Modulation of HDL metabolism : studies in APOE*3-Leiden.CETP mice

Haan, W. de

Chapter 1

GENERAL INTRODUCTION

Contents General Introduction

1. Lipids and lipoprotein metabolism

Triglycerides (TG) and cholesterol are the most common dietary lipids. TG serve as an important energy source for muscle tissue and can be stored in adipose tissue. Cholesterol is an important component of the cell membrane and the precursor of vitamin D, bile acids and steroid hormones. Since TG and cholesterol are hydrophobic molecules, they are transported in the blood in specialized particles called lipoproteins. Lipoproteins consist of a hydrophobic core containing cholesteryl esters (CE) and TG, which is surrounded by a polar surface of phospholipids, unesterified cholesterol and apolipoproteins. Apolipoproteins stabilize the lipid particle. In addition, they regulate the transport and redistribution of lipids by modulation of enzyme activities in plasma and by serving as ligands for cell surface receptors. Lipoproteins are divided in five main classes according to their density, namely (in order with increasing density): chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high density lipoproteins (HDL).[1,2] A schematic representation of lipoprotein metabolism is depicted in Figure 1, and explained in sections 1.1-1.3.

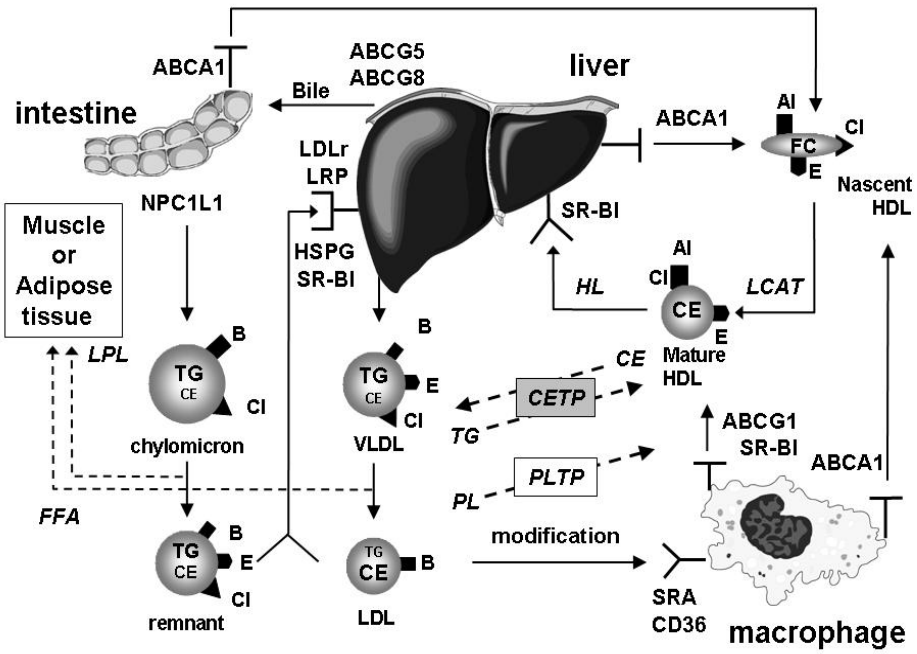

Figure 1. Schematic overview of lipoprotein metabolism. See text for explanation.

1.1 Chylomicrons

TG are the major dietary lipids, and other dietary lipids include phospholipids and cholesterol. In the intestine, lipids are lipolyzed, the lipolysis products are taken up by the enterocyte, and lipids are re-synthesized.[3-6] Enterocytes synthesize apoB48 which is lipidated in the endoplasmatic reticulum (ER) by the microsomal TG transfer protein (MTP), resulting in the formation of a small apoB48 containing particle which fuses with large apoB48-free lipid droplets to form a prechylomicron which moves to the Golgi, and is subsequently excreted via exocytosis.[3,5] The chylomicron which than contains apoB48, apoAI and apoAIV enters the lymph and subsequently the blood where chylomicrons acquire exchangeable apolipoproteins apoCI, apoCII, apoCIII and apoE whereas apoAI and apoAIV can dissociate from the particle and stay in the plasma in a free form or become associated with HDL.[5,7] Chylomicrons can exchange lipids with other lipoproteins. TG and CE are exchanged via the cholesteryl ester transfer protein (CETP), phospholipids via the phospholipid transfer protein (PLTP) and cholesterol via passive diffusion.[8,9,10,11] Chylomicrons transport dietary TG and cholesterol to various parts of the body where TG are hydrolyzed by lipoprotein lipase (LPL), an enzyme attached to the endothelium. Since LPL expression is highest on adipose tissue in the postprandial state, fatty acids (FA) released by LPL are predominantly taken up by adipose tissue, where they are stored as TG, and the remainder is taken up by muscle (skeletal muscle and heart) for use as energy source.[12,13] Chylomicron remnants which are relatively rich in cholesterol and apoE can then be taken up by the liver mainly via the apoE-recognizing receptors LDL receptor (LDLr) and LDLr-related protein (LRP). In addition, uptake can occur via interaction of apoE with cell surface-bound heparin sulfate proteoglycans (HSPG) or scavenger receptor class B type I (SR-BI).[14-18] During fasting, the intestine can produce smaller, less TG-rich, VLDL particles via a similar pathway.[5,6]

1.2 VLDL and LDL

The liver thus takes up chylomicron remnants, but can also synthesize new lipids as the liver contains several lipogenic enzymes including FA synthase (FAS) and stearoyl CoA desaturase (SCD1) for TG synthesis and HMG-CoA reductase for cholesterol synthesis. Hepatic lipids can be stored as TG and CE or can be excreted as VLDL particles. Assembly of VLDL involves a similar pathway as chylomicron synthesis including the transfer of lipids to apoB-100 (or, in some animal species including mice also apoB-48) by MTP and subsequent fusion with protein-free lipid droplets formed in the ER to form mature VLDL which is secreted into the circulation and then is enriched with apoCI, apoCII, apoCIII and apoE.[17,19,20] Similarly to chylomicrons, VLDL can exchange TG, CE and phospholipids via CETP and PLTP, and cholesterol via

passive diffusion.[8,9,10,11] VLDL particles undergo similar LPL-mediated degradation as chylomicrons, resulting in the uptake of liberated FA by tissues. In contrast to chylomicrons which are synthesized in the postprandial state, VLDL ensures a supply of FA as energy source for muscle tissue in the fasted state as LPL is highest on muscle tissue during fasting.[12,13] During lipolysis, VLDL becomes depleted of TG leading to conversion of VLDL via IDL to LDL and eventually to small dense LDL (sdLDL).[2,17] Just like chylomicron remnants, VLDL remnants are taken up mainly via apoE by the LDLr and LRP, with additional roles for HSPG and SR-BI.[1,2,16-18,21,22] The lipolytic end product LDL is virtually depleted of TG, has lost most of its apolipoproteins except for apoB-100 and is taken up mainly via apoB-100 by the LDLr in the liver and by tissues involved in hormone synthesis such as the adrenals and gonads for cholesterol supply.

1.3 HDL

In contrast to apoB-containing lipoproteins, HDL is generally believed to be anti-atherogenic, mainly because of its involvement in the reverse cholesterol transport (RCT). This process describes the transport of cholesterol from the periphery back to the liver, after which cholesterol is secreted via the bile into the feces. The liver and intestine both synthesize the major HDL apolipoprotein, apoAI, and release it into the circulation. Subsequently, apoAI is lipidated via the ATP binding cassette transporter A1 (ABCA1), which is also mainly expressed in the liver and in the intestine. This is a crucial step in HDL formation as subjects with ABCA1 gene mutations as well as mice lacking ABCA1 have very low HDL levels.[23-26] During this process nascent discoidal HDL (HDL-3) is formed, a small lipoprotein particle mainly consisting of apoAI and phospholipids. While the liver and intestine are essential for the initial lipidation of apoAI, nascent HDL can take up additional cholesterol and other lipids from the periphery via ABCAI or from other lipoproteins via PLTP.[8,9] The acquired cholesterol is esterified by lecitin:cholesterol acyltransferase (LCAT), allowing the resulting CE to accumulate in the core. Esterification of cholesterol by LCAT is also essential in HDL metabolism, as patients or mice lacking LCAT have low HDL levels.[27,28] Following cholesterol esterifcation by LCAT, HDL becomes a spherical HDL-2 particle which contains not only apoAI but can also acquire apoAII, apoAIV, apoAV, apoCI, apoCII, apoCIII and apoE. It has been suggested that more cholesterol from the periphery, including from macrophages in the vessel wall can be taken up in the mature particle via ABCG1.[29] Cholesteryl esters can be transferred from HDL to TG-rich lipoprotein particles by CETP,[10,11] or selectively taken up by the liver via SR-BI.[30,31] TG and phospholipids in HDL can be lipolyzed by hepatic lipase (HL) and endothelial lipase (EL).[32-34] Once taken up by the liver, HDL-derived cholesterol can be stored, used for the assembly of new lipoproteins, or

converted into bile acids (initiated by Cyp7A1 or Cyp27A1) or neutral sterols. In the liver, ABCG5 and ABCG8 are involved in secretion of sterols into the bile, after which sterols enter the intestine and are reabsorbed (so-called enterohepatic circulation) or excreted into the feces.[33,35-38] In addition to its role in reverse cholesterol transport, HDL has anti-oxidative, anti-inflammatory and anti-thrombotic properties.

