Atherosclerosis: The 21st Century Epidemic
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Lipids: HDL, LDL, Role in Primary Prevention, the Message from Trials?

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Lipid changes: What have we learned?

Blood lipids and lipoproteins are the strongest determinants of risk of cardiovascular disease [1]. Cholesterol levels are associated with ischemic heart disease in both middle and old age [2]. There are approximately log-linear associations between total and non-HDL-cholesterol levels regardless of smoking status, and at different levels of blood pressure or body-mass index (BMI). In populations with very low levels of non-HDL cholesterol like rural China before 1990 coronary heart disease was extremely rare [3]. In contrast, ischemic heart disease was extremely prevalent in countries with very high cholesterol levels like Finland in the 1970s and 1980s and since then mortality from coronary heart disease has fallen by approximately 80% as the population level of blood cholesterol has declined [4]. Recently a mutation in the gene encoding for the enzyme PCSK9 was found to be associated with 20-40% lower LDL-cholesterol levels than the population mean [5]. Since this condition is lifelong, such individuals have approximately 90% lower risk of suffering a coronary heart disease event. While such individuals have no other specific characteristics and live in an environment with usual exposure to modifiable risk factors, they can be regarded as participants in 'nature's own randomized trial' (so-called Mendelian randomization) of cholesterol lowering [6].

The epidemiological evidence for a protecting role of high blood levels of HDL-cholesterol is also impressive. The Prospective Studies Collaboration found a log-linear inverse relationship between HDL-cholesterol and mortality from coronary heart disease, regardless of presence of other risk factors [2]. People with exceptional longevity have been shown to have significantly higher blood levels of HDL-cholesterol, larger HDL, and also LDL particle sizes [7].

Randomized clinical trials have provided overwhelming and conclusive evidence that reduction in LDL-cholesterol blood levels reduce the risk of cardiovascular disease. Already in the 1960s and 1970s trials in patients with documented coronary heart disease as well as in healthy individuals with moderate hypercholesterolemia showed that lowering cholesterol with diet or drugs reduced the risk of coronary events [8-11]. The lack of significant effect on

all-cause mortality however, left the medical community mostly skeptical about the over-all benefit of such treatment. Also the favorable results of treatment with partial ileal bypass surgery to reduce the reabsorption of cholesterol and thus the plasma level of LDL-cholesterol [12] or with the new drug gemfibrozil to modify lipid composition in plasma [13] left most physicians unimpressed because of lack of impact on all-cause mortality in the trials.

It was only in 1994 that the first large-scale randomized trial provided evidence that effective lowering of LDL-cholesterol using a statin in patients with established coronary heart disease prolonged life [14]. The trial called 4S used simvastatin to lower LDL-cholesterol a mean of 35% compared to placebo and showed a relative reduction of all-cause mortality of 30% with no excess mortality from non-coronary disease. The trial was followed by a very large number of randomized studies in a variety of patient populations using several different statins at both moderate and high doses. The results of these trials have been summarized in two prospective meta-analyses, the first comprising 14 trials with over 90,000 participants [15] and the second with additional 12 trials comprising a total of 170,000 participants [16]. These analyses demonstrate that the long-term effect per 1 mmol/L (38.6 mg/dl) lowering of LDL-cholesterol is a relative risk reduction of 22% of suffering any major vascular event (myocardial infarction, stroke or coronary revascularization procedure). In trials comparing moderate and high doses of statins the improvement in risk reductions per unit reduction of LDL-cholesterol was similar to the results of trials comparing active statin treatment with placebo. There was no difference in effects of statins between trials performed in secondary or primary prevention populations. The explanation for this is most likely that statins act through retardation of the atherosclerotic process, or even in some instances stabilization or regression of atheroma plaques [17]. The development of the atherosclerotic lesions that ultimately leads to the athero-thrombotic events starts early in life in populations with relatively high blood cholesterol levels [18].

An excess number of LDL particles undergo oxidation and at hemodynamically vulnerable parts of the arterial vessels get trapped in the sub intimal space where they are taken up by monocytes that are transformed into macrophages. Ultimately these cells end up as foam cells in plaques and attract inflammatory molecules that further intensify the pathological process. The main mode of action of statins is most likely that they lead to a marked reduction in the number of LDL-particles, because of the reduced synthesis of mevalonate, the building brick of cholesterol, although several other mechanisms resulting from the reduced availability of mevalonate may contribute to the beneficial result.

In the meta-analyses the trials that included statin-naïve patients at baseline, their weighted mean LDL-cholesterol concentration was 3.70 mmol/L (143 mg/dl) which is very close to the average level found in adults in Western countries. The relative risk reduction was, however, independent of the baseline concentration of LDL-cholesterol, even at levels less than 2.0 mmol/L (77 mg/dl). This may still be exceeding the usual levels of LDL-cholesterol in populations where coronary heart disease is rare such as rural China, where mean population levels in many communities could be less than 1 mmol/L [19].

In the JUPITER study the 17,802 participants were selected, based on age (men >50 years, women >60 years), LDL-cholesterol levels less than 3.4 mmol/L (130 mg/dl) and C-reactive protein [20]. This trial was stopped before the planned duration of 60 months because the 50% reduction in LDL-cholesterol provided by rosuvastatin 20 mg daily resulted in a highly significant 44% relative risk reduction in the primary end point, a composite of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. Prior to this trial, primary prevention of cardiovascular disease with statins had been demonstrated in populations selected based on modest or mild hypercholesterolemia [21,22], with type 2 diabetes [23], or hypertension [24]. In the very large Heart Protection Study (n>20,000) that mainly comprised patients with prior cardiovascular disease, there were statistically significant benefits of statin therapy also in subgroups selected based on high risk because of diabetes, hypertension and advanced age [25].

While the beneficial effects of LDL-cholesterol reduction have been established without any doubt, the benefit of raising blood HDL-cholesterol has been far more difficult to determine, mainly because until recently there have been few methods to effectively provide such change. Non-pharmacological methods that raise HDL-cholesterol modestly are smoking cessation, physical aerobic exercise, weight loss, increased intake of food rich in n-3 polyunsaturated fatty acids and soy protein and alcohol consumption [26]. Statins may increase HDL-cholesterol modestly; fibrates and niacin are somewhat more effective. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) compared the effect of the fibrate gemfibrozil with placebo in a long-term trial [27]. In this study gemfibrozil did not change LDL-cholesterol levels but increased HDL-cholesterol levels by 6% (ref.VA-HIT). This led to a significant decrease in the primary endpoint of non-fatal acute myocardial infarction or coronary death compared to placebo. It is, however, uncertain what mechanisms were responsible for this since gemfibrozil reduces serum triglyceride levels substantially, which

might lead to an increase in LDL particle size, that make them less atherogenic [28]. Niacin is a drug developed in the 1950s and at full dose of 2 or more grams per day might increase HDL-cholesterol levels 15-30% [29]. In the Coronary Drug project niacin provided a significant reduction in the rate of myocardial infarction in patients with previous coronary heart disease, but the main mechanism behind this effect is subject to discussion [30,31]. Recently a new class of drugs has been developed that inhibit the enzyme cholesterol-ester transfer protein (CETP) that facilitates the transfer of lipids between lipoprotein particles. One of these drugs (torcetrapib) increased the plasma level of HDL-cholesterol by 80% or more and decreased LDL-cholesterol by 30% or more but a controlled clinical trial was stopped prematurely because of excess mortality and morbidity in the actively treated group [32]. This was ascribed the adverse effects that torcetrapib had on the renin-angiotensin system, leading to increase in systemic blood pressure and other adverse effect. Two other controlled trials also failed to demonstrate any beneficial developments of atherosclerosis as shown with various ultrasound techniques [33,34]. At present two other CETP-inhibitors, dalcetrapib and anacetrapib are being developed, capable of raising HDL-cholesterol levels by 30-100%, and testing has so far not unveiled any adverse effects [35,36].

HDL-particles have been shown to exert several properties that theoretically might have favorable effects on the atherosclerotic process [37]. Apart from being able to transport cholesterol from the plaque to the liver, mainly through passing cholesterol over to other lipoprotein particles such as LDL that are taken up by the LDL-receptors, the HDL particle has anti-inflammatory and anti-oxidative properties and may provide improvement in endothelial function and endothelial repair [38].

Future use of lipid-lowering

Few preventive measures have been studied as extensively as lipid-lowering drugs, in particular statins. Still, several questions remain unanswered. Since statins are among the safest classes of drugs used long-term, should we start using them more extensively and start earlier in life? While the typical recipients of statins in Western societies are middle-aged or elderly people with established atherosclerosis, we know that this condition starts in childhood and develops mostly slowly over several decades before causing symptoms. If starting statin use earlier in life, on what criteria should we select the candidates for treatment? This might be a family history, presence of other high-risk conditions, like diabetes, metabolic syndrome or frank obesity, but also lipoprotein levels or imaging techniques. Use of traditional

risk factors such as age, gender, smoking, blood pressure and cholesterol levels may be insufficient since we know that the majority of patients coming to the coronary care unit with acute myocardial infarction are neither particularly hypercholesterolemic nor do they have clusters of such risk factors [39,40]. Against a more widespread use of statins at younger ages have been the cost, the branding of healthy people as patients and the fear of adverse effects. Today, however, the cost is relatively minimal since statins have become off patent, a vast proportion of healthy people consume a large variety of medications such as vitamin pills or 'natural health products' without necessarily identifying themselves as patients. Tens of thousands of participants in double-blind placebo-controlled trials have demonstrated that adverse effects occur equally frequently in placebo groups, so there is a strong reason to suspect the many alleged adverse effects of statins as a nocebo-effect. Many reject the idea of consuming 'artificial' or 'synthetic' drugs over long periods because of fear of corrupting their body. It is less well known that statins have 'always' been around in nature. The first statin drugs were produced from fermentation broths using various soil dwelling molds. The source of lovastatin is a fermentation broth using *aspergillus terreus* [41]. A more widespread source is oyster mushrooms (*pleurotus ostreatus*) that have been part of the diet for generations in South Asia and are also increasingly being grown in sawdust cultures in kitchens in Western countries. Oyster mushrooms may contain as much as 6 mg lovastatin per gram of the fruiting bodies [42]. Even more frequently is the lovastatin-containing *Monascus purpureus* used in daily food consumption, better known as 'red yeast rice', having been in use in traditional Chinese cooking for at least 1000 years [43]. In controlled clinical trials of red yeast rice products in China, typical reductions in LDL-cholesterol was 20-30 mg/dl (0.5-0.75 mmol/L) [44].

Are there then no real risks of long-term adverse effects of statins? We know that statins might cause a dose-dependent rise in liver enzymes in the blood in 1-2% of users but serious liver damage has not been observed. The combination of statins with other drugs that are eliminated via the same metabolic pathway as statins may lead to blood concentrations of statins that may cause myopathies and rhabdomyolysis. This is particularly true for people of East Asian origin and when using high doses of certain statins, e.g. simvastatin. In the SEARCH study that compared moderate (20 mg/day) and high doses (80 mg/day) of simvastatin there were 4.2 cases of myopathy per 1000 patients treated the first year with 80 mg/day compared to only 0.2 cases per 1000 patients treated with 20 mg/day [45]. Combination of simvastatin should be avoided with drugs such as erythromycin, cyclosporin, gemfibrozil, ketokonazol, itrakonazol, HIV-protease inhibitors

and nefazodon, amiodarone and verapamil, but also other drugs used less frequently and consumption of grapefruit juice in more than small quantities should be avoided [46]. Meta-analyses of statin drugs have indicated that there is a small risk of developing diabetes and that this risk may be dose-dependent [47,48]. It is, however, uncertain whether this risk has any long-term consequences as a large proportion of participants in the trials have had metabolic syndrome with borderline serum levels of Hemoglobin A1c or serum glucose and only minimal increases in such levels might have changed the patient's status to frank diabetes.

Despite these caveats statins are today safely in daily use by hundreds of millions of people and will remain an important tool to limit the adverse consequences of adopting a diet and lifestyle that promotes atherosclerosis. Whether other modifications of blood lipids will add to the favorable effects of statins remains to be proven in the next decade.

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