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Review article

Atherogenic markers in predicting cardiovascular risk and targeting residual cardiovascular risk

Alberico L. Catapano[a,*], Lale Tokgözoğlu[b,**], Alberto Mello e Silva[c], Eric Bruckert[d]

[a] Department of Pharmacological and Biomolecular Sciences, University of Milan, Multimedica IRCCS, Via Balzaretti, 9 20133, Milan, Italy
[b] Department of Cardiology, Hacettepe University, Ankara, Turkey
[c] Hospital Egas Moniz, Centro Hospitalar de Lisboa Ocidental, Serviço de Medicina I, Rua da Junqueira 126, 1349-019, Lisbon, Portugal
[d] Hopital Pitié Salpêtrière et Université Paris Sorbonne, 83 Boulevard de l'hôpital, 75013, Paris, France

HIGHLIGHTS

- LDL-C is the primary target in cardiovascular (CV) disease prevention.
- Non-HDL-C and apolipoprotein B (apoB) are markers of atherogenic lipoproteins.
- The associations of non-HDL-C and apoB with CV risk is conflicting.
- Statins can control LDL-C levels, but a residual risk of CV events still remains.
- Targeting other markers, including non-HDL-C and apoB, may be beneficial.

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ABSTRACT

Low-density lipoprotein (LDL) cholesterol (LDL-C) is the primary target in cardiovascular (CV) disease prevention and is commonly used in estimating CV risk; however, alternative markers may be needed when LDL-C is not an appropriate marker (e.g. in the presence of low LDL-C levels or elevated triglyceride [TG] levels). Non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apoB) are markers of atherogenic lipoproteins with evidenced associations with CV risk and are, therefore, recommended as secondary targets, appropriate for use in the presence of elevated TG levels. The reported strength of the associations of non-HDL-C and apoB in comparison to LDL-C is conflicting between studies, potentially due to discordance of the markers which can alter their predictive pattern.

Although LDL-C levels are commonly managed with statin treatment, a residual risk of CV events still remains, and an abnormal lipid profile can persist. Combination therapy to further reduce LDL-C levels can be beneficial; a statin therapy combined with other LDL-C-lowering therapy further reduced the number of CV events. In addition, targeting other markers, including non-HDL-C, apoB, total cholesterol and TGs may also be beneficial, specifically in patients with low HDL-C and elevated TG levels. More clinical evidence is required before definitive recommendations can be made; however, a statin–fenofibrate combination demonstrated favourable reductions in major CV events in these specific patients.

1. Introduction

The association between elevated levels of low-density lipoprotein (LDL) cholesterol (LDL-C) and increased risk of cardiovascular (CV) disease (CVD) is the basis for guidelines recommending LDL-C as the primary target in CVD prevention. This is supported by a large body of genetic, biochemical and epidemiological evidence demonstrating a causal role of LDL in CVD, and clinical evidence demonstrating that reduction of LDL-C is associated with a reduction in the risk of CVD [1,2]. Although there is overwhelming evidence for the causality of LDL-C, there are other potential markers that also influence CVD risk through atherosclerosis and other mechanisms [3]. Non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apoB) are recommended as secondary targets in the joint European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) 2016 guidelines, and should be considered as alternatives in risk estimations

* Corresponding author.
** Corresponding author.
E-mail addresses: alberico.catapano@unimi.it (A.L. Catapano), laletok@gmail.com (L. Tokgözoğlu).

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when LDL-C is not appropriate, for example, when triglyceride (TG) levels are high [1]. Conflicting evidence on the associations between these lipid markers and CV events raises the question of the most appropriate measure for CV risk. An overview of the clinical evidence for these associations will be discussed here.

