High-density lipoprotein cholesterol and triglycerides in the statin era: A pending issue?☆,☆☆

HDL-Cholestérol et triglycérides à l’ère des statines : une question non résolue ?

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Received 1st December 2008; accepted 1st December 2008
Available online 23 February 2009

KEYWORDS
HDL-Cholesterol; Triglycerides; Statins; Metabolic syndrome

Statins are highly effective for lowering low-density lipoprotein (LDL) cholesterol and reaching LDL targets, but have a limited impact on triglycerides and high-density lipoprotein (HDL) cholesterol. In this issue of the journal, Laforest et al. demonstrate that high triglyceride and low HDL-cholesterol concentrations are frequent in patients treated with hypolipidaemic agents, mostly statins [1]. In this study, patients with high triglycerides and low HDL-cholesterol also had more additional risk factors, in particular diabetes and hypertension. These findings raise questions about the relevance of lipid disturbances with statin treatment in high-risk patients.

Is there any point in paying attention to hypertriglyceridemia and low HDL-cholesterol in these patients? Studies in families with premature coronary disease have indeed shown that a low HDL level was the most common abnormality and was most often associated with Hypertriglyceridemia [2]. In recent statin trials in high-risk patients, the prevalence of an HDL-cholesterol concentration less than 43 mg/dl was high, between 40% [3] and 60% [4]. Low HDL-cholesterol was predictive of major cardiovascular events. In the placebo arm of the Heart protection study (HPS), patients with HDL-cholesterol less than 35 mg/dl had a 43% higher risk than those with HDL-cholesterol greater than 43 mg/dl [4]. Treatment with simvastatin decreased this gap only moderately (33% higher risk for HDL-cholesterol less than 35 mg/dl while on statin treatment). An excess of risk remained in patients with low HDL-cholesterol receiving a high dosage of statin and in
those with a LDL-cholesterol concentration less than 70 mg/dl in the Treating to new targets (TNT) trial [3]. Epidemiological studies have reported a 20 to 30% increase in cardiovascular risk for each 10 mg/dl (0.26 mmol/l) decrease in HDL-cholesterol level [5]. Even in subjects with spontaneously very low LDL-cholesterol concentrations (< 60 mg/dl), HDL-cholesterol is an independent predictor of coronary risk, with a 10% risk increase for every 10 mg/dl decrease in HDL-cholesterol [6].

Another point to be emphasized is the growing prevalence of metabolic syndrome (MS). Hypertriglyceridemia and low HDL-cholesterol are two of the five criteria in the definition of MS [7]. In patients with MS, Hypertriglyceridemia derives from an increased production and secretion of very LDL triglycerides by the liver, which are induced by an increased flux of free fatty acids from the abdominal fat to the liver and/or a higher activity of stearoyl-coA desaturase in the liver [8]. A lower level of HDL-cholesterol in patients with MS is related mainly to hypercatabolism of HDL-apo A-1, in the liver [8]. A lower level of HDL-cholesterol in patients with MS is very often found in high-risk patients. In the TNT trial, 56% of the patients had MS and these individuals had a 44% higher risk of cardiovascular events [10]. Both Hypertriglyceridemia and low HDL-cholesterol were each associated with an increased risk. In patients with MS, the increased risk of a cardiovascular event was reduced significantly with atorvastatin 80 mg by 29% beyond that achieved with a lower dosage (atorvastatin 10 mg), and a greater risk reduction was found for each additional component of MS [10]. Unfortunately, the Euroaspiré surveys in patients with coronary artery disease have shown that the prevalence of abdominal obesity has increased steadily from 42 to 55% of the population during the past 12 years [11].

Physician are thus more and more frequently facing a problem of high triglycerides or low HDL-cholesterol in patients with vascular disease. Should the clinician ignore it or try to improve it? Brown et al. reported a meta-analysis of 23 studies evaluating the combined effects on cardiovascular prevention of simultaneous LDL-cholesterol lowering and HDL-cholesterol elevation [12]. There was a strong linear relationship between a composite lipoprotein variable (the sum of percentage HDL increase and percentage LDL decrease) and coronary stenosis progression or regression. A similar relationship was found with clinical events. So, there is a real basis for trying to increase HDL-cholesterol even after LDL-cholesterol lowering.

