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How to assess and manage cardiovascular risk associated with lipid alterations beyond LDL

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Abstract

Background and aims: The maintenance of clinically recommended levels of low-density lipoprotein cholesterol (LDL-C) through a statin therapy is a gold standard in the management of patients with dyslipidaemia and cardiovascular disease (CVD). However, even when LDL-C levels are at or below clinically recommended target levels, residual cardiovascular (CV) risk still remains. Therefore, assessing lipoproteins beyond LDL-C in managing CV risk is imperative.
Methods: A working group of clinical experts have assessed the role of lipoproteins other than LDL-C in identifying the CV risk in patients with dyslipidaemia and CVD and in the management of atherogenic dyslipidaemia associated with a number of other diseases. The recommendations, in line with the European guidelines, are presented.
Results: A thorough evaluation of clinical data by the expert working group resulted in recommendations to consider non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (apoB), remnant cholesterol and lipoprotein(a) (Lp[a]) as biomarkers of residual CV risk in patients with CVD. Elevated Lp(a) levels were also suggested to be a causal factor. The experts highlighted the significance of non-HDL-C and triglycerides (TG) in atherogenic dyslipidaemia associated with type 2 diabetes, metabolic syndrome, chronic kidney disease (CKD) and familial combined hyperlipidaemia (FCH). The working group recommended combinatorial therapeutic approaches in high-risk patients, including agents impacting on TG and HDL-C levels.
Conclusions: Evaluation of a lipoprotein landscape when LDL-C levels remain low strongly supports the role of non-HDL-C, Lp(a) and TGs in identifying patients with increased residual risk of CV and in selecting their treatment strategy.

Keywords: Atherogenic dyslipidaemia; Cardiovascular disease; Cardiovascular risk; Non-high-density lipoprotein cholesterol; High-density lipoprotein cholesterol; Lipoprotein(a); Apolipoprotein B; Triglycerides

Introduction

In patients with established cardiovascular disease (CVD), residual cardiovascular (CV) risk persists despite the achievement of target low-density lipoprotein cholesterol (LDL-C) levels with statin therapy. Furthermore, the introduction of combination therapy and more potent cholesterol-lowering agents, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, has resulted in LDL-C being reduced to unprecedentedly low levels, making the contribution of other lipid parameters an important consideration in the management of residual CV risk.

A group of experts including cardiologists, endocrinologists and internists convened and were asked to provide advice on this topic. The main objective was for the experts to produce clinical best practice approaches for common and complex clinical situations found in patients with dyslipidaemia and residual risk. The expert working group were asked to consider a series of questions on CV risk

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associated with lipid alterations beyond LDL-C and to make recommendations on how best to assess and manage this risk. This article contains background information, evidence and guidance, which supports the recommendations of the expert working group.

How to manage residual risk related to triglyceride/high-density lipoprotein cholesterol abnormalities and what is the best marker for this category of patients: non-high-density lipoprotein cholesterol, apolipoprotein B, remnant lipoprotein cholesterol or non-fasting triglycerides?

The crucial role of dyslipidaemia, especially hypercholesterolaemia, in the development of CVD is documented beyond any doubt by genetic, pathology, observational and intervention studies [1]. Although LDL-C reduction is the primary target of therapy, accumulating evidence suggests that other lipoprotein-lipid measurements may provide a predictive value over and above that of LDL-C. However, it is currently unclear which lipoprotein-lipid marker is the best marker for estimating residual risk.

Expert working group opinion on the best marker to predict residual risk

- Evidence is most supportive for non-high-density lipoprotein cholesterol (non-HDL-C) as a predictor of residual CVD risk
- Emerging evidence for remnant cholesterol as an independent risk factor, although no direct measurement is available in clinical practice and there is no evidence that lowering remnant cholesterol translates to a reduction in CV outcomes
- High-density lipoprotein cholesterol (HDL-C) is a good predictor of risk but it has no role to play as a therapeutic target
- Insufficient evidence that apolipoprotein B (apoB) is superior to LDL-C (but apoB can be considered as an alternative risk marker, especially in subjects with high triglycerides [TGs])

European guidelines on CVD prevention in clinical practice state that non-HDL-C is a reasonable alternative treatment goal, while acknowledging that it has not been used as an endpoint in therapeutic trials [1]. This consensus is supported by a meta-analysis from Robinson and colleagues demonstrating that lipid-modifying drugs, for example statins or fibrates, used in monotherapy elicit an approximately 1:1 relationship between non-HDL-C lowering and coronary heart disease (CHD) reduction [2]. In addition, the results of a meta-analysis investigating the association between on-statin LDL-C, non-HDL-C, apoB and the risk of future CV events demonstrate that, among statin-treated patients, non-HDL-C has a stronger association with risk of major CV events than either LDL-C or apoB. Furthermore, reduction in non-HDL-C levels appears to contribute a larger proportion of the atheroprotective effect of statin intervention than LDL-C or apoB does [3]. Box 1 summarises the current recommendations on managing residual risk from the European guidelines [1].

Box 1. Current ESC (2016) recommendations on the management of residual risk

- Non-HDL-C is a reasonable and practical alternative target to LDL-C because it does not require fasting
- Non-HDL-C target values may be an alternate target if non-fasting samples are obtained, and goals should be <2.6mmol/l, <3.3mmol/l and <3.8mmol/l (<100mg/dl, <130mg/dl and <145mg/dl) with very high, high and low-to-moderate CV risk, respectively
- Non-HDL-C is a secondary goal in people with elevated TGs. In the same subjects, although not generally recommended, apoB levels at <80mg/dl and <100mg/dl can be reasonable goals for subjects with very high and high CV risk, respectively
- Remnant cholesterol is not suggested as a predictor or main target for therapy
- Low HDL-C is associated with increased CV risk but manoeuvres to increase HDL-C have not been associated with a decreased CV risk
- There is no evidence that apoB is a better predictor of CVD than LDL-C

CV, cardiovascular; CVD, CV disease; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.
Adapted from Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37(29):2315–81.

The current European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias recommend non-HDL-C as a strong independent risk factor that should be considered as a risk marker, especially in subjects with high TGs [4]. The guidelines also recommend that TG levels are indicated for risk estimation because they add information on risk and that apoB can be considered as an alternative risk marker, especially in subjects with high TGs [4]. Fasting and non-fasting blood samples have been shown to give similar results for total cholesterol, LDL-C and HDL-C. However, TGs are affected by food, resulting in on average a ~0.3mmol/l (27mg/dl) higher plasma level, depending on the time frame and composition of the last meal. To characterise severe dyslipidaemia, or for follow-up of patients with hypertriglyceridaemia, fasting samples are recommended [4].