2. Markers of atherogenic risk

2.1. Non-high-density lipoprotein cholesterol and apolipoprotein B

Non-HDL-C (total cholesterol minus HDL-C) represents a measure of the atherogenic lipoproteins very low-density lipoproteins (VLDL), VLDL remnants, intermediate-density lipoprotein, LDL and lipoprotein (a). Apolipoprotein B relates well to non-HDL-C and represents a measure of atherogenic lipoproteins VLDL, intermediate-density lipoproteins and LDL particles [1,4]. There is evidence to demonstrate that these markers of atherogenic lipoproteins are associated with CV risk; lowering non-HDL-C reduced the risk of coronary heart disease (CHD) in a meta-analysis of studies with various lipid-modifying therapies, and apoB was strongly associated with onset of ischaemic heart disease in a population-based study [5,6]. The strength of these associations in comparison with those of other lipids and lipoproteins can vary widely between reports. The AMORIS study identified apoB as an important risk factor for fatal myocardial infarction with stronger predictive power than LDL-C [7]. Similarly, Sniderman et al. (2011) [8] supported this finding in a meta-analysis of epidemiological studies, which indicated that apoB is a stronger predictor of CV risk than LDL-C, followed by non-HDL-C, with LDL-C being the least strong. These studies suggest apoB may be, therefore, a superior marker for predicting CV risk than the current guideline-recommended LDL-C. Another meta-analysis by Boekholdt et al. (2012) [9] also demonstrated associations between LDL-C, non-HDL-C and apoB with the risk of major CV events, but determined a stronger association for non-HDL-C than for LDL-C and apoB. The proportions of treatment effect that are explained by changes in lipid or apo B levels are shown in Fig. 1. The proportion of treatment effect explained by non-HDL-C was larger than by LDL-C and by apoB [9].

Conversely to studies indicating superiority of apoB or non-HDL-C for predicting CV risk, other studies have not observed any differences in the associations between LDL-C, non-HDL-C and apoB. For example, Parish et al. (2012) [3] found no difference in the strength of association with major coronary events or revascularisation between these lipoproteins, and The Emerging Risk Factors Collaboration found a similar prediction of CHD risk with non-HDL-C and apoB [10].

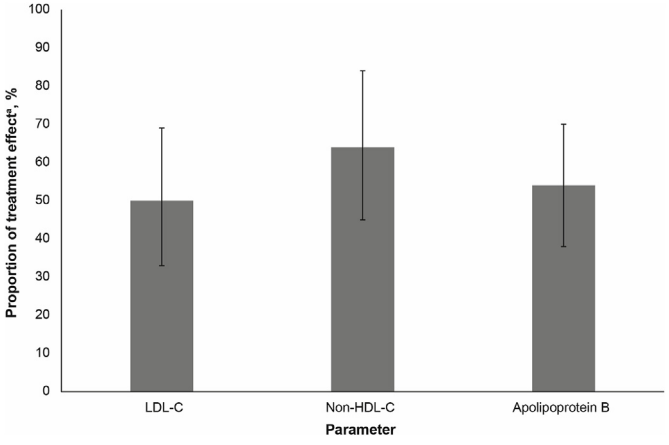

Fig. 1. Proportion of treatment effect explained by lipid or apoB levels. Adapted from Boekholdt et al. (2012) [9].
[a]Indicates the proportion of treatment effect explained by a lipid or apoB parameter.
HDL-C: non-high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Based on the evidenced association between different lipoproteins and CV events, it may be beneficial to consider markers other than LDL-C when estimating risk. The ESC/EAS 2016 guidelines recommend non-HDL-C and apoB lipid analyses should be considered in CV risk estimation, particularly in patients with high levels of TG. The advantages and disadvantages of LDL-C, non-HDL-C and apoB as predictive markers for CV risk are summarised in Table 1 [1,2].

