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GENERAL INTRODUCTION

Coronary artery disease (CAD) continues to be the leading cause of morbidity and mortality among adults in the developed world.[1] Atherosclerosis, the underlying process, is affected by both genetic and lifestyle factors.[2] Independent risk factors include age, gender, hypertension, smoking, diabetes, family history of premature CAD, and elevated low-density lipoprotein cholesterol (LDL-c) levels.[3;4] In addition, many prospective epidemiologic studies have indicated that low high-density lipoprotein cholesterol (HDL-c) is a significant independent risk factor for CAD[5-8]. Since effective therapeutic lowering of LDL-c has been achieved through the use of statins and fibrates,[7;9-13] increasing HDL-c has now become a main target for the pharmaceutical industry.[13]

Chapter 1 gives an introduction on HDL metabolism and the different therapeutic strategies to raise HDL-c. In this quest for novel drugs, cholesteryl ester transfer protein (CETP) represents an important target since this protein plays a key role in HDL metabolism.[15] The latter is highlighted by the discovery that genetic CETP deficiency is a main cause of high HDL-c in Asian populations.[16] However, studying the relationship between decreased CETP function and the risk of CAD it is not clear what role CETP plays in human atherogenesis.[16-19] In the Regression Growth Evaluation Statin Study (REGRESS) in which males with proven CAD were investigated, a common CETP gene polymorphism was shown to be associated with the progression of coronary atherosclerosis.[20] In addition, a pharmacogenetic interaction between genotype and the response to cholesterol-lowering therapy (pravastatin) was identified. Further studies, described in **chapter 2 and 3**, however, show that a single CETP gene marker, is insufficient to predict response to lipid-lowering drugs, and cardiovascular endpoints in both treated and untreated individuals. Specifically, chapter 2 describes this in the Cholesterol and Recurrent Events (CARE) study while chapter 3 summarizes all currently available data in a meta-analysis.

Nevertheless, the important role of CETP in HDL metabolism and its association with lipids, lipoproteins and atherosclerosis is highlighted in **chapter 4, 5 and 6**. Chapter 4 describes the effect of CETP concentration on lipids, lipoproteins, coronary atherosclerosis, and pravastatin treatment in men with established CAD. Chapter 5 describes the effect of CETP concentration on lipids, lipoproteins, intima media thickness and Atorvastatin or Simvastatin treatment in patients with Familial Hypercholesterolemia (Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study). In addition, CETP and its association with coronary atherosclerosis was studied in patients with non-insulin dependent diabetes mellitus (Diabetes Atherosclerosis Intervention Study (DAIS)) who were treated with placebo or a fibrate (Chapter 6).

Despite the lack of insight when it comes to human CETP function, the inverse association between CETP activity and HDL-c levels suggests that CETP inhibition is warranted. It will no doubt provide crucial information on the exact role of this protein in atherogenesis. The first data of CETP inhibition in humans are described in **chapter 7**. Finally, **chapter 8** reviews the currently available information on CETP inhibition in both animals and humans.

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