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GENERAL DISCUSSION

CETP, the focus of this thesis, has been implicated in atherosclerosis but the mechanisms that underlie this relation have remained a mystery since the CETP gene was cloned. The availability of informative CETP gene polymorphisms and measurements of CETP activity and CETP concentration in plasma have been useful tools to investigate the associations between gene, protein, biological effects on lipid, and (coronary) atherosclerosis.

The initial results of the studies described in this thesis suggest that the TaqIB CETP gene polymorphism cannot predict clinical outcome of a complex chronic disease such as atherosclerosis. Compilation of most of the published TaqIB data in our meta-analyses has given us better insight. There exists a significant association between this polymorphism and CAD, the fully adjusted risk of CAD was 20% lower in B2B2 individuals, than in B1B1 individuals, and it was shown to be largely mediated by HDL cholesterol levels. In addition, this association appears to only exist in patients without prevalent CAD.

In patients of the REGRESS, ASAP and DAIS, we found that increasing CETP concentrations were associated with an atherogenic lipid profile and surrogate endpoints for CAD. In addition, CETP concentration was also shown to affect the response to therapy in terms of lipid-lowering. The combined data of the above three studies are discussed below.
At baseline, diffuse atherosclerosis, as assessed by mean luminal diameter, was more pronounced in type 2 diabetic patients with median or high CETP concentrations. This relationship was not seen in both men with proven CAD and FH patients at baseline.
After two years treatments with placebo, men with proven CAD (REGRESS) and high baseline CETP levels had a three-fold greater progression of coronary atherosclerosis than men with CAD but low CETP levels. After more than 3 years placebo treatment, this was surprisingly not found in patients with type 2 diabetes. Apparently, treatment with placebo did not induce a different angiographic response in these diabetic patients with high and low levels of CETP concentration. This is not unexpected, considering that it took almost 57 years (mean age of the study population) to create the different effects on baseline. Unfortunately, we have no CETP concentration data on placebo-treated patients with FH.
Regarding CETP concentration and the response to various lipid-lowering strategies, we observed some interesting differences between the REGRESS, the DAIS and the ASAP studies. In the REGRESS, the pravastatin-induced LDL cholesterol lowering and triglycerides lowering was more pronounced in patients with high CETP levels compared to patients with low CETP levels. In the ASAP study, two statins were also shown to better reduce LDL cholesterol and triglyceride levels in those patients with high CETP levels. However, in FH patients with high CETP levels, this was

not sufficient to fully correct the atherogenic lipid profile. This in turn resulted in a positive relation between baseline CETP levels and intima-media thickness after two years treatment. The difference of statin treatment on angiographic response in both studies could be explained by the different patient populations. FH patients have much higher LDL cholesterol levels (8.1 mmol/l) compared to men with CAD in the REGRESS (4.3 mmol/l) and this difference becomes even more pronounced when comparing both patient populations with high CETP levels (8.9 mmol/l and 4.6 mmol/l, respectively). In addition, only 25% of the FH patients had a history of CAD.
Interactions between CETP concentration and statin therapy in men with CAD and FH patients proved to be very different from CETP concentration and fenofibrate therapy (a primarily triglyceride-reducing drug).in diabetic patients. Fenofibrate reduced LDL cholesterol levels most efficiently in diabetic patients with low CETP levels, an effect not seen in diabetic patients with high CETP levels. The effect of fenofibrate on reducing triglyceride levels was independent of CETP concentration at baseline, which is also different than seen with statin treatment. These results imply that high CETP concentration is clearly detrimental in these patient cohorts and that this determines, in part, the response to lipid lowering. In this respect, CETP measurements prior to starting medication appear warranted but these results will first need confirmation. Especially since the effect of on surrogate endpoints were similar in both FH and diabetic patients. Both resulted in more progression of atherosclerosis in patients with high CETP levels. Overall, the relationship between CETP concentration, lipids, lipoproteins and surrogate endpoints of coronary artery disease as described in this thesis suggest that CETP is not a cause of atherosclerosis, but a modulator of atherosclerosis. Nonetheless, plasma CETP concentration appears to determine, to a certain extent, the efficacy of statins as well as fenofibrate to reduce TC and LDL cholesterol levels as clearly shown in the ASAP and DAIS trials.

As of yet, little is known about CETP inhibition in man. Speculating as to which patients would benefit most from CETP inhibition, we would opt for hypercholesterolemia in Westernised countries, where high-fat and cholesterol-rich diets increase plasma LDL cholesterol levels and down-regulate hepatic LDL receptors. In terms of the reverse cholesterol transport, CETP inhibition would here force delivery of cholesterol through HDL to the liver for subsequent secretion into the bile. In the presence of fully functional HDL cholesterol uptake mechanisms this may be more desirable than uploading atherogenic LDL particles with cholesterol esters from HDL. However, it remains to be elucidated how the uptake of HDL-associated lipids is controlled in humans. This is of utmost importance when considering that CETP inhibition will result in the accumulation of large cholesteryl ester-enriched HDL particles. Nonetheless, HDL s role in human metabolism exceeds that of mediating reverse cholesterol trans-

port. HDL also influences endothelial function and exerts anti-oxidative, anti-thrombotic and anti-inflammatory effects. At present, it is unclear which of these functions contributes most to the anti-atherogenicity of HDL.

Although it is clear that CETP plays a key role in human lipid metabolism, additional research is needed to establish its complex function and action between atheroprotective lipoproteins, HDL, and atherogenic lipoproteins such as LDL. To date, it is premature to predict the effects of therapeutic CETP inhibition in humans. Its success in clinical practice will largely depend on successful co-application with evidence-based LDL cholesterol lowering and triglyceride-lowering therapy.

Nonetheless, if a CETP inhibition-related increase in HDL cholesterol proves to mediate general vascular protection, than the combination of statins and CETP inhibition will bring us a new era of cardiovascular prevention! **A cause worthwhile.**