2.2. Discordance in markers of cardiovascular risk

Discordant markers may contribute to the conflicting evidence for non-HDL-C and apoB as predictors of risk in studies performing analyses with them as independent markers. Markers LDL-C, non-HDL-C and apoB are concordant when the apoB particles contain an average amount of cholesterol, and become discordant when they contain more or less cholesterol than average. When these markers are concordant, LDL-C, non-HDL-C and apoB can predict risk equally well; whereas, when markers are discordant (e.g. metabolic syndrome or diabetes mellitus) their predictive pattern can differ [11]. When using discordance analysis, where variables were analysed by concordance or discordance, apoB was more strongly associated with CV risk than LDL-C and non-HDL-C [12].

3. Residual cardiovascular risk

The LDL-C lowering effects of statins and the substantial reduction in CV morbidity and mortality has been well documented [13–18]. Despite this, there remains a residual risk of CV events with statin treatment in clinical trials, even in patients achieving target LDL-C levels [19,20]. Combination therapy can further reduce CV risk; treatment with statin plus an additional LDL-C-lowering therapy results in a reduced number of CV events compared with statin monotherapy [21,22]. In the IMPROVE-IT trial in patients who had recently had an acute coronary syndrome (ACS), simvastatin–ezetimibe combination lowered LDL-C by 24% compared with statin monotherapy and, additionally, reduced non-HDL-C, apoB, total cholesterol and TGs to a greater extent [21]. In the FOURIER trial in patients with atherosclerotic CVD, evolocumab added to statin therapy further lowered LDL-C levels by 59% compared with statin monotherapy, non-HDL-C levels by 52% and apoB by 49% [22]. Therefore, high-risk patients may benefit by lowering lipid levels beyond current target levels through combination therapy.

Atherogenic dyslipidaemia, characterised by abnormalities in LDL, HDL-C and TGs, is very common in patients with type 2 diabetes mellitus or metabolic syndrome [23,24]. The DYSIS study indicated that these abnormalities can persist in statin-treated patients; 58.1% of patients did not achieve target LDL-C goals. Additionally, 22.7% of patients had low HDL-C levels and 47.3% of patients had elevated TG levels, rising to 24.0% and 54.3%, respectively, in those with diabetes. The number of patients with abnormal levels of atherogenic lipoproteins, despite being treated with statins, was substantial [24]. Residual abnormal levels of lipoproteins other than LDL-C could be one potential cause of residual CV risk.

The PROVE IT-TIMI 22 trial identified that in statin-treated patients after an ACS, those with lower TG levels (National Cholesterol Education Program [NCEP] cut-point of < 150 mg/dl) had fewer CHD events than patients with higher TG levels (≥ 150 mg/dl; 13.2% *vs* 17.6%, respectively). The CHD risk was lowest when both LDL-C and TG levels in statin-treated patients were low (NCEP cut-points of $<$ 70 mg/dl and < 150 mg/dl, respectively), compared with when levels were high (NCEP cut-points of ≥ 70 mg/dl and ≥ 150 mg/dl, respectively; CHD event rate 11.7% *vs* 17.9%) (Table 2). Therefore, targeting TG in addition to LDL-C in patients with a residual CV risk after an ACS may be beneficial in further reducing the risk of CVD [25].

In the ACCORD Lipid trial, no CV benefit was observed in patients

Table 1
Advantages and disadvantages of LDL-C, non-HDL-C and apoB as markers for predicting CV risk [1,2].

Marker	Advantage	Disadvantage
LDL-C	Causality for CVD proven and well-studied Primary target in guidelines	Less reliable when TGs are high
Non-HDL-C	Associated with CV risk in some studies More reliable in patients with high TGs Secondary target in most guidelines	Not evaluated as a primary target in RCTs
apoB	Associated with CV risk in some studies Reliable analysis, even with high TGs Secondary target in most guidelines	Not evaluated as a primary target in RCTs Analysis not always available

apoB: apolipoprotein B; CV: cardiovascular; CVD: cardiovascular disease; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; RCT: randomised controlled trial; TG: triglyceride.

Table 2
Risk of death, myocardial infarction and recurrent acute coronary syndrome with LDL-C and TG cut-points. Adapted from Miller et al. (2008) [25].