Lifestyle modifications remain the first mandatory recommendation [13]. The favourable effects of exercise and of smoking cessation in high-risk subjects are not disputed. Among a number of positive effects on arterial physiopathology and cardiovascular outcome, they are both associated with a moderate increase in HDL-cholesterol [13]. Exercise and diet are the cornerstone of treatment for MS [7]. When they lead to a reduction in abdominal obesity, they are associated with a reduction in Hypertriglyceridemia and an increase in HDL-cholesterol. At the moment, all of these non-pharmacological interventions are clearly the most established approaches in high-risk patients with residual perturbations of HDL-cholesterol or triglycerides under statin therapy.

Fibrates are peroxisome proliferator-activated receptor α agonists that upregulate the expression of several genes involved in the metabolism of HDL (apo A-I, All, ABC A1, SR-B1) and triglycerides (lipoprotein lipase). They increase HDL-cholesterol by 5 to 10% and decrease triglycerides by 25 to 45%. Despite this favourable metabolic profile, the results of clinical trials with fibrates have been conflicting, with a risk reduction in the Helsinki heart study [14] and the Veterans affairs high-density lipoprotein cholesterol intervention trial (VA-HIT) [15] but a non-significant effect in the recent FIELD trial [16]. The combination of fibrates with statins increases the risk of hepatic but most of all muscular toxicity. The use of gemfibrozil in combination with a statin must be avoided because of a particularly high risk of myotoxicity [13]. The effect of adding fenofibrate to statin therapy is being assessed in the Action to control cardiovascular risk in diabetes (ACCORD) trial in diabetic patients.

Nicotinic acid (niacin) is the most effective available agent for increasing HDL-cholesterol (+20%) and it also lowers triglycerides by 20%, LDL cholesterol by 15 to 20% and lipoprotein(a). These favourable metabolic effects have been associated with a reduction in coronary events and all-cause mortality in the Coronary drug project (CDP) trial [17]. Imaging studies have also reported a benefit of its combination with resins or statins on atherosclerosis burden and favourable trends in clinical events [13]. Widespread use is, however, limited by its adverse effects, especially flushing. A new formulation combining niacin with a prostaglandin-D2 receptor antagonist reduces flushing [18] and is being evaluated in the HPS2-THRIVE trial in coronary patients treated with statins.

Novel HDL-based therapies are being developed that increase HDL or promote cholesterol efflux and reverse transport. These developments could open new avenues in lipid prevention. However, circulating HDL-cholesterol levels alone represent an imperfect measure of therapeutic efficacy. Recent studies have shown that some apo A-1 and ABC A1 gene mutations did not increase cardiovascular risk despite low HDL-cholesterol [19,20]. On the other hand, increased HDL-cholesterol concentrations are not protective in some circumstances such as with estrogen therapy. The most unfortunate result in the development of new lipid-modifying treatments was the 40% increase in cardiovascular mortality in the Investigation of lipid level management to understand its impact in atherosclerotic events (ILLUMINATE) trial with torcetrapib, a potent cholesteryl ester transfer protein inhibitor, despite a 72% increase in HDL-cholesterol concentration [21]. Even if this very unfavorable outcome may have been induced partly by molecule-specific effects of torcetrapib with increases in aldosterone levels and blood pressure, an increase in the sole HDL-cholesterol concentration does not necessary mean a stimulation of the net reverse cholesterol transport, which is the central point in HDL-associated vascular protection [13]. Unfortunately, the assessment of the reverse transport is nowadays only conceivable in a research setting [22].

Statin trials have shown a benefit across the whole range of HDL-cholesterol values and up to high triglycerides values (400–500 mg/dl) [3,4]. When should the physician consider the combination of a statin with an HDL-cholesterol raising and/or a triglyceride-lowering agent? It has been proposed to consider this option in the higher-risk patient (with arterial disease or high-risk type 2 diabetes) with persistent
low HDL-cholesterol (< 35 mg/dl in men and 40 mg/dl in women) and/or high triglycerides (> 250 mg/dl) while on statins and despite good adherence to lifestyle modifications [23]. Specialist advice about lipids may be useful in these circumstances.

Statins remain a cornerstone of cardiovascular prevention. In the absence of data assessing the benefit/risk ratio of the combination of statins with other drugs, lifestyle intervention is pivotal in high-risk patients with residual low HDL-cholesterol or high triglycerides. With careful attention, some patients may benefit from such a combination. The development of new HDL-raising therapies may modify the strategy in the future.

References


