Improving cardiovascular disease prevention : from risk assessment to novel therapy
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Chapter 1

General introduction & Outline of the thesis

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GENERAL INTRODUCTION

Coronary artery disease (CAD) is the worldwide leading cause of mortality and morbidity. In 2001, the worldwide number of deaths from CAD was around 7.1 million, comprising 12.2% of the 56.2 million people who died in this year (1). In the fight against this burden of disease, several prevention strategies have been developed, which include treatment with aspirin, antihypertensive agents and HMG-CoA reductase inhibitors (statins). Despite the clinical benefit of this approach (2-4), a considerable level of CAD risk remains in patients subjected to these prevention strategies. For example, in a recent large clinical trial that compared CAD risk reducing ability of high-dose versus low-dose statin therapy, risk of recurrent CAD in the intensive treatment arm was still 20% (5). Of note, almost 80% of these patients received aspirin therapy, had normal levels of systolic and diastolic blood pressure, and were adequately treated according to currently recommended target values of low-density lipoprotein (LDL) cholesterol. These observations, as well as the worldwide rising prevalence of major CAD risk factors such as obesity and diabetes mellitus, are reason for negativism regarding CAD prevalence in the future. Indeed, recent projections for 2030 clearly demonstrate that, despite the continuous spread of HIV/AIDS in many regions, CAD is likely to remain the leading cause of death by that year (1, 6).

In view of the above mentioned considerations, intensive efforts are being conducted to further improve efficacy of prevention strategies. Given the prominent role in the process of atherosclerosis played by lipoproteins, as well as the clear clinical benefit of statin therapy, evaluation and improvement of lipoprotein management is at the center of these efforts. First of all, lipoprotein-related CAD risk assessment is subject to intense evaluation, since a more precise identification of high-risk individuals leads to a better detection of those who will have most benefit from statin therapy. This might ultimately add to clinical benefit of such therapy. A second point of attention pertains to the procedure of statin treatment monitoring, since a better detection of patients who will have benefit from more intensive therapy might also increase treatment efficacy. Third, there is an intensive search for alternative lipoprotein treatment targets to further reduce risk of CAD. In view of this, most attention is being paid to the high-density lipoprotein (HDL). This thesis will address all of these points to some extent. In part I, focus will be on CAD risk assessment (Chapters 2-4) and monitoring of statin therapy (Chapters 5 and 6). In view of its emphasis on development of novel therapeutic strategies, part II describes several aspects of the cholesteryl ester transfer protein (CETP), which is an enzyme with a central role in HDL metabolism (Chapter 7-10). Pharmacological inhibition of this enzyme results in increase of the anti-atherogenic lipid fraction (HDL cholesterol), which is supposed to reduce risk of CAD.
OUTLINE OF THE THESIS

Part I – Risk assessment and treatment
Accuracy of CAD risk management programs relies on a precise identification of individuals who will have most benefit from preventive therapy. In other words, it is essential to discriminate individuals who are likely to develop CAD from those who are not. To this end, several risk calculators have been developed (7, 8), which take into account the presence of major CAD risk factors. Such calculators generally include measurements of LDL cholesterol and HDL cholesterol to represent lipoprotein-related risk, but recent reports suggest that other lipoprotein parameters might be more suitable. In chapter 2, we evaluate whether measurements of LDL particle size and/or LDL particle number might provide better insights into lipoprotein-related CAD risk than levels of LDL cholesterol do. The scientific rationale for this study question is provided by the concept that smaller LDL particles exhibit a higher atherogenic potency than larger particles do. As such, these alternative parameters are hypothesized to have the potential to improve CAD risk assessment, since they might represent risk information that is incompletely captured by measurements of LDL cholesterol per se. In chapter 3, focus is shifted towards the anti-atherogenic lipoprotein fraction. This chapter provides a detailed evaluation of plasma levels of HDL cholesterol and its major apolipoprotein (apolipoprotein A-I) in relation to risk of CAD. The main objective of this study was to determine whether these parameters are still negatively related to CAD risk at very high levels. This information is relevant to considerations as to which of these two parameters is most suitable for CAD risk assessment. Chapter 4 addresses the question whether a composite parameter, including both the pro-atherogenic and the anti-atherogenic lipoprotein fraction, adds to accuracy of CAD risk assessment in the general population. This parameter, i.e. the ratio of apolipoprotein B to A-I (apolipoprotein B/A-I), has frequently been hypothesized to be the best variable to reflect lipoprotein-related risk, but studies reporting direct comparisons with standard lipoprotein parameters are lacking. The emphasis put on this composite parameter finds its origin in the fact that, in contrast to LDL cholesterol, apolipoprotein B represents all atherogenic lipoproteins, including VLDL, LDL, IDL and lp(a) (9). In addition, the fixed apolipoprotein B:lipoprotein ratio of 1:1 results in the advantage of apolipoprotein B to be more sensitive to changes in lipoprotein size and number, which are considered to independently affect CAD risk. When it comes to the denominator, cumulating evidence demonstrates that, in contrast to the HDL cholesterol content, apolipoprotein A-I is the mediator of the anti-atherogenic potency associated with this lipoprotein (9).