Rate of recurrent events, %		
Lipid cut-point	LDL-C < 70 mg/dl	LDL-C ≥ 70 mg/dl
TG < 150 mg/dl	11.7	15.0
TG ≥ 150 mg/dl	16.5	17.9

LDL-C: low-density lipoprotein cholesterol; TG: triglyceride.

with type 2 diabetes mellitus treated with a statin–fenofibrate combination compared with those treated with statin monotherapy (CV event rate 10.1% in both groups). There was, however, a reduced major CV event rate in a subgroup of patients with low HDL-C and high TG levels treated with a statin–fenofibrate combination compared with statin monotherapy (12.4% *vs* 17.3%, respectively) [26].

Currently, the ESC/EAS guidelines primarily approach lipid management by targeting LDL-C. Recommendations are to reduce LDL-C as much as possible, particularly in high-risk patients. As less extensively studied lipids, non-HDL-C and apoB are recommended as secondary targets; however, more clinical evidence is needed before recommendations can be made for targeting HDL-C or TGs [1].

4. Conclusions

The evidenced association of elevated LDL-C with increased CV risk is well documented and, consequently, LDL-C is the primary target for CVD prevention [1,2]. In addition, there is clinical evidence, although conflicting, to suggest that non-HDL-C and apoB are also strongly associated with CV risk [3,5–10]. These markers could, therefore, be considered in analyses for estimations of CV risk, especially when LDL-C is not an appropriate marker, for example in the presence of elevated TG levels [1].

Although CV risk is reduced substantially by the LDL-C lowering effects of statins, patients still have a residual CV risk [20]. Combination therapy to further reduce CV risk linked with elevated LDL-C and targeting other lipids, mainly TGs, may be beneficial for further reducing the residual risk [21,22]. TG levels are a marker of TG-rich lipoproteins and their remnants, and lower levels are often associated with lower levels of remnant lipoproteins. More clinical evidence is needed before making definitive recommendations, but the authors suggest that the current focus on TG levels should be shifted to focus on remnant lipoprotein levels and their implications for CV risk [27].

Additionally, two randomised controlled trials (REDUCE-IT) [28] [NCT01492361, https://clinicaltrials.gov] and the ongoing STRENGTH [NCT02104817, https://clinicaltrials.gov]) have been designed to evaluate the efficacy of Omega 3 fatty acids (ethyl eicosapentaenoic acid or ethyl eicosapentaenoic acid/docosahexaenoic acid) in reducing major adverse CV events in patients at high risk of CVD, when added to LDL-C-lowering therapy. As reported by the REDUCE-IT trial, among statin-treated patients with elevated TG levels, the risk of ischemic events was significantly reduced following treatment with icosapent ethyl [28].

Conflicts of interest

ALC has received grants from Pfizer, Sanofi, Regeneron, Merck, Mediolanum, non-financial support from SigmaTau, Menarini, Kowa, Recordati, Eli Lilly, personal fees from Astrazeneca, Genzyme, Bayer, SigmaTau, Menarini, Kowa, Eli Lilly, Recordati, Pfizer, Sanofi, Mediolanum, Merck, Aegerion, Amgen, outside the submitted work.

LT has received personal fees from Amgen, Sanofi, Pfizer, NovoNordisk, MSD, Actelion, Recordati, Kowa, Abbott, Novartis, Mylan, outside the submitted work.

AMS has received honoraria or consultation fees from Amgen, AstraZeneca, Jaba-Recordati, Merck, Mylan, Novartis and Tecnimede, and has participated in sponsored speaker's bureau for Amgen, Merck, Mylan and Tecnimede.

EB has received personal fees from AstraZeneca, Amgen, MSD, Sanofi and Regeneron, Unilever, Danone, Lilly, Ionis Pharmaceuticals, Akcea, Alexion Pharma, outside the submitted work.

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