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The metabolic and pharmacologic bases for treating atherogenic dyslipidaemia

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Dyslipoproteinaemia is a cardinal feature of the metabolic syndrome that accelerates atherosclerosis. It is characterized by high plasma concentrations of triglyceride-rich and apolipoprotein (apo) B-containing lipoproteins, with depressed high-density lipoprotein (HDL) and increased small dense low-density lipoprotein (LDL) particle concentrations. Dysregulation of lipoprotein metabolism in the metabolic syndrome may be due to a combination of overproduction of very-low density lipoprotein (VLDL) apoB, decreased catabolism of apoB-containing particles, and increased catabolism of HDL apoA-I particles. These abnormalities are due to a global metabolic effect of insulin resistance and visceral obesity. Lifestyle modifications (dietary restriction and increased exercise) and pharmacological treatments favourably alter lipoprotein transport by decreasing the hepatic secretion of VLDL-apoB and the catabolism of HDL apoA-I, as well as by increasing the clearance of LDL-apoB. The safety and tolerability of combination drug therapy based on statins is important and merits further investigation. There are several pipeline therapies for correcting

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triglyceride-rich lipoprotein and HDL metabolism. However, their clinical efficacy, safety and cost-effectiveness remain to be demonstrated.

Practice points

- Dysregulation of VLDL is integral to atherogenic dyslipidaemia, which results from hepatic insulin resistance due to ectopic fat accumulation in visceral adipose tissue and liver.
- Dysregulation of lipoprotein metabolism in these subjects is due to a combination of overproduction of VLDL-apoB, decreased catabolism of apoB-containing particles, and increased catabolism of HDL-apoA-I particles.
- LDL-cholesterol, non-HDL-cholesterol and apoB have been identified as the primary target of lipid-regulating therapy in patients at increased risk of CVD.
- Management of obesity should initially focus on lifestyle modifications including weight loss, dietary modifications and exercise. Lipid-regulating agents may be used as second-line strategy to optimize the regulation of dyslipoproteinaemia.
- Statins are recommended first-line lipid-regulating agent. The use of statin in combination with other lipid-regulating agents is considered to improve lipid treatment efficacy but safety and tolerability must be considered carefully.

Research agenda

- Continued research into the underlying mechanisms responsible for atherogenic dyslipidaemia in subjects with obesity and type 2 diabetes.
- Understanding mechanisms of action of lipid-regulating agents on TRL and HDL metabolism.
- More evidence for the use of combination therapies from cardiovascular disease outcome studies.
- Development of pipeline agents that regulate TRL and/or HDL metabolism.

Introduction

Dysregulation of lipoprotein metabolism is central to the development of atherosclerosis [1]. Prospective epidemiological studies consistently demonstrate that elevated plasma low-density lipoprotein-cholesterol (LDL-C) is associated with increased risk of cardiovascular disease (CVD) [2–5]. Although the causal role of LDL-C in the development of atherosclerosis is well established, it does not fully account for the increase in risk of CVD [6]. Residual risk may partly be due to atherogenic dyslipidaemia, which clusters with hypertension, central obesity and insulin resistance, collectively known as metabolic syndrome (MetS) [7]. We review the metabolic and pharmacologic bases for the treatment of the atherogenic lipid phenotype.

Atherogenic dyslipidaemia: biochemical features and cardiovascular risk

Definition and prevalence

Atherogenic dyslipidaemia is characterized by high plasma triglycerides, low high-density lipoprotein-cholesterol (HDL-C) and a high concentration of apolipoprotein (apo) B-containing lipoproteins, particularly elevated small, dense LDL particles [8–10]. More than 85% of Caucasian adults (age >35 yr) with a mild-to-moderate elevation in plasma triglyceride and low HDL-C phenotype have the MetS [11]. Fig. 1 compares the lipid and lipoprotein profiles between normal and MetS individuals.