2. Atherosclerosis

2.1 Dyslipidemia

The apoB-containing lipoproteins (*i.e.* chylomicrons, VLDL, LDL) are considered to be atherogenic since these particles can enter the arterial wall, become modified by *e.g.* oxidation and aggregation, after which they can be taken up by arterial macrophages that subsequently turn into foam cells and initiate the atherosclerotic process (see section 2).[1,2,39,40]
HDL is protective in atherosclerosis because of its role in RCT as described above. In addition HDL also has antioxidative, anti-inflammatory and anti-thrombotic properties. HDL inhibits the oxidation of LDL by transition metal ions and 12/15-lipooxygenase-mediated formation of lipid hydroperoxides. HDL can scavenge oxygen-derived free radicals and carries antioxidative proteins including paraoxonase, platelet-activation factor acetylhydrolase (PAF-AH) and glutathione peroxidase. In addition, apoAI may also have anti-oxidative functions. HDL is anti-inflammatory as it can repress induction of cell adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which reduces leukocyte attachment to the vessel wall. Other anti-inflammatory properties probably also result from its ability to remove cholesterol and oxysterols from the vessel wall and because of its anti-oxidative actions.[35,41,42] HDL improves vasorelaxation via stimulation of nitric oxide (NO) and prostacyclin synthesis which are both stimulators of vasorelaxation. Its stimulatory effects on NO and the ability of HDL to inhibit tissue factors render HDL anti-thrombotic as well.[41,42]
Dyslipidemia as characterized by high plasma levels of cholesterol and TG in VLDL and LDL particles and low plasma levels of HDL-C, is thus an important risk factor for the development of atherosclerosis. Dyslidemia can be caused by genetic disorders (*i.e.* primary dyslipidemia). Impaired lipoprotein clearance by defects in the LDLr or genes that interact with the LDLr, such as apoE and apoB, results in familial hypercholesterolemia (FH). Defects in LPL or genes interacting with LPL, for example deficiency of apoCII, the cofactor for LPL, are main causes of familial hypertriglyceridemia. Hypoalphalipoproteinemia (low HDL) can be caused by mutations in apoAI, ABCA1 and LCAT. Secondary dyslipidemias are not caused by a monogenetic disorder but by other

diseases, life style or medication. These include obesity, diabetes, hypothyroidism, exercise, diets rich in saturated fat, glucocorticoids, retinoic acid derivates, and HIV protease inhibitors.[43,44] Dyslipidemia is a major risk factor for coronary heart disease (CHD) (see section 2.2). In addition to dyslipidema, other lipid-unrelated factors can also increase CHD risk. These lipid unrelated risk factors for CHD include homocysteinemia, hypertension and infection.[45]

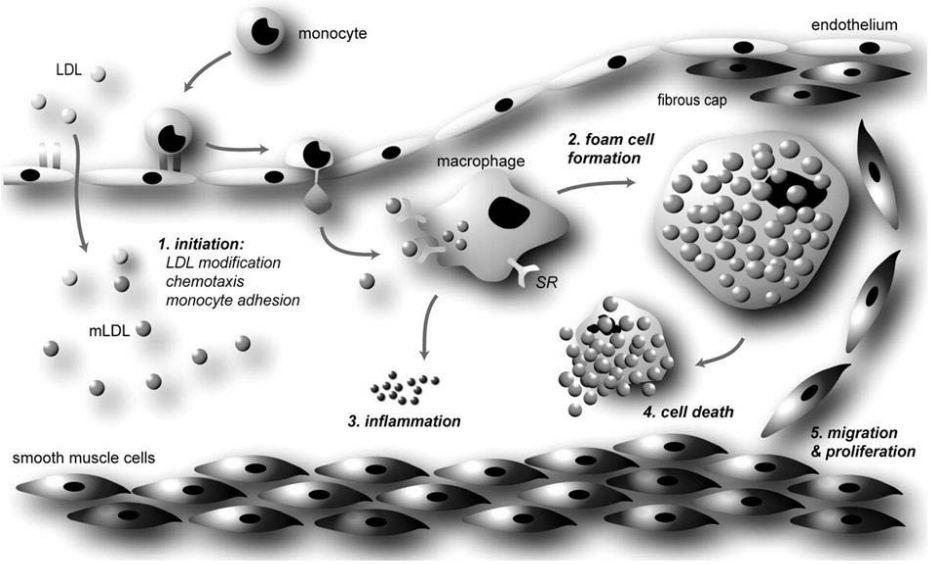

Figure 2. pathogenesis of atherosclerosis development. Adapted from de Winther *et al*.[46] See text for explanation.

2.2 Atherosclerosis

Atherosclerosis is a complex disorder in which lipids and fibrous elements accumulate in the vessel wall (Fig. 2). The innermost layer of a healthy vessel is the thin intima, consisting of a monolayer of endothelial cells (EC) on the luminal side and the internal elastic lamina consisting of elastic fibers. The second layer, the media, consists of smooth muscle cells (SMC) and the third layer, adventitia, consists of connective tissue with fibroblasts and SMC.[39] Atherosclerosis starts with the infiltration of atherogenic lipoproteins such as LDL into the vessel wall where LDL-apoB can interact with proteoglycans which can lead to retention of LDL in the vessel wall. Once trapped, LDL can be modified (*e.g.* by oxidation or aggregation). Accumulation of oxidized LDL stimulates EC to produce inflammatory cytokines, such as chemoattractant

molecules (*e.g.* monocyte chemoattractant protein-1, MCP-1) and growth factors (e.g. macrophage colony-stimulation factor M-CSF) and they begin to express adhesion molecules such as VCAM-1, ICAM, E-selectin, P-selectin, ß2 integrin, Very late antigen-4 (VLA-4) and platelet cell adhesion molecule (PCAM-1). Leukocytes such as monocytes and T cells are attracted and adhere to and migrate into the vessel wall via these adhesion molecules. Activation of leukocyte Toll-like receptors (TLRs) in the vessel wall leads to production of more pro-inflammatory molecules including cytokines and proteases. Within the plaque, monocytes become macrophages that take up LDL after extensive oxidation by reactive oxygen produced by EC and several enzymes including myeloperoxidase, sphingomyelinase and secretory phospholipase. The uptake of oxidized LDL occurs mainly via the scavenger receptors scavenger receptor-A (SR-A), cluster designation (CD)36 and CD68 which are upregulated by cytokines present in the plaque. Internalized cholesterol is esterified by acyl CoA:cholesterol acyltransferase-1 (ACAT-1) and is stored in lipid droplets, and the macrophage becomes a lipid-rich foam cell. In the macrophage foam cell, CE can be hydrolyzed again and the cell can dispose cholesterol via efflux via ABCA1 and ABCG1 to apoE produced by the macrophage and HDL. Early lesions consisting of macrophage foam cells and T cells are called fatty streaks and give no symptoms but are precursors of more advanced lesions.[39,40,45,47]
When the lesion becomes more advanced, interactions between inflammatory cells, ECs and SMCs evoke a chronic inflammatory state, more cytokines are expressed and SMCs migrate into the plaque. SMCs and macrophage foam cells accumulate and die leaving their lipid content behind leading to accumulation of a lipid-rich necrotic debris which is usually covered by a fibrous cap consisting of SMCs and extracellular matrix excreted by these SMCs. The plaques can become more complex e.g. by calcification. The large plaque can lead to ischemic symptoms when it blocks blood flow. In addition, the plaque can lead to an acute block of blood flow when it ruptures. The stability of a plaque depends on its composition. Vunerable plaques have thin fibrous caps and a large number of leukocytes, mainly as macrophages produce proteases that degrade the extracellular matrix of the fibrous cap. Plaque rupture exposes pro-thrombotic material which activates a coagulation cascade leading to thrombosis and an acute blockage of blood flow and infarction.[39,40,45,47]

2.3 Animal models to study lipid metabolism and atherosclerosis

To study atherosclerosis *in vivo*, several animal models have been used. Non-human primates develop atherosclerosis very similar to humans but are a less suitable model because of ethical issues, high costs and because it takes very long to develop atherosclerosis.[48] Therefore, in early atherosclerosis studies, birds, especially pigeons, chickens and quails[49-51] were used, as they are relatively hypercholesterolemic and atherosclerosis prone.[49-52] Another

atherosclerosis-susceptible model used in early studies is the swine,[48,53,54] a major drawback is however the size of the animals leading to high costs and the need for large amounts of experimental agents.[48] Dogs and rats are resistant to atherosclerosis and cats develop no human-like lesions and are, therefore, also not suitable models.[48,52,55] The hamster is sensitive for cholesterol-enriched diets and develops mild fatty streak-like atherosclerotic lesions and is, therefore, used in some studies.[48,55] Rabbits, a widely used animal model, have as herbivores naturally low cholesterol levels and no atherosclerosis development. On atherogenic diets, however, rabbits are atherosclerosis prone but lesions are macrophage-rich and have a fatty streak-like appearance.[52] The Watanabe heritable hyperlipidemic (WHHL) rabbit has a defect in the LDLr and is therefore hyperlipidemic, susceptible to atherosclerosis and able to develop more advanced lesions.[56,57] A drawback of rabbits is that atherosclerosis development is dependent on infections as pathogen-free rabbits develop no atherosclerosis.[48] Another drawback is that they have no HL which is important in HDL metabolism.[58]

The mouse is a widely used model for atherosclerosis studies because of low costs and availability of several strains and genetically modified mice. Wild-type mice have a plasma cholesterol of approximately 2 mM, which is almost all confined to the HDL fraction, while VLDL and LDL are virtually absent. These animals require an extreme atherogenic diet to develop atherosclerosis.[59,60] Since mice are exceptionally suitable for genetic modification, several atherosclerosis-prone mouse models have been generated, such as apoE-knockout ($apoE^{-/-}$), LDLr-knockout ($LDLr^{-/-}$) and APOE*3-Leiden transgenic (E3L) mice. Nowadays these mice are widely used as animal model in atherosclerosis research.

