IHD found in observational studies.

The aim of this review is first to summarize current evidence of elevated levels of remnant cholesterol as a causal risk factor for IHD including results from observational studies, experimental studies, genetic studies, and randomized clinical intervention trials. Second, we describe measurement of remnants, the pathophysiology behind the atherogenicity of remnants, and presence of elevated remnant cholesterol levels in high risk patient groups. Finally, we review present and future pharmacological approaches to lowering remnant cholesterol levels.

2. Remnant cholesterol levels and observational risk of ischemic heart disease

Large observational studies, and meta-analyses thereof, have shown that elevated triglycerides are associated with increased risk of cardiovascular disease (Austin, 1991; Hokanson & Austin, 1996; Nordestgaard et al., 2007; Freiberg et al., 2008; Di Angelantonio et al., 2009; Chapman et al., 2011; Varbo et al., 2011b); however, the association of elevated remnant cholesterol levels with cardiovascular disease risk is not as thoroughly studied. Although there has been many studies of the association of remnant cholesterol levels with cardiovascular disease, most have been relatively small case–control studies (Devaraj et al., 1998; Sakata et al., 1998; Kugiyama et al., 1999; Takeichi et al., 1999; Masuoka et al., 1998, 2000a, 2000b; Song et al., 2000; Higashi et al., 2001; Karpe et al., 2001; Inoue et al., 2004; Miwa et al., 2004; Oi et al., 2004; Hopkins et al., 2005; Lamon-Fava et al., 2008; Hiki et al., 2009) or observational studies (McNamara et al., 2001; Fukushima et al., 2001, 2004; Imke et al., 2005; Nakamura et al., 2005) using different assays (and thereby definitions) for determining remnant cholesterol levels. Most of the studies measured remnant cholesterol in the fasting state; however, studies of triglyceride levels, which are highly correlated with remnant cholesterol levels (Fig. 1), have shown that elevated nonfasting levels of triglycerides are consistently associated with increased risk of cardiovascular disease, and are possibly more useful for predicting risk of cardiovascular disease than fasting levels of triglycerides (Bansal et al., 2007; Freiberg et al., 2008; Mora et al., 2008; Stalenhoef & de Graaf, 2008; Nordestgaard et al., 2007, 2009; Kolovou et al., 2011; Langsted et al., 2011; Nordestgaard & Freiberg, 2011; Varbo et al., 2011b).

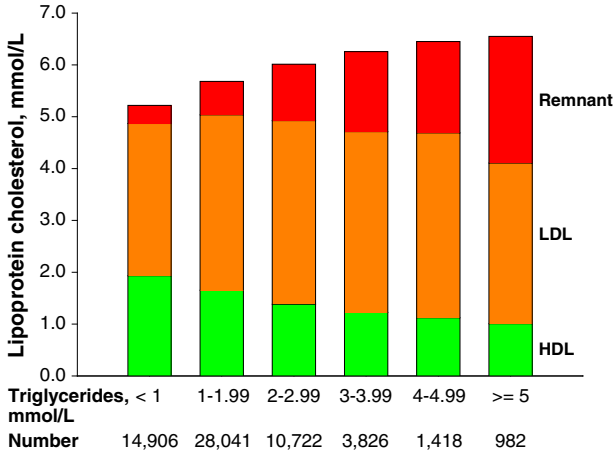

Fig. 1. Lipoprotein cholesterol as a function of increasing levels of nonfasting triglycerides. Data are from the Copenhagen General Population Study. $R^2 = 0.96$ for the correlation of remnant cholesterol levels with triglyceride levels. HDL = high-density lipoprotein, LDL = low-density lipoprotein.
Modified from Varbo et al. J Am Coll Cardiol 2013;61:427–436.

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