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Atherosclerosis Supplements 19 (2015) 1–12

ATHEROSCLEROSIS
SUPPLEMENTS

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A review of the evidence on reducing macrovascular risk in patients with atherogenic dyslipidaemia: A report from an expert consensus meeting on the role of fenofibrate–statin combination therapy

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Abstract

A meeting of European experts in cardiovascular (CV) disease and lipids was convened in Paris, France, on 10 November 2014 to discuss lipid profile, and in particular atherogenic dyslipidaemia (AD), and associated CV risk. Key points that were raised and discussed during the meeting are summarised in this paper, which also accounts for further discussion and agreement on these points by the group of experts. Elevated levels of low-density lipoprotein cholesterol (LDL-c) are commonly associated with a greater CV risk than low LDL-c levels, and are routinely managed with statins. However, even for patients controlled on statins and achieving low LDL-c levels, abnormal lipid profiles observed in some patients (i.e. elevated triglyceride levels, with/without low levels of high-density lipoprotein cholesterol [HDL-c]) have been linked to the presence of a residual CV risk. Therefore, it is recommended that both triglyceride and HDL-c levels be measured, to allow for the overall CV residual risk to be adequately managed. Favourable safety and clinical data support the combination of statins with other lipid-lowering agents, such as fenofibrate. Patients who have elevated triglyceride levels plus low levels of HDL-c are most likely to achieve clinical benefit from fenofibrate–statin combination therapy. In these patients with AD, achieving target non-HDL-c levels should be a key focus of CV risk management, and the use of non-HDL-c was advocated to provide a better measure of CV risk than LDL-c levels.

Keywords: Atherogenic dyslipidaemia; cardiovascular risk; cholesterol; combination therapy; fenofibrate; statins; triglycerides

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Conversion factors
cholesterol mg/dL = mmol/L × 38.6
triglycerides mg/dL = mmol/L × 88.5
glucose mg/dL = mmol/L × 18

Introduction

A meeting of European experts in cardiovascular (CV) disease and lipids was convened in Paris, France, on 10 November 2014 to discuss current understanding of atherogenic dyslipidaemia (AD) and its associated macrovascular risk. The meeting was co-chaired by Alberico Catapano and Roberto Ferrari who moderated group discussions on the evidence base supporting the role of fenofibrate–statin combination therapy in reducing macrovascular risk in patients with AD, following introductory presentations by Carlos Aguiar, Michel Farnier and Alberto Zambon. This paper summarises the experts' current understanding within the context of the literature, and reviews the key points discussed both during and after the meeting.

Current understanding of atherogenic dyslipidaemia, cardiovascular risk and first-line statin therapy

Atherogenic dyslipidaemia

Atherogenic dyslipidaemia is characterised by increased levels of total triglycerides and very-low-density lipoprotein (VLDL) triglycerides, decreased levels of high-density lipoprotein cholesterol (HDL-c), as well as levels of low-density lipoprotein cholesterol (LDL-c) that are normal or moderately increased (Table 1) [1-4]. The LDL particles in AD are smaller and more dense, and have an increased atherogenic potential [5]; small, dense HDL particles also occur [6].

Prevalence of AD was reported in the Dyslipidemia International Study, which was conducted on 22 063 statin-treated outpatients (with or without diabetes) in Europe and Canada [7], and showed that elevated triglycerides and/or low HDL-c levels were persistent in these patients. AD is, however, generally under-treated and under-controlled [8]; understanding of the pathophysiology underlying AD is limited and further research is warranted.

Lipid abnormalities and associated macrovascular risk

Epidemiological data support the significant association between high levels of LDL-c and increased CV risk compared with low levels of LDL-c. Moreover, there is a high level of concordance between epidemiological, genetic and clinical-trial data sets in support of this relationship [10,11]. For example, observational epidemiology estimates derived from >25 000 individuals in prospective cohort studies showed that a one standard deviation increase in LDL-c was associated with an increased risk of myocardial infarction (MI) (odds ratio [OR]: 1.54; 95% confidence interval [CI]: 1.45, 1.63). Likewise, a Mendelian randomisation study showed that a one standard deviation increase in LDL-c conferred by genetic score increased MI risk significantly (OR: 2.13; 95% CI: 1.69, 2.69; $p = 2\times10^{-10}$) [12].

Understanding the direct effects of LDL-c levels on CV risk is simpler than comprehending those based on HDL-c levels and triglycerides. Unlike LDL, HDL is highly heterogeneous in terms of its physicochemical properties, size, shape, density, apolipoprotein composition and surface charge, which reflects the diverse functions of HDL [13]. Beyond reverse cholesterol transport, HDL subpopulations also exert antioxidant, anti-inflammatory, cytoprotective, vasodilatory, anti-infectious and immunomodulatory effects [14]; HDL particles may improve glucose metabolism [15] and play a role in the development of type 2 diabetes mellitus (T2DM) [16,17]. HDL-c levels (together with triglycerides) can help in the assessment of the residual CV risk in statin-treated patients who have low LDL-c levels, but may still be at risk for CV events due to high triglyceride and/or low HDL-c levels. Findings from two meta-analyses demonstrated that individuals on statin treatment with low levels of HDL-c (≤0.9 mmol/L) experienced a higher incidence of major CV events than those with HDL-c >1.1 mmol/L, not only in the general population but also in patients with T2DM [18,19]. Importantly, these findings emphasise the higher CV-event burden associated with low levels of HDL-c in patients with T2DM compared with the general population. Although low HDL-c is predictive of increased CV risk, the complexity of its metabolic interrelationship with additional risk factors (e.g. LDL-c and triglyceride levels) must be considered.

The prevalence of low HDL-c and high triglyceride levels in patients with proven CV disease has been evaluated in a number of studies and shows the importance of AD as a potential CV risk factor [20,21]. Furthermore, data from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction), ACCORD-Lipid (Action to Control Cardiovascular Risk in Diabetes), IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) and TNT (Treating to New Targets) studies demonstrate that higher triglyceride levels are associated with higher rates of death and major CV events [22,23]. In addition, data from these key clinical studies highlight that combinations of high levels of LDL-c plus high triglyceride levels (PROVE IT-TIMI 22) and low levels of HDL-c plus high triglyceride levels (ACCORD-Lipid) are associated with the highest risk of major CV events [23,24]. In the ACCORD-Lipid study in particular, patients with AD (defined as high levels of triglycerides [≥2.31 mmol/L] and low levels of HDL-c

Table 1.
Lipid profile in atherogenic dyslipidaemia [1-4].

Lipid parameter	Atherogenic dyslipidaemia	Thresholds[a]
LDL-c	• Normal/moderate increase in LDL-c levels • Increase in small, dense LDL particles	n/a
HDL-c	• Decrease in HDL-c levels • Increase in small, dense HDL particles	Men: <1.0 mmol/L Women: <1.3 mmol/L
Triglycerides	• Increase in total triglycerides • Increase in VLDL triglycerides	≥1.7 mmol/L

[a] According to the International Atherosclerosis Society's definition of the metabolic syndrome [9].
-c = cholesterol, HDL = high-density lipoprotein, LDL = low-density lipoprotein, VLDL = very-low-density lipoprotein.