A next step in the process to improve CAD risk management programs is a critical evaluation of algorithms for the monitoring of statin treatment. In currently available guidelines (10), treatment effect is recommended to be monitored by means of plasma LDL cholesterol levels, with the ultimate goal to reach specific target values for this parameter. However, several lipoprotein parameters have been put forward as more appropriate treatment targets, since these parameters are hypothesized to better identify patients who are still at increased risk despite
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treatment. These alternative parameters include apolipoprotein B, non-HDL cholesterol and apolipoprotein B/A-I. Non-HDL cholesterol is calculated as the difference between total cholesterol and HDL cholesterol, and is a quantification of cholesterol present in all lipoproteins except HDL. Studies that address the question whether these alternative parameters are indeed better risk indicators in patients receiving statin therapy are scarce. Therefore, we performed a post-hoc analysis in two large prospective studies to address this study question, results of which are presented in chapter 5. Since such alternative parameters cannot be routinely used without definition of exact target values, a second post-hoc analysis was performed to calculate such values (chapter 6).

Part II – Novel Therapy

Although existing clinical guidelines should be improved where possible, most additional CAD risk reduction might be expected to come from targeting novel risk factors. In view of this, several non-lipoprotein risk factors, in particular C-reactive protein, are subject to intensive research (11). When it comes to lipoprotein metabolism, most attention is currently being paid to targeting the HDL particle. The basis for this approach is provided by numerous epidemiological studies showing an independent inverse relationship between levels of HDL cholesterol and risk of future CAD. In the second part of this thesis, we address several issues surrounding this approach. First of all, we focus on potential mechanisms by which HDL metabolism could be affected. To this purpose, chapter 7 provides a review of genetic disorders that give rise to changes of plasma HDL cholesterol concentration. In an attempt to identify future targets for therapy, this review evaluates the consequences for atherosclerosis associated with the presence of these disorders. At the time of preparation of this thesis, most scientific progress had been made with inhibition of the cholesteryl ester transfer protein (CETP). This protein exerts its function at a central point in HDL metabolism. It facilitates the energy neutral transport of triglycerides from apolipoprotein B-containing lipoproteins to HDL, in exchange for cholesteryl esters. Pharmacological inhibition of CETP results in entrapment of cholesteryl esters within the HDL particle, leading to increased plasma HDL cholesterol levels. To better study the effects of this approach, we set out to identify novel CETP gene defects in The Netherlands. To this purpose, we screened Dutch patients with familial hyperalphalipoproteinemia and selected those subjects with low CETP activity. Resulting data and a close exploration of one family with genetic CETP deficiency are described in chapter 8. Although HDL cholesterol levels were strongly increased in the CETP deficient individuals, the number of subjects was too low to draw any conclusion with respect to consequences for CAD risk. To nevertheless address this study question, we investigated the relationship between a common CETP polymorphism and risk of future CAD in a large study population (Chapter 9). The final chapter, chapter 10, provides a review of mechanisms by which inhibition of CETP might modulate the process of atherosclerosis. This chapter ends with some concluding remarks surrounding the ultimate question whether this novel approach will indeed exert its anticipated action, i.e. reduction of CAD risk.
REFERENCES