The apoE-knockout mouse has highly impaired VLDL and LDL clearance, as apoE is important in the uptake of lipoprotein remnants by the liver. Therefore, plasma cholesterol is increased in these mice (approx. 8 mM on chow and up to 70 mM on a high cholesterol-containing diet) and present mainly in VLDL and LDL. Therefore, these animals already develop atherosclerosis on a chow diet[61-64] and heterozygote apoE-knockout mice develop atherosclerosis on an atherogenic diet.[65] Lack of macrophage apoE also contributes substantially to the atherosclerosis susceptibility of these mice as mice lacking apoE specifically in the macrophage have increased foam cell formation and atherosclerosis.[66]

LDLr knockout mice have also highly impaired VLDL and LDL clearance and increased plasma cholesterol levels, as the LDLr is important in uptake of these lipoproteins by the liver. However, their phenotype is milder than that of apoE-knockout mice and they therefore need an atherogenic diet to develop atherosclerosis.[67,68] A drawback of both $apoE^{-/-}$ and $LDLr^{-/-}$ mice is that they do not respond in a human-like manner to pharmacotherapeutic interventions like statins and fibrates, with respect to their lipid-lowering properties.[69]

E3L mice carry a construct containing apoE*3-Leiden, a mutation of apoE characterized by a tandem duplication of codons 120-126 that causes hyperlipidemia in humans,[70,71] together with apoCI that elevates plasma TG. As a result, E3L mice have somewhat increased levels of plasma cholesterol and TG on a chow diet,[70] but their phenotype with respect to plasma lipids is milder than that of apoE-knockout and LDLr-knockout mice, and the mice need an atherogenic diet for inducing atherosclerosis development.[72,73] A major advantage of E3L mice is that they respond in a human-like manner to pharmaceutical interventions including statins and fibrates with respect to lipid lowering.[69] Probably because mice lack CETP, an important protein in HDL metabolism, E3L mice do not properly respond to HDL modulating therapy. Therefore, we have crossbred E3L mice with CETP transgenic mice.[74-77]

3. Factors regulating lipid metabolism

3.1 Apolipoproteins

Apolipoproteins stabilize the lipoprotein particle and have functions in lipid and lipoprotein metabolism. Several apolipoproteins are known and they all have their own functions.
ApoAI and apoAII are the two major HDL-associated apolipoproteins and are both required for normal HDL synthesis. ApoAI is present on most HDL particles and constitutes 70% of HDL protein. ApoAII is present on two third of the HDL particles and constitutes 20% of HDL protein content.[33,36] ApoAI is synthesized in the liver and intestine and is lipidated to form HDL. In humans and mice, apoAI deficiency leads to a large decrease in HDL[78,79] and increase in atherosclerosis.[80] ApoAII is synthesized in the liver, and apoAII deficiency also reduces HDL levels,[81] indicating that both apoAI and apoAII are needed for HDL synthesis. ApoAIV is expressed in the intestine, increases HDL levels and protects against atherosclerosis in mice.[82,83] It may also be involved in chylomicron synthesis[84,85] and is important in regulation of food intake.[86] ApoAV is a more recently discovered apolipoprotein that reduces TG levels.[87] ApoAV stimulates LPL-mediated TG lipolysis and inhibits VLDL production which may explain the effect of apoAV on TG levels.[88]
ApoB is present on chylomicrons, VLDL, IDL and LDL. ApoB consists in two forms: apoB48 is expressed by the intestine and is present on chylomicrons, whereas apoB100 is expressed in the liver and present on VLDL. In several species including mice both apoB forms are expressed by the liver. ApoB is required in the assembly of chylomicrons and VLDL and serves as ligand for lipoprotein clearance by the LDLr in liver and other tissues.[89] Mutations in the apoB gene can lead to hypolipidemia or, when the LDLr binding domain is affected, to hyperlipidemia.[90]

ApoE is present on chylomicrons, VLDL, IDL and HDL. ApoE is crucial for the efficient uptake of lipoprotein remnants by the liver.[91] However, at high concentrations, apoE inhibits LPL that may lead to hypertriglyceridemia.[92] Lack of apoE in mice severely increases atherosclerosis development[61-64] and apoE deletion in macrophage increases foam cell formation and atherosclerosis.[66]
An interesting apolipoprotein which, despite its small size, has many functions in lipid metabolism but also in inflammation is apoCI. ApoCI is mainly synthesized in the liver but also in macrophages. ApoCI is released into the circulation, is present on chylomicrons, VLDL, LDL and HDL and is highly exchangeable between these lipoproteins. ApoCI is the smallest of the apolipoproteins (57 amino acids, 6.6 kDa) and highly positively charged. The apoCI peptide forms 2 α-helices which are separated by a flexible linker. ApoCI has many functions in lipoprotein metabolism. Overexpression of apoCI leads to highly increased TG levels and mildly elevated total cholesterol levels in mice,[93] while apoCI knockout mice have decreased TG levels and decreased HDL levels at least on an apoE-knockout background. The elevated TG and cholesterol levels in apoCI-overexpressing mice are mainly confined to VLDL and were initially explained by an inhibitory effect of apoCI on lipoprotein clearance via the LDLr and other classical apoE-recognizing receptors.[94-98] Later, apoCI was found to be an inhibitor of LPL[93] which explains the relative large elevation in TG as compared to cholesterol in apoCI overexpressing mice. In addition, apoCI affects HDL metabolism by stimulation of LCAT,[99,100] inhibition of HL,[101,102] and inhibition of CETP.[103] These effects on HDL thus suggest that apoCI may causally increase HDL levels. Overall, apoCI expression is atherogenic, at least in absence of CETP, probably because of the induction of hyperlipidemia.[104] In addition to affecting plasma cholesterol and TG levels, apoCI has also a role in endodermal lipid metabolism as mice overexpressing high levels of apoCI have skin abnormalities.[105] In addition, apoCI is involved in regulation of inflammation as it enhances the early response to LPS.[106]
Other members of the apoC family are also involved in regulating TG lipolysis. ApoCII is the cofactor for LPL, is essential for lipolysis of TG, and apoCII deficiency thus leads to severe hyperlipidemia.[107,108] ApoCIII, on the other hand, is the main endogenous LPL inhibitor. Overexpression of apoCIII thus leads to elevated TG levels and apoCIII-deficiency to decreased TG levels.[109,110] ApoCIII may also increase intestinal lipid uptake and VLDL production.[111]

3.2 Cholesteryl ester transfer protein

The human CETP gene is located on the long arm of chromosome 16 (16q12-16q21).[112] The gene is 25 kb and consist of 16 exons between 32 to 250 bp which account for 8% of the total gene sequence.[113,114] CETP gene expression is regulated by several factors, including the zinc finger proteins SP1 and

SP3,[115,116] ARP-1,[117] C/EBP,[118] and lipids, directly, or indirectly via SREBP[119,120] and LXR.[11,121-124] In addition to the normal full-length mRNA, an alternatively spliced mRNA can be expressed in which exon 9 is removed. The exon 9-deleted protein is inactive and inhibits secretion of the normal CETP protein[125,126] and may also be involved in the regulation of plasma CETP activity. CETP is expressed mainly in the liver, adipose tissue and in macrophage-rich tissues and is a 74 kDa (476 aa) glycoprotein.[114] CETP is highly hydrophobic as it consists of 45% hydrophobic amino acids which form a hydrophobic pocket for the binding of neutral lipids.[127] CETP circulates in the plasma at a concentration of approx. 1-3 μg/mL and is mainly bound to HDL (74%).[11,128] CETP transfers neutral lipids (*i.e.* TG and CE) between plasma lipoproteins leading to a net transfer of CE from HDL to VLDL and a reciprocal transfer of TG from VLDL to HDL.[11]

As CETP transfers CE out of HDL, CETP activity leads to decreased HDL-C levels. Since HDL-C is associated with reduced cardiovascular disease (CVD) risk, CETP has been suggested to be atherogenic. Albeit that CETP-deficiency thus was expected to be atheroprotective, studies involving CETP-deficient subjects showed controversial results. In Japanese subjects a CETP mutation has been identified that leads to complete CETP deficiency (Intron14+1 G>A)[129] and another mutation that leads to a marked reduction of CETP (D442G).[130] Both mutations indeed increase HDL levels, especially those of large HDL. The HDL of CETP-deficient subjects is enriched in CE and poor in TG. TG and LDL-C levels are not or only mildly affected and LDL particles are smaller and more heterogeneous compared to LDL of normal subjects.[130-133] Although their high HDL levels suggest protection from atherosclerosis, CETP deficient subjects are susceptible to atherosclerosis development.[134] Remarkably, prevalence of CETP-deficiency in people over 80 years is reduced indicating that CETP deficiency does not reduce overall mortality.[135] Zong *et al.*[136] showed even an increase of CHD in carriers of a CETP mutation with HDL-C levels between 1-1.5 mM. However, CHD prevalence was similar in patients with higher HDL levels with and without CETP mutations. Another study showed that high HDL (>2 mM) protects against CHD independent of CETP mutations.[137] The relation between CETP deficiency and atherosclerosis thus remains controversial. However, these mutations are often linked to HL deficiency.[134] Together with the low number of subjects, this makes it difficult to study the effect of CETP on atherosclerosis.[133,138]

Besides the Intron14+1 G>A and D442G mutations, some other CETP gene polymorphisms have been identified. These polymorphisms affect plasma CETP activity to a milder extent, but these mutations are more common and, therefore, easier to study in large patient groups. The TaqIB polymorphism which is in strong linkage disequilibrium with -C629A[139] is the most widely studied CETP polymorphism. The B2 allele is clearly associated with reduced CETP levels and higher HDL levels. However, again literature is inconsistent

about effect of the TaqIB phenotype on CHD risk. The B2 allele has either been associated with reduced CHD risk,[140-143] no effect on CHD risk,[144-146] or even an increased CHD risk.[147,148] A recent review showed that the odds ratio for CVD risk was 1.45 in B2B2 carriers versus B1B1 carriers in population based studies, while the odds ratio in high risk populations was 0.84 for B2B2 carriers versus B1B1. This difference could possibly be explained by selection for a lower frequency of B2B2 carriers in high risk populations. However the effect of this common CETP gene variant on CVD was only modest.[149] Mutations in the CETP gene that cause low CETP mass thus clearly cause higher HDL-C levels, but the effect of CETP mutations on atherosclerosis is controversial.

