The puzzle of high-density lipoprotein in cardiovascular prevention
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chapter 1

General introduction
INTRODUCTION

Despite impressive progress in the field of cardiovascular prevention during the last 3 decades, coronary artery disease (CAD) still remains the leading cause of death world-wide. The primary pathophysiological mechanism underlying CAD is atherosclerosis. Atherosclerosis is a degenerative process and as a consequence of aging everyone will eventually develop atherosclerosis. However, the rate and progression of this process depends on a combination of genetic as well as environmental factors. Important risk factors for developing atherosclerosis are gender, hypertension, smoking and diabetes (1). One of the main risk factors accelerating the atherosclerotic process is the presence of high cholesterol levels. In line, cardiovascular risk estimation engines, such as the Framingham Risk Score and the PROCAM risk score, all include measurements of cholesterol levels (2). A drawback of measuring cholesterol levels is that their predictive value is restricted to the population level, whereas their discriminative value for an individual is rather poor. The latter is emphasized by the fact that the majority of cardiovascular events occurs in people with normal cholesterol levels and/or low risk estimates (3). In view of these considerations, intensive efforts are being conducted to further improve the accuracy of risk estimation.

For this purpose, low-density lipoprotein (LDL) cholesterol is regarded as the most atherogenic fraction in cholesterol measurements and is traditionally used as the cornerstone in lipid lowering therapy. More recently, it has been suggested that various subclasses within the atherogenic LDL cholesterol fraction may be differently associated with CAD risk. Particularly, the small dense LDL particles are thought to be extremely atherogenic as compared to the larger LDL particles (4). In this context individuals with similar LDL cholesterol levels may have higher or lower numbers of atherogenic small LDL particles and, as a result, may differ in terms of absolute CAD risk.

This heterogeneity in terms of the cholesterol content per particle is not sufficiently reflected by measuring the cholesterol levels in plasma. This observation has led to the concept that risk estimates may be improved by directly measuring the different particles or indirectly by measuring the apolipoproteins of the particles, as a reflection of the atherogenecity of the particles. Refining current risk estimates with this information may more accurately identify individuals at high risk of cardiovascular events and may simultaneously reduce the number of ‘undertreated’ subjects. This might ultimately add to an optimal treatment benefit from lipid lowering therapy.

After having identified who is at increased risk for developing a cardiovascular event, effective treatment of the lipid abnormality is the next step. Thus far, cardiovascular therapy has mainly focused on LDL cholesterol. Despite the reduction of LDL cholesterol to treatment goals, only a 20-30% overall reduction in the number of cardiovascular events has been achieved in random-
ized clinical trials (5). These findings have led to the search for alternative treatment options in lipid therapy.

From epidemiological studies it is common knowledge that there is a strong and inverse relationship between the levels of high density lipoprotein (HDL) and the risk of CAD(6). Studies in families with premature coronary disease have shown that a low HDL level was the most common abnormality (7) and epidemiological studies have reported a 20 to 30% increase in cardiovascular risk for each 0.26 mmol/l decrease in HDL cholesterol level (8). Even in subjects with spontaneously very low LDL cholesterol concentrations (< 1.55 mmol/l), HDL cholesterol is an independent predictor of coronary risk, with a 10% risk increase for every 0.26 mmol/l decrease in HDL cholesterol (9). These observations have contributed to the fact that treating low HDL may be a strategy in the fight against atherosclerosis even after LDL cholesterol lowering. In contrast to LDL, however, HDL is a complex molecule which is believed to have different anti-atherogenic functions. This finding has delayed the development of effective therapeutic interventions to increase low HDL cholesterol levels.

Traditionally, the anti-atherogenic effects of HDL were confined to its role in the reverse cholesterol transport (RCT) pathway. Reverse cholesterol transport is a term used to describe the efflux of excess cellular cholesterol from peripheral tissues and its return to the liver for excretion in the bile and ultimately in the feces (10). In this pathway, cholesterol is effluxed

![Scheme of the RCT pathway, adapted from Ashen NEJM 2005](image)
from arterial macrophages to HDL through the action of membrane transporters such as ATP binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1). Following its efflux to the HDL particle, cholesterol may then be esterified by the enzyme lecithin:cholesterol acyltranferase (LCAT), and is ultimately transported by HDL to the liver, either directly via the scavenger receptor BI (SR-BI) or following its transfer to apolipoprotein B-containing lipoproteins by the cholesteryl ester transfer protein (CETP). The final step is the excretion of cholesterol in the feces.

Promotion of RCT could therefore be an effective strategy for reducing risk associated with atherosclerotic vascular disease. Interfering in the different molecular mechanisms regulating RCT, results in changes in HDL cholesterol levels, and consequently in promotion of RCT. These developments could open new avenues in lipid prevention. In this thesis we mainly focus on the role of CETP and its relation to treatment of HDL levels.

OUTLINE OF THE THESIS

This thesis consists of two parts. Part one focuses on CAD risk assessment by refining current lipid tests. In this part we describe alternative lipoprotein parameters and their relation to CAD risk. In the second part we switch to the pathophysiology and treatment of low HDL cholesterol levels, with special emphasis on the role of CETP in HDL metabolism.

**Part I: refining current cholesterol lipid tests for assessment of future CAD risk.**

In chapter 2 and 3 we assess the independent relationship of LDL and HDL particle number as measured by nuclear magnetic resonance spectroscopy with risk of future CAD. In chapter 2 we focus on the pro-atherogenic LDL fractions. This chapter assesses whether measuring LDL particle number and LDL particle size have the capacity to improve the prediction of future CAD compared to measuring levels of traditional LDL cholesterol.

In chapter 3 we switch to the anti-atherogenic HDL fraction. This chapter addresses the independent relationship of HDL particle concentration and size to the risk of future CAD. In chapter 4, we evaluated whether the composite parameter representing both the pro-atherogenic and anti-atherogenic lipoprotein fraction, i.e. the ratio of apolipoprotein B to A-I (apolipoprotein B/A-I ratio) adds to the accuracy of CAD risk assessments in the general population.

**Part II: Impact of low HDL cholesterol and CETP on reverse cholesterol transport and coronary artery disease.**

Traditionally, HDL cholesterol levels were used as an ‘indirect’ measure for the reverse cholesterol transport pathway. In chapter 5 we evaluated the relation between HDL cholesterol and fecal sterol excretion in patients with low HDL cholesterol levels due to a genetic defect. The
protein CETP plays a key role in lipid metabolism and in reverse cholesterol transport by transferring triglycerides and cholesterol between lipoproteins, leading to lower HDL cholesterol levels. Chapter 6 evaluates whether the levels of CETP affects the postprandial changes in HDL cholesterol levels. In chapter 7 we present the results of a large case control study nested in a prospective population study. This study assesses the relation between a common CETP promoter polymorphism, which is associated with low CETP plasma levels and higher HDL cholesterol levels, and risk of CAD.

Chapter 8 provides a review of CETP metabolism and CETP inhibitors. In chapter 9 we focus on mechanisms by which inhibition of CETP might affect the process of atherosclerosis. Furthermore, we discuss the effects of CETP inhibition on fecal sterol excretion. In chapter 10 we describe the effects of CETP inhibition in subjects with isolated low HDL cholesterol levels. A summary of these studies is provided in chapter 11 as well as a perspective on the future of risk assessments and the role of CETP inhibition as a therapeutic target.
REFERENCES