In addition to human studies, animal models have been used to experimentally address the effect of CETP on atherosclerosis further. Since wild-type mice are naturally deficient for CETP, CETP transgenic mice have been created.[121,150,151] These mice have reduced HDL-C levels in plasma.[150,151] Simian CETP expression in wild-type mice increases atherosclerosis.[151] Since LDLr$^{-/-}$ and apoE$^{-/-}$ mice are hyperlipidemic and have a more human like lipoprotein profile, they have been considered as relevant mouse models to study atherosclerosis. Similarly to wild-type mice, CETP expression in both hyperlipidemic mice increases atherosclerosis.[152] Also, in E3L mice, CETP expression leads to a higher VLDL, lower HDL and increases atherosclerosis by 7-fold.[75]

CETP thus increases atherosclerosis in wild-type mice and in hyperlipidemic mice in which VLDL clearance is impaired to some extent. However, CETP has been shown to be anti-atherogenic in other mouse models. LCAT overexpressing mice have a high increase of plasma levels of large HDL, CETP expression in these mice reduces HDL levels and atherosclerosis.[153] Similarly, SR-BI-deficient mice accumulate large HDL. In this model, CETP expression reduces atherosclerosis[154] as explained by normalization of dysfunctional HDL. However, CETP expression did not reduce atherosclerosis in SR-BI mice in another study despite of HDL normalization (Van Eck *et al.* unpublished results). The latter may be related to the finding that SR-BI-deficiency not only results in dysfunctional HDL, but also increases oxidative stress,[155] which is not relieved upon CETP expression. In mice with hypertriglyceridemia due to apoCIII overexpression and in diabetic mice, CETP expression protects against atherosclerosis development, probably by reduction of total cholesterol levels.[156-158]

CETP is thus protective in mouse models of diabetes and hypertriglyceridemia, possibly related to a plasma cholesterol lowering effect of CETP in these models. Also when HDL accumulates CETP is protective by reducing HDL via an alternative route. In animal models with a more humanized lipoprotein profile however, CETP is atherogenic.

3.3 Nuclear receptors

Since several nuclear receptors are important in regulating expression of genes in lipid metabolism, they are potential targets in drug development.
Peroxisome proliferator-activated receptors (PPARs) are important regulators of expression of genes involved in lipid and glucose metabolism. PPARs are activated by FA and ecosanoids and heterodimerize with RXR to affect gene expression by binding to DR-1 responsive elements. PPARα is expressed in several metabolically active tissues including liver and muscle where it is important for regulation of genes involved in lipid metabolism such as apoCIII, LPL and apoAI (the latter in humans, but not in mice). PPARγ is expressed in adipose tissue, macrophages, colon and placenta and is important in regulation of lipid and glucose metabolism and adipocyte differentiation. PPARγ activation makes tissues more insulin sensitive and agonists are therefore applied in diabetes. PPARδ is expressed at low levels in a variety of tissues, is involved in lipid and glucose metabolism[159-162] and is regarded as novel target in the treatment of dyslipidemia and insulin resistance.[163]
Sterol Regulatory Element Binding Proteins (SREBPs) are other important regulators in lipid metabolism. SREBPs are activated when cells are depleted of cholesterol. Three SREBP isoforms exist, namely SREBP1a, SREBP1c and SREBP2. SREBP1a and SEBP1c are derived from the same gene by use of alternative transcription start sites. SREBP1a is a potent activator of all SREBP responsive genes, these genes are involved in cholesterol, FA and TG synthesis and include HMG-CoA reductase, FAS and SCD. SREBP1c mainly activates genes for FA synthesis and SREBP2 activates genes in cholesterol synthesis.[164] SREBP1c and SREBP2 also induce genes important for the synthesis of NADPH which is used in lipid biosynthesis.
Another group of receptors important in regulation of lipid metabolism include LXR, FXR, PXR and RXR. LXR consists in 2 forms, LXRα and LXRß which are both activated by oxysterols (*i.e.* cholesterol derivates). LXRα is mainly expressed in liver and macrophages while LXRß is more ubiquitously expressed. Upon activation, LXR forms a heterodimer with RXR which binds to LXR-responsive elements to affect expression of genes in lipid metabolism such as apoE, CETP, ABCA1 and SREBP1c.[165,166] In mouse models, LXR agonism shows protection against atherosclerosis, but leads also to hypertriglyceridemia due to increased VLDL production.[167,168] FXR and PXR also form heterodimers with RXR to regulate gene expression. FXR is activated by bile acids and target genes include Cyp7a1 and PLTP. FXR plays an important role in the regulation of synthesis, excretion and reuptake of bile acids from the intestine but also reduces plasma lipid levels.[166] PXR is activated by xenobiotics and increases expression of the Cyp3a enzymes to increase removal of xenobiotics by the body. PXR increases hepatic TG synthesis and may affect HDL metabolism but the effect of PXR on overall lipid metabolism is unknown.[162,166,169]

4. Pharmacological interventions in dyslipidemia

High LDL-C and low HDL-C are associated with increased CVD risk. Several anti-atherogenic drugs have been developed that mainly aim at reducing (V)LDL levels, including statins, fibrates, bile acid binding resins and cholesterol uptake inhibitors.

4.1 Statins

Statins are the most widely used drugs to reduce plasma (V)LDL-C levels. The first statins were fungal derivatives (*e.g.* pravastatin and simvastatin) but later more potent fully synthetic statins including atorvastatin and rosuvastatin were developed. Statins show structural similarities to the cholesterol precursor hydroxymethylglutaryl-coenzyme A (HMG-CoA) and, therefore, they block entry of HMG-CoA to HMG-CoA reductase, an enzyme important in cholesterol synthesis.[170,171] Via this action, statins inhibit cholesterol synthesis in the liver and its subsequent release in the plasma within VLDL particles.[172] In addition, to compensate for hepatic cholesterol depletion, the LDLr is upregulated and uptake of lipoproteins from the plasma is increased, which contributes to the reduction in plasma cholesterol levels.[173] Statins reduce not only cholesterol levels but also TG which may contribute to their anti-atherogenic effects.[174] In addition, statins mildly increase HDL-C levels (up to +10%).[175] Atorvastatin treatment has been associated with a decrease in CETP mass[176-178] and activity.[177-180] however whether a reduction in CETP is the causal factor for the observed HDL increase has not been established yet. In addition to lipid lowering, statins improve endothelial function, are anti-oxidative and are anti-inflammatory contributing to its atheroprotective actions. Statins also inhibit cell proliferation and are, therefore, anticarcinogenic and statins may inhibit kidney graft rejection.[181] Statins decrease plasma (V)LDL-C efficiently up to -40%[182] and the combined actions of statins lead to a reduction of cardiovascular events of about -20% per mM cholesterol reduction.[183]

4.2 Fibrates

Fibrates are PPARα agonists, and therefore affect transcription of many genes in lipid metabolism leading to a net reduction of mainly plasma TG (up to -50%) and a mild reduction in plasma cholesterol.[160,184,185] The reduction in plasma TG may be a consequence of increased TG lipolysis caused by upregulation of LPL[186] and downregulation of the LPL inhibitor apoCIII.[187-189] TG may also be reduced by increased hepatic ß-oxidation and reduced FA synthesis.[189-192] In addition, fibrates mildly increase HDL-C (up to +20%).[175,193] Fibrates induce apoAI expression in humans but not in mice which may contribute to the observed HDL increase in humans.[194] Another difference

between humans and mice is that mice do not express CETP. CETP activity in humans is reduced upon treatment with fibrates[195] but if this contributes to the HDL increase in humans is still unknown. The clinical benefit of fibrates is uncertain.[184,185] A recent meta analysis shows a reduction of non fatal MI (-22%) but not of other cardiovascular events including cardiovascular mortality.[184]

4.3 Bile acid binding resins and cholesterol uptake inhibitors

Other cholesterol lowering drugs available are bile acid binding resins and cholesterol uptake inhibitors. Resins bind bile acids in the intestine, which interrupts the enterohepatic circulation of bile acids and results in an increased excretion of bile acids via the feces. This results in an increased production of new bile acids from cholesterol in the liver and therefore lowers plasma cholesterol levels. Resins reduce plasma cholesterol levels up to -25%.[196-198] Cholesterol uptake inhibitors such as ezetimibe reduce intestinal cholesterol absorption via Niemann-Pick C1 Like 1 (NPC1L1), a protein essential in cholesterol uptake from the intestine.[199] On top of statin treatment, ezetimibe reduces cholesterol by an additional -16%, but does not affect IMT, possibly related to a low baseline IMT of the study subjects. The effect of ezetimibe on clinical endpoints is still uncertain.[200]

Via effective plasma cholesterol lowering, statins, fibrates, bile acid binding resins and cholesterol uptake inhibitors prevent up to 40% of cardiovascular events, a significant residual risk thus remains. Therefore several new drugs to prevent CVD further are under development. As HDL has been suggested to be a more important predictor of CVD development,[201] one group of these new drugs are aimed to increase HDL and include niacin and CETP inhibitors.

4.4 Niacin

Niacin (nicotinic acid, vitamin B3) is the most potent HDL-raising drug used in the clinic. In addition to raising HDL-C (up to +35%),[196,202-204] niacin decreases plasma LDL-C and TG levels (up to -25 and -50% respectively). The reduction in TG and cholesterol may be explained as niacin decreases hormone sensitive lipase activity via the GRP109A. This rapidly decreases plasma FA. Therefore, less FA are available for TG synthesis in the liver and subsequent VLDL production.[204] Niacin may also decrease TG synthesis via a direct effect on TG production in hepatocytes.[205,206] The underlying mechanism of the HDL increase is also not fully understood but is possibly related to CETP.[207] Niacin reduces IMT progression[38] and overall mortality (-11%)[208] but is not well tolerated because it causes severe flushing via increasing plasma prostaglandins.

Addition of the prostaglandin D_2 receptor 1 blocker laropiprant reduces niacin mediated flushing and makes niacin therefore a better tolerated drug.[203]

4.5 CETP inhibitors

As CETP decreases HDL, various strategies have been developed to inhibit CETP activity to increase HDL levels. Two natural CETP inhibitors are known. The lipid transfer inhibitory protein (LTIP), also called apoF, has been detected in LDL and inhibits the involvement of LDL in the actions of CETP.[209,210] In addition, apoCI has been discovered as the main endogenous inhibitor of CETP activity on HDL.[103]
The first experiments to evaluate the effect of inhibition of CETP were performed with antibodies against CETP. These antibodies were indeed able to increase HDL in hamsters and rabbits.[211-213] Antisense oligodeoxynucleotides (ODNs) against CETP also reduced CETP mRNA and increased HDL in rabbits,[214] and were also able to reduce the aortic cholesterol content and lesion area.[215] Atherosclerosis could also be reduced in rabbits by vaccination to generate auto-antibodies against CETP.[216] The first chemical compound designed to inhibit CETP tested in rabbits was JTT-705. JTT-705 inhibits CETP by the formation of a disulphide bond with CETP. In rabbits, JTT-705 indeed increased HDL, decreased non HDL-C and reduced atherosclerosis.[217] In a second study in which rabbits were fed a high cholesterol diet, JTT-705 failed to reduce atherosclerosis despite of an increase in HDL.[218] A second CETP inhibitor is torcetrapib, which inhibits CETP via the formation of an inactive complex with CETP and HDL.[219] Torcetrapib increases HDL and reduces atherosclerosis in rabbits.[220] In humans, both JTT-705 and torcetrapib are well tolerated in short term studies, despite of a small increase in blood pressure in torcetrapib treated subjects. Both compounds raise HDL-C in humans.[221-224] JTT-705 is only tested in short term studies in humans, and therefore its effect on atherosclerosis and cardiovascular events in humans is still unknown. Torcetrapib is tested in long term studies in combination with atorvastatin. Despite of a HDL increase of about 60% however, torcetrapib in combination with atorvastatin treatment failed to reduce atherosclerosis, as assessed by Intima Media Thickness (IMT) an Intravascular Ultrasound (IVUS), compared to atorvastatin alone.[225-227] Moreover, more people died in the torcetrapib treated group as compared to the atorvastatin alone group and cardiovascular event rates were increased rather than decreased by torcetrapib.[228] These adverse effects may well be compound-specific, but further studies into the mechanism of the adverse effects are necessary to evaluate if CETP inhibition is still a promising strategy in the search for new anti-atherogenic drugs. In addition, it is still unknown if the combination with atorvastatin extinguished a protective effect of torcetrapib. Therefore further studies are needed to evaluate if torcetrapib or other CETP inhibitors alone are able to reduce atherosclerosis. A

new CETP inhibitor is anacetrapib, a torcetrapib-like compound that increases HDL in humans without affecting blood pressure.[229] If anacetrapib will decrease atherosclerosis is however still unknown.

5. Outline of this thesis

Statins, fibrates and cholesterol absorption inhibitors lower plasma cholesterol very efficiently (up to 40%). However, efficient cholesterol lowering only prevents a fraction of cardiovascular events. Therefore new therapeutic strategies to further reduce cardiovascular events are necessary. HDL-raising therapy may be such a new strategy, and CETP is an important factor in regulating HDL levels. In this thesis we evaluate the mechanism underlying the effects of pharmaceutical intervention on HDL metabolism in E3L.CETP mice.
In humans statins and fibrates mildly increase HDL. This effect is not observed in E3L mice, despite a human-like cholesterol lowering effect. To evaluate whether the HDL increase as seen in humans depends on CETP expression, we treated E3L.CETP and E3L mice with a diet rich in fat and cholesterol, and added fenofibrate (**chapter 2**) or atorvastatin (**chapter 3**). The most potent HDL raising drug available is niacin, but the mechanism underlying the HDL increase is still unknown. In **chapter 4** we treated E3L.CETP mice with niacin to evaluate the involvement of CETP in niacin's HDL raising properties.
Torcetrapib has been the first CETP inhibitor tested in large clinical trials, and is able to increase HDL by about 60%. However, despite the large increase in HDL, humans treated with atorvastatin and torcetrapib showed no reduction in atherosclerosis (measured by IMT and IVUS) as compared to patients treated with atorvastatin only. Moreover, torcetrapib treatment led to adverse effects including an increase in cardiovascular events and increased death rate. To study the effects of torcetrapib with and without atorvastatin and to study the adverse effects of torcetrapib, in **chapter 5** we treated E3L.CETP mice with torcetrapib and atorvastatin.
In **chapter 6** we studied another mechanism to interfere with HDL metabolism. In literature, PXR agonists are shown to increase HDL levels in wild type mice. However, other studies suggest that PXR activation decreases rather than increases HDL. In addition, the effect of PXR on HDL in the presence of CETP is not known. To evaluate the effect of PXR in a model with a human like lipoprotein profile, we treated E3L and E3L.CETP mice with a high fat/cholesterol diet with and without the PXR agonist pregnenolone-16α-carbonitrile (PCN).
ApoCI has several functions in HDL metabolism. ApoCI is the main endogenous HDL associated CETP inhibitor, the second LCAT activator, and apoCI inhibits HL. The effect of apoCI on HDL clearance and overall HDL levels is however not known. Therefore, we studied the effect of apoCI on SR-BI *in vitro* and overall effect of apoCI in HDL metabolism *in vivo* in **chapter 7**.

In **chapter 8** we focused on the CETP-inhibitory effect of apoCI. As full length apoCI increases VLDL levels by LPL reduction, full length apoCI is not a good agent to increase HDL by CETP inhibition. Therefore we used an array of apoCI peptides to identify a peptide that inhibits CETP but does not inhibit LPL efficiently.
Chapter 9 gives an overview of animal models that are used to study HDL metabolism. The results of the studies described in this thesis and the future perspectives are discussed in **chapter 10**.

References

1. Mahley RW, Innerarity TL, Rall SC, Jr., Weisgraber KH. Plasma lipoproteins: apolipoprotein structure and function. J.Lipid Res. 1984; 25:1277-1294.
2. Kwiterovich PO, Jr. The metabolic pathways of high-density lipoprotein, low-density lipoprotein, and triglycerides: a current review. Am.J.Cardiol. 2000; 86:5L-10L.
3. Mansbach CM and Gorelick F. Development and physiological regulation of intestinal lipid absorption. II. Dietary lipid absorption, complex lipid synthesis, and the intracellular packaging and secretion of chylomicrons. Am.J.Physiol Gastrointest.Liver Physiol. 2007; 293:G645-G650.
4. Hussain MM. A proposed model for the assembly of chylomicrons. Atherosclerosis. 2000; 148:1-15.
5. Mu H and Hoy CE. The digestion of dietary triacylglycerols. Prog.Lipid Res. 2004; 43:105-133.
6. Shen H, Howles P, Tso P. From interaction of lipidic vehicles with intestinal epithelial cell membranes to the formation and secretion of chylomicrons. Adv.Drug Deliv.Rev. 2001; 50 Suppl 1:S103-25.
7. Utermann G and Beisiegel U. Apolipoprotein A-IV: a protein occurring in human mesenteric lymph chylomicrons and free in plasma. Isolation and quantification. Eur.J.Biochem. 1979; 99:333-343.
8. Tall AR, Forester LR, Bongiovanni GL. Facilitation of phosphatidylcholine transfer into high density lipoproteins by an apolipoprotein in the density 1.20-1.26 g/ml fraction of plasma. J.Lipid Res. 1983; 24:277-289.
9. Huuskonen J, Olkkonen VM, Jauhiainen M, Ehnholm C. The impact of phospholipid transfer protein (PLTP) on HDL metabolism. Atherosclerosis. 2001; 155:269-281.
10. Morton RE and Zilversmit DB. Inter-relationship of lipids transferred by the lipid-transfer protein isolated from human lipoprotein-deficient plasma. J.Biol.Chem. 1983; 258:11751-11757.
11. Le Goff W, Guerin M, Chapman MJ. Pharmacological modulation of cholesteryl ester transfer protein, a new therapeutic target in atherogenic dyslipidemia. Pharmacol.Ther. 2004; 101:17-38.
12. Sugden MC, Holness MJ, Howard RM. Changes in lipoprotein lipase activities in adipose tissue, heart and skeletal muscle during continuous or interrupted feeding. Biochem.J. 1993; 292:113-119.
13. Ruge T, Wu G, Olivecrona T, Olivecrona G. Nutritional regulation of lipoprotein lipase in mice. Int.J.Biochem.Cell Biol. 2004; 36:320-329.
14. Out R, Hoekstra M, de Jager SC, de Vos P, van der Westhuyzen DR, Webb NR, Van Eck M, Biessen EA, van Berkel TJ. Adenovirus-mediated hepatic overexpression of

scavenger receptor class B type I accelerates chylomicron metabolism in C57BL/6J mice. J.Lipid Res. 2005; 46:1172-1181.
15. Out R, Kruijt JK, Rensen PC, Hildebrand RB, de Vos P, Van Eck M, van Berkel TJ. Scavenger receptor BI plays a role in facilitating chylomicron metabolism. J.Biol.Chem. 2004; 279:18401-18406.
16. Ji ZS, Fazio S, Lee YL, Mahley RW. Secretion-capture role for apolipoprotein E in remnant lipoprotein metabolism involving cell surface heparan sulfate proteoglycans. J.Biol.Chem. 1994; 269:2764-2772.
17. Ginsberg HN. Lipoprotein physiology. Endocrinol.Metab Clin.North Am. 1998; 27:503-519.
18. Mahley RW and Innerarity TL. Lipoprotein receptors and cholesterol homeostasis. Biochim.Biophys.Acta. 1983; 737:197-222.
19. Shelness GS and Sellers JA. Very-low-density lipoprotein assembly and secretion. Curr.Opin.Lipidol. 2001; 12:151-157.
20. Gotto AM, Jr., Pownall HJ, HAVEL RJ. Introduction to the plasma lipoproteins. Methods Enzymol. 1986; 128:3-41.:3-41.
21. Shelness GS and Ledford AS. Evolution and mechanism of apolipoprotein B-containing lipoprotein assembly. Curr.Opin.Lipidol. 2005; 16:325-332.
22. Van Eck M, Hoekstra M, Out R, Bos IS, Kruijt JK, Hildebrand RB, van Berkel TJ. Scavenger receptor BI facilitates the metabolism of VLDL lipoproteins in vivo. J.Lipid Res. 2008; 49:136-146.
23. Bodzioch M, Orso E, Klucken J, Langmann T, Bottcher A, Diederich W, Drobnik W, Barlage S, Buchler C, Porsch-Ozcurumez M, Kaminski WE, Hahmann HW, Oette K, Rothe G, Aslanidis C, Lackner KJ, Schmitz G. The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. Nat.Genet. 1999; 22:347-351.
24. Brooks-Wilson A, Marcil M, Clee SM, Zhang LH, Roomp K, van Dam M, Yu L, Brewer C, Collins JA, Molhuizen HO, Loubser O, Ouelette BF, Fichter K, Ashbourne-Excoffon KJ, Sensen CW, Scherer S, Mott S, Denis M, Martindale D, Frohlich J, Morgan K, Koop B, Pimstone S, Kastelein JJ, Genest J, Jr., Hayden MR. Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. Nat.Genet. 1999; 22:336-345.
25. Rust S, Rosier M, Funke H, Real J, Amoura Z, Piette JC, Deleuze JF, Brewer HB, Duverger N, Denefle P, Assmann G. Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. Nat.Genet. 1999; 22:352-355.
26. McNeish J, Aiello RJ, Guyot D, Turi T, Gabel C, Aldinger C, Hoppe KL, Roach ML, Royer LJ, de Wet J, Broccardo C, Chimini G, Francone OL. High density lipoprotein deficiency and foam cell accumulation in mice with targeted disruption of ATP-binding cassette transporter-1. Proc.Natl.Acad.Sci.U.S.A 2000; 97:4245-4250.
27. Sakai N, Vaisman BL, Koch CA, Hoyt RF, Jr., Meyn SM, Talley GD, Paiz JA, Brewer HB, Jr., Santamarina-Fojo S. Targeted disruption of the mouse lecithin:cholesterol acyltransferase (LCAT) gene. Generation of a new animal model for human LCAT deficiency. J.Biol.Chem. 1997; 272:7506-7510.
28. Kuivenhoven JA, Pritchard H, Hill J, Frohlich J, Assmann G, Kastelein J. The molecular pathology of lecithin:cholesterol acyltransferase (LCAT) deficiency syndromes. J.Lipid Res. 1997; 38:191-205.
29. Wang N, Lan D, Chen W, Matsuura F, Tall AR. ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to high-density lipoproteins. Proc.Natl.Acad.Sci.U.S.A. 2004; 101:9774-9779.
30. Out R, Hoekstra M, Spijkers JA, Kruijt JK, Van Eck M, Bos IS, Twisk J, van Berkel TJ. Scavenger receptor class B type I is solely responsible for the selective uptake of

cholesteryl esters from HDL by the liver and the adrenals in mice. J.Lipid Res. 2004; 45:2088-2095.
31. Acton S, Rigotti A, Landschulz KT, Xu S, Hobbs HH, Krieger M. Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. Science. 1996; 271:518-520.
32. Shirai K, Barnhart RL, Jackson RL. Hydrolysis of human plasma high density lipoprotein 2- phospholipids and triglycerides by hepatic lipase. Biochem.Biophys.Res.Commun. 1981; 100:591-599.
33. Rader DJ. Molecular regulation of HDL metabolism and function: implications for novel therapies. J.Clin.Invest. 2006; 116:3090-3100.
34. Jaye M, Lynch KJ, Krawiec J, Marchadier D, Maugeais C, Doan K, South V, Amin D, Perrone M, Rader DJ. A novel endothelial-derived lipase that modulates HDL metabolism. Nat.Genet. 1999; 21:424-428.
35. Tall AR. Cholesterol efflux pathways and other potential mechanisms involved in the athero-protective effect of high density lipoproteins. J.Intern.Med. 2008; 263:256-273.
36. Joy T and Hegele RA. Is raising HDL a futile strategy for atheroprotection? Nat.Rev.Drug Discov. 2008; 7:143-155.
37. Chiang JY. Regulation of bile acid synthesis: pathways, nuclear receptors, and mechanisms. J.Hepatol. 2004; 40:539-551.
38. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation. 2004; 110:3512-3517.
39. Lusis AJ. Atherosclerosis. Nature. 2000; 407:233-241.
40. Glass CK and Witztum JL. Atherosclerosis. the road ahead. Cell. 2001; 104:503-516.
41. Hersberger M and von Eckardstein A. Low high-density lipoprotein cholesterol: physiological background, clinical importance and drug treatment. Drugs. 2003; 63:1907-1945.
42. Assmann G and Gotto AM, Jr. HDL cholesterol and protective factors in atherosclerosis. Circulation. 2004; 109:III8-14.
43. Berglund L and Ramakrishnan R. Lipoprotein(a): an elusive cardiovascular risk factor. Arterioscler.Thromb.Vasc.Biol. 2004; 24:2219-2226.
44. Garg A and Simha V. Update on dyslipidemia. J.Clin.Endocrinol.Metab. 2007; 92:1581-1589.
45. Ross R. Atherosclerosis--an inflammatory disease. N.Engl.J.Med. 1999; 340:115-126.
46. de Winther MP, Kanters E, Kraal G, Hofker MH. Nuclear factor kappaB signaling in atherogenesis. Arterioscler.Thromb.Vasc.Biol. 2005; 25:904-914.
47. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N.Engl.J.Med. 2005; 352:1685-1695.
48. Russell JC and Proctor SD. Small animal models of cardiovascular disease: tools for the study of the roles of metabolic syndrome, dyslipidemia, and atherosclerosis. Cardiovasc.Pathol. 2006; 15:318-330.
49. Fisher H, Feigenbaum A, Leveille GA. Weiss HS, Griminger P. Biochemical observations on aortas of chickens. Effect of different fats and varying levels of protein, fat and cholesterol. J.Nutr. 1959; 69:163-71.:163-171.
50. Shih JC, Pullman EP, Kao KJ. Genetic selection, general characterization, and histology of atherosclerosis-susceptible and -resistant Japanese quail. Atherosclerosis. 1983; 49:41-53.

51. Jerome WG and Lewis JC. Early atherogenesis in White Carneau pigeons. II. Ultrastructural and cytochemical observations. Am.J.Pathol. 1985; 119:210-222.
52. Armstrong ML and Heistad DD. Animal models of atherosclerosis. Atherosclerosis. 1990; 85:15-23.
53. Holvoet P, Theilmeier G, Shivalkar B, Flameng W, Collen D. LDL hypercholesterolemia is associated with accumulation of oxidized LDL, atherosclerotic plaque growth, and compensatory vessel enlargement in coronary arteries of miniature pigs. Arterioscler.Thromb.Vasc.Biol. 1998; 18:415-422.
54. Ratcliffe HL and Luginbuhl H. The domestic pig: a model for experimental atherosclerosis. Atherosclerosis. 1971; 13:133-136.
55. Moghadasian MH. Experimental atherosclerosis: a historical overview. Life Sci. 2002; 70:855-865.
56. Finking G and Hanke H. Nikolaj Nikolajewitsch Anitschkow (1885-1964) established the cholesterol-fed rabbit as a model for atherosclerosis research. Atherosclerosis. 1997; 135:1-7.
57. Buja LM, Kita T, Goldstein JL, Watanabe Y, Brown MS. Cellular pathology of progressive atherosclerosis in the WHHL rabbit. An animal model of familial hypercholesterolemia. Arteriosclerosis. 1983; 3:87-101.
58. Clay MA, Hopkins GJ, Ehnholm CP, Barter PJ. The rabbit as an animal model of hepatic lipase deficiency. Biochim.Biophys.Acta. 1989; 1002:173-181.
59. Paigen B, Morrow A, Brandon C, Mitchell D, Holmes P. Variation in susceptibility to atherosclerosis among inbred strains of mice. Atherosclerosis. 1985; 57:65-73.
60. Nishina PM, Verstuyft J, Paigen B. Synthetic low and high fat diets for the study of atherosclerosis in the mouse. J.Lipid Res. 1990; 31:859-869.
61. Nakashima Y, Plump AS, Raines EW, Breslow JL, Ross R. ApoE-deficient mice develop lesions of all phases of atherosclerosis throughout the arterial tree. Arterioscler.Thromb. 1994; 14:133-140.
62. Plump AS, Smith JD, Hayek T, Aalto-Setala K, Walsh A, Verstuyft JG, Rubin EM, Breslow JL. Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. Cell. 1992; 71:343-353.
63. Piedrahita JA, Zhang SH, Hagaman JR, Oliver PM, Maeda N. Generation of mice carrying a mutant apolipoprotein E gene inactivated by gene targeting in embryonic stem cells. Proc.Natl.Acad.Sci.U.S.A. 1992; 89:4471-4475.
64. Zhang SH, Reddick RL, Piedrahita JA, Maeda N. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein E. Science. 1992; 258:468-471.
65. van Ree JH, van den Broek WJ, Dahlmans VE, Groot PH, Vidgeon-Hart M, Frants RR, Wieringa B, Havekes LM, Hofker MH. Diet-induced hypercholesterolemia and atherosclerosis in heterozygous apolipoprotein E-deficient mice. Atherosclerosis. 1994; 111:25-37.
66. Fazio S, Babaev VR, Murray AB, Hasty AH, Carter KJ, Gleaves LA, Atkinson JB, Linton MF. Increased atherosclerosis in mice reconstituted with apolipoprotein E null macrophages. Proc.Natl.Acad.Sci.U.S.A. 1997; 94:4647-4652.
67. Ishibashi S, Brown MS, Goldstein JL, Gerard RD, Hammer RE, Herz J. Hypercholesterolemia in low density lipoprotein receptor knockout mice and its reversal by adenovirus-mediated gene delivery. J.Clin.Invest. 1993; 92:883-893.
68. Ishibashi S, Goldstein JL, Brown MS, Herz J, Burns DK. Massive xanthomatosis and atherosclerosis in cholesterol-fed low density lipoprotein receptor-negative mice. J.Clin.Invest. 1994; 93:1885-1893.

69. Zadelaar S, Kleemann R, Verschuren L, de Vries-Van der Weij, van der HJ, Princen HM, Kooistra T. Mouse models for atherosclerosis and pharmaceutical modifiers. Arterioscler.Thromb.Vasc.Biol. 2007; 27:1706-1721.
70. van den Maagdenberg AM, Hofker MH, Krimpenfort PJ, de B, I, van Vlijmen B, van der BH, Havekes LM, Frants RR. Transgenic mice carrying the apolipoprotein E3-Leiden gene exhibit hyperlipoproteinemia. J.Biol.Chem. 1993; 268:10540-10545.
71. van den Maagdenberg AM, de Knijff P, Stalenhoef AF, Gevers Leuven JA, Havekes LM, Frants RR. Apolipoprotein E*3-Leiden allele results from a partial gene duplication in exon 4. Biochem.Biophys.Res.Commun. 1989; 165:851-857.
72. van Vlijmen BJ, van den Maagdenberg AM, Gijbels MJ, van der BH, HogenEsch H, Frants RR, Hofker MH, Havekes LM. Diet-induced hyperlipoproteinemia and atherosclerosis in apolipoprotein E3-Leiden transgenic mice. J.Clin.Invest 1994; 93:1403-1410.
73. Lutgens E, Daemen M, Kockx M, Doevendans P, Hofker M, Havekes L, Wellens H, de Muinck ED. Atherosclerosis in APOE*3-Leiden transgenic mice: from proliferative to atheromatous stage. Circulation. 1999; 99:276-283.
74. de Haan W, van der Hoogt CC, Westerterp M, Hoekstra M, Dallinga-Thie GM, Princen HM, Romijn JA, Jukema JW, Havekes LM, Rensen PC. Atorvastatin increases HDL cholesterol by reducing CETP expression in cholesterol-fed APOE*3-Leiden.CETP mice. Atherosclerosis. 2008; 197:57-63.
75. Westerterp M, van der Hoogt CC, de Haan W, Offerman EH, Dallinga-Thie GM, Jukema JW, Havekes LM, Rensen PC. Cholesteryl ester transfer protein decreases high-density lipoprotein and severely aggravates atherosclerosis in APOE*3-Leiden mice. Arterioscler.Thromb.Vasc.Biol. 2006; 26:2552-2559.
76. van der Hoogt CC, de Haan W, Westerterp M, Hoekstra M, Dallinga-Thie GM, Romijn JA, Princen HM, Jukema JW, Havekes LM, Rensen PC. Fenofibrate increases HDL-cholesterol by reducing cholesteryl ester transfer protein expression. J.Lipid Res. 2007; 48:1763-1771.
77. de Haan W, de Vries-Van der Weij J, van der Hoorn JW, Gautier T, van der Hoogt CC, Westerterp M, Romijn JA, Jukema JW, Havekes LM, Princen HM, Rensen PC. Torcetrapib does not reduce atherosclerosis beyond atorvastatin and induces more proinflammatory lesions than atorvastatin. Circulation. 2008; 117:2515-2522.
78. Williamson R, Lee D, Hagaman J, Maeda N. Marked reduction of high density lipoprotein cholesterol in mice genetically modified to lack apolipoprotein A-I. Proc.Natl.Acad.Sci.U.S.A. 1992; 89:7134-7138.
79. Schaefer EJ, Heaton WH, Wetzel MG, Brewer HB, Jr. Plasma apolipoprotein A-1 absence associated with a marked reduction of high density lipoproteins and premature coronary artery disease. Arteriosclerosis. 1982; 2:16-26.
80. Moore RE, Navab M, Millar JS, Zimetti F, Hama S, Rothblat GH, Rader DJ. Increased atherosclerosis in mice lacking apolipoprotein A-I attributable to both impaired reverse cholesterol transport and increased inflammation. Circ.Res. 2005; 97:763-771.
81. Weng W and Breslow JL. Dramatically decreased high density lipoprotein cholesterol, increased remnant clearance, and insulin hypersensitivity in apolipoprotein A-II knockout mice suggest a complex role for apolipoprotein A-II in atherosclerosis susceptibility. Proc.Natl.Acad.Sci.U.S.A. 1996; 93:14788-14794.
82. Duverger N, Tremp G, Caillaud JM, Emmanuel F, Castro G, Fruchart JC, Steinmetz A, Denefle P. Protection against atherogenesis in mice mediated by human apolipoprotein A-IV. Science. 1996; 273:966-968.

83. Ostos MA, Conconi M, Vergnes L, Baroukh N, Ribalta J, Girona J, Caillaud JM, Ochoa A, Zakin MM. Antioxidative and antiatherosclerotic effects of human apolipoprotein A-IV in apolipoprotein E-deficient mice. Arterioscler.Thromb.Vasc.Biol. 2001; 21:1023-1028.
84. Lu S, Yao Y, Cheng X, Mitchell S, Leng S, Meng S, Gallagher JW, Shelness GS, Morris GS, Mahan J, Frase S, Mansbach CM, Weinberg RB, Black DD. Overexpression of apolipoprotein A-IV enhances lipid secretion in IPEC-1 cells by increasing chylomicron size. J.Biol.Chem. 2006; 281:3473-3483.
85. Green PH, Glickman RM, Riley JW, Quinet E. Human apolipoprotein A-IV. Intestinal origin and distribution in plasma. J.Clin.Invest. 1980; 65:911-919.
86. Tso P and Liu M. Apolipoprotein A-IV, food intake, and obesity. Physiol Behav. 2004; 83:631-643.
87. Pennacchio LA, Olivier M, Hubacek JA, Cohen JC, Cox DR, Fruchart JC, Krauss RM, Rubin EM. An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. Science. 2001; 294:169-173.
88. Schaap FG, Rensen PC, Voshol PJ, Vrins C, van der Vliet HN, Chamuleau RA, Havekes LM, Groen AK, van Dijk KW. ApoAV reduces plasma triglycerides by inhibiting very low density lipoprotein-triglyceride (VLDL-TG) production and stimulating lipoprotein lipase-mediated VLDL-TG hydrolysis. J.Biol.Chem. 2004; 279:27941-27947.
89. Boren J, Lee I, Zhu W, Arnold K, Taylor S, Innerarity TL. Identification of the low density lipoprotein receptor-binding site in apolipoprotein B100 and the modulation of its binding activity by the carboxyl terminus in familial defective apo-B100. J.Clin.Invest. 1998; 101:1084-1093.
90. Whitfield AJ, Barrett PH, van Bockxmeer FM, Burnett JR. Lipid disorders and mutations in the APOB gene. Clin.Chem. 2004; 50:1725-1732.
91. Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science. 1988; 240:622-630.
92. Rensen PC and van Berkel TJ. Apolipoprotein E effectively inhibits lipoprotein lipase-mediated lipolysis of chylomicron-like triglyceride-rich lipid emulsions in vitro and in vivo. J.Biol.Chem. 1996; 271:14791-14799.
93. Berbee JF, van der Hoogt CC, Sundararaman D, Havekes LM, Rensen PC. Severe hypertriglyceridemia in human APOC1 transgenic mice is caused by apoC-I-induced inhibition of LPL. J.Lipid Res. 2005; 46:297-306.
94. Jong MC, Hofker MH, Havekes LM. Role of ApoCs in lipoprotein metabolism: functional differences between ApoC1, ApoC2, and ApoC3. Arterioscler.Thromb.Vasc.Biol. 1999; 19:472-484.
95. Jong MC, Dahlmans VE, van Gorp PJ, van Dijk KW, Breuer ML, Hofker MH, Havekes LM. In the absence of the low density lipoprotein receptor, human apolipoprotein C1 overexpression in transgenic mice inhibits the hepatic uptake of very low density lipoproteins via a receptor-associated protein-sensitive pathway. J.Clin.Invest. 1996; 98:2259-2267.
96. van Ree JH, Hofker MH, van den Broek WJ, van Deursen JM, van der BH, Frants RR, Wieringa B, Havekes LM. Increased response to cholesterol feeding in apolipoprotein C1-deficient mice. Biochem.J. 1995; 305:905-911.
97. Jong MC, van Ree JH, Dahlmans VE, Frants RR, Hofker MH, Havekes LM. Reduced very-low-density lipoprotein fractional catabolic rate in apolipoprotein C1-deficient mice. Biochem.J. 1997; 321:445-450.

98. Shachter NS, Ebara T, Ramakrishnan R, Steiner G, Breslow JL, Ginsberg HN, Smith JD. Combined hyperlipidemia in transgenic mice overexpressing human apolipoprotein Cl. J.Clin.Invest. 1996; 98:846-855.
99. Soutar AK, Garner CW, Baker HN, Sparrow JT, Jackson RL, Gotto AM, Smith LC. Effect of the human plasma apolipoproteins and phosphatidylcholine acyl donor on the activity of lecithin: cholesterol acyltransferase. Biochemistry. 1975; 14:3057-3064.
100. Jonas A, Sweeny SA, Herbert PN. Discoidal complexes of A and C apolipoproteins with lipids and their reactions with lecithin: cholesterol acyltransferase. J.Biol.Chem. 1984; 259:6369-6375.
101. Kinnunen PK and Ehnolm C. Effect of serum and C-apoproteins from very low density lipoproteins on human postheparin plasma hepatic lipase. FEBS Lett. 1976; 65:354-357.
102. Conde-Knape K, Bensadoun A, Sobel JH, Cohn JS, Shachter NS. Overexpression of apoC-I in apoE-null mice: severe hypertriglyceridemia due to inhibition of hepatic lipase. J.Lipid Res. 2002; 43:2136-2145.
103. Gautier T, Masson D, de Barros JP, Athias A, Gambert P, Aunis D, Metz-Boutigue MH, Lagrost L. Human apolipoprotein C-I accounts for the ability of plasma high density lipoproteins to inhibit the cholesteryl ester transfer protein activity. J.Biol.Chem. 2000; 275:37504-37509.
104. Westerterp M, Van Eck M, de Haan W, Offerman EH, van Berkel TJ, Havekes LM, Rensen PC. Apolipoprotein CI aggravates atherosclerosis development in ApoE-knockout mice despite mediating cholesterol efflux from macrophages. Atherosclerosis. 2007; 195:e9-16.
105. Jong MC, Gijbels MJ, Dahlmans VE, Gorp PJ, Koopman SJ, Ponec M, Hofker MH, Havekes LM. Hyperlipidemia and cutaneous abnormalities in transgenic mice overexpressing human apolipoprotein C1. J.Clin.Invest. 1998; 101:145-152.
106. Berbee JF, van der Hoogt CC, Kleemann R, Schippers EF, Kitchens RL, van Dissel JT, Bakker-Woudenberg IA, Havekes LM, Rensen PC. Apolipoprotein CI stimulates the response to lipopolysaccharide and reduces mortality in gram-negative sepsis. FASEB J. 2006; 20:2162-2164.
107. Reina M, Brunzell JD, Deeb SS. Molecular basis of familial chylomicronemia: mutations in the lipoprotein lipase and apolipoprotein C-II genes. J.Lipid Res. 1992; 33:1823-1832.
108. Santamarina-Fojo S. The familial chylomicronemia syndrome. Endocrinol.Metab Clin.North Am. 1998; 27:551-67.
109. Jong MC, Rensen PC, Dahlmans VE, van der BH, van Berkel TJ, Havekes LM. Apolipoprotein C-III deficiency accelerates triglyceride hydrolysis by lipoprotein lipase in wild-type and apoE knockout mice. J.Lipid Res. 2001; 42:1578-1585.
110. McConathy WJ, Gesquiere JC, Bass H, Tartar A, Fruchart JC, Wang CS. Inhibition of lipoprotein lipase activity by synthetic peptides of apolipoprotein C-III. J.Lipid Res. 1992; 33:995-1003.
111. van Dijk KW, Rensen PC, Voshol PJ, Havekes LM. The role and mode of action of apolipoproteins CIII and AV: synergistic actors in triglyceride metabolism? Curr.Opin.Lipidol. 2004; 15:239-246.
112. Lusis AJ, Zollman S, Sparkes RS, Klisak I, Mohandas T, Drayna D, Lawn RM. Assignment of the human gene for cholesteryl ester transfer protein to chromosome 16q12-16q21. Genomics. 1987; 1:232-235.

113. Agellon LB, Quinet EM, Gillette TG, Drayna DT, Brown ML, Tall AR. Organization of the human cholesteryl ester transfer protein gene. Biochemistry. 1990; 29:1372-1376.
114. Drayna D, Jarnagin AS, McLean J, Henzel W, Kohr W, Fielding C, Lawn R. Cloning and sequencing of human cholesteryl ester transfer protein cDNA. Nature. 1987; 327:632-634.
115. Dachet C, Poirier O, Cambien F, Chapman J, Rouis M. New functional promoter polymorphism, CETP/-629, in cholesteryl ester transfer protein (CETP) gene related to CETP mass and high density lipoprotein cholesterol levels: role of Sp1/Sp3 in transcriptional regulation. Arterioscler.Thromb.Vasc.Biol. 2000; 20:507-515.
116. Le Goff W, Guerin M, Petit L, Chapman MJ, Thillet J. Regulation of human CETP gene expression: role of SP1 and SP3 transcription factors at promoter sites -690, -629, and -37. J.Lipid Res. 2003; 44:1322-1331.
117. Gaudet F and Ginsburg GS. Transcriptional regulation of the cholesteryl ester transfer protein gene by the orphan nuclear hormone receptor apolipoprotein AI regulatory protein-1. J.Biol.Chem. 1995; 270:29916-29922.
118. Agellon LB, Zhang P, Jiang XC, Mendelsohn L, Tall AR. The CCAAT/enhancer-binding protein trans-activates the human cholesteryl ester transfer protein gene promoter. J.Biol.Chem. 1992; 267:22336-22339.
119. Chouinard RA, Jr., Luo Y, Osborne TF, Walsh A, Tall AR. Sterol regulatory element binding protein-1 activates the cholesteryl ester transfer protein gene in vivo but is not required for sterol up-regulation of gene expression. J.Biol.Chem. 1998; 273:22409-22414.
120. Gauthier B, Robb M, Gaudet F, Ginsburg GS, McPherson R. Characterization of a cholesterol response element (CRE) in the promoter of the cholesteryl ester transfer protein gene: functional role of the transcription factors SREBP-1a, -2, and YY1. J.Lipid Res. 1999; 40:1284-1293.
121. Jiang XC, Agellon LB, Walsh A, Breslow JL, Tall A. Dietary cholesterol increases transcription of the human cholesteryl ester transfer protein gene in transgenic mice. Dependence on natural flanking sequences. J.Clin.Invest. 1992; 90:1290-1295.
122. Jiang XC, Beyer TP, Li Z, Liu J, Quan W, Schmidt RJ, Zhang Y, Bensch WR, Eacho PI, Cao G. Enlargement of high density lipoprotein in mice via liver X receptor activation requires apolipoprotein E and is abolished by cholesteryl ester transfer protein expression. J.Biol.Chem. 2003; 278:49072-49078.
123. Luo Y and Tall AR. Sterol upregulation of human CETP expression in vitro and in transgenic mice by an LXR element. J.Clin.Invest 2000; 105:513-520.
124. Oliveira HC, Chouinard RA, Agellon LB, Bruce C, Ma L, Walsh A, Breslow JL, Tall AR. Human cholesteryl ester transfer protein gene proximal promoter contains dietary cholesterol positive responsive elements and mediates expression in small intestine and periphery while predominant liver and spleen expression is controlled by 5'-distal sequences. Cis-acting sequences mapped in transgenic mice. J.Biol.Chem. 1996; 271:31831-31838.
125. Inazu A, Quinet EM, Wang S, Brown ML, Stevenson S, Barr ML, Moulin P, Tall AR. Alternative splicing of the mRNA encoding the human cholesteryl ester transfer protein. Biochemistry. 1992; 31:2352-2358.
126. Quinet E, Yang TP, Marinos C, Tall A. Inhibition of the cellular secretion of cholesteryl ester transfer protein by a variant protein formed by alternative splicing of mRNA. J.Biol.Chem. 1993; 268:16891-16894.

127. Yamashita S, Hirano K, Sakai N, Matsuzawa Y. Molecular biology and pathophysiological aspects of plasma cholesteryl ester transfer protein. Biochim.Biophys.Acta. 2000; 1529:257-275.
128. Nishida HI, Arai H, Nishida T. Cholesterol ester transfer mediated by lipid transfer protein as influenced by changes in the charge characteristics of plasma lipoproteins. J.Biol.Chem. 1993; 268:16352-16360.
129. Brown ML, Inazu A, Hesler CB, Agellon LB, Mann C, Whitlock ME, Marcel YL, Milne RW, Koizumi J, Mabuchi H. Molecular basis of lipid transfer protein deficiency in a family with increased high-density lipoproteins. Nature. 1989; 342:448-451.
130. Inazu A, Jiang XC, Haraki T, Yagi K, Kamon N, Koizumi J, Mabuchi H, Takeda R, Takata K, Moriyama Y. Genetic cholesteryl ester transfer protein deficiency caused by two prevalent mutations as a major determinant of increased levels of high density lipoprotein cholesterol. J.Clin.Invest. 1994; 94:1872-1882.
131. Arai H, Yamamoto A, Matsuzawa Y, Saito Y, Yamada N, Oikawa S, Mabuchi H, Teramoto T, Sasaki J, Nakaya N, Itakura H, Ishikawa Y, Ouchi Y, Horibe H, Egashira T, Hattori H, Shirahashi N, Kita T. Polymorphisms in four genes related to triglyceride and HDL-cholesterol levels in the general Japanese population in 2000. J.Atheroscler.Thromb. 2005; 12:240-250.
132. Yamashita S, Matsuzawa Y, Okazaki M, Kako H, Yasugi T, Akioka H, Hirano K, Tarui S. Small polydisperse low density lipoproteins in familial hyperalphalipoproteinemia with complete deficiency of cholesteryl ester transfer activity. Atherosclerosis. 1988; 70:7-12.
133. Yamashita S, Sakai N, Hirano K, Arai T, Ishigami M, Maruyama T, Matsuzawa Y. Molecular genetics of plasma cholesteryl ester transfer protein. Curr.Opin.Lipidol. 1997; 8:101-110.
134. Hirano K, Yamashita S, Kuga Y, Sakai N, Nozaki S, Kihara S, Arai T, Yanagi K, Takami S, Menju M, . Atherosclerotic disease in marked hyperalphalipoproteinemia. Combined reduction of cholesteryl ester transfer protein and hepatic triglyceride lipase. Arterioscler.Thromb.Vasc.Biol. 1995; 15:1849-1856.
135. Hirano K, Yamashita S, Nakajima N, Arai T, Maruyama T, Yoshida Y, Ishigami M, Sakai N, Kameda-Takemura K, Matsuzawa Y. Genetic cholesteryl ester transfer protein deficiency is extremely frequent in the Omagari area of Japan. Marked hyperalphalipoproteinemia caused by CETP gene mutation is not associated with longevity. Arterioscler.Thromb.Vasc.Biol. 1997; 17:1053-1059.
136. Zhong S, Sharp DS, Grove JS, Bruce C, Yano K, Curb JD, Tall AR. Increased coronary heart disease in Japanese-American men with mutation in the cholesteryl ester transfer protein gene despite increased HDL levels. J.Clin.Invest. 1996; 97:2917-2923.
137. Moriyama Y, Okamura T, Inazu A, Doi M, Iso H, Mouri Y, Ishikawa Y, Suzuki H, Iida M, Koizumi J, Mabuchi H, Komachi Y. A low prevalence of coronary heart disease among subjects with increased high-density lipoprotein cholesterol levels, including those with plasma cholesteryl ester transfer protein deficiency. Prev.Med. 1998; 27:659-667.
138. de Grooth GJ, Klerkx AH, Stroes ES, Stalenhoef AF, Kastelein JJ, Kuivenhoven JA. A review of CETP and its relation to atherosclerosis. J.Lipid Res. 2004; 45:1967-1974.
139. Klerkx AH, Tanck MW, Kastelein JJ, Molhuizen HO, Jukema JW, Zwinderman AH, Kuivenhoven JA. Haplotype analysis of the CETP gene: not TaqIB, but the closely

linked -629C-->A polymorphism and a novel promoter variant are independently associated with CETP concentration. Hum.Mol.Genet. 2003; 12:111-123.
140. Hsieh MC, Chen CC, Wang JY, Chong IW, Yhe CJ, Shin SJ, Lin SR. Cholesteryl ester transfer protein B1B1 genotype is associated with a parental history of cardiovascular diseases in Taiwanese people. Med.Princ.Pract. 2008; 17:143-148.
141. Freeman DJ, Samani NJ, Wilson V, McMahon AD, Braund PS, Cheng S, Caslake MJ, Packard CJ, Gaffney D. A polymorphism of the cholesteryl ester transfer protein gene predicts cardiovascular events in non-smokers in the West of Scotland Coronary Prevention Study. Eur.Heart J. 2003; 24:1833-1842.
142. Ordovas JM, Cupples LA, Corella D, Otvos JD, Osgood D, Martinez A, Lahoz C, Coltell O, Wilson PW, Schaefer EJ. Association of cholesteryl ester transfer protein-TaqIB polymorphism with variations in lipoprotein subclasses and coronary heart disease risk: the Framingham study. Arterioscler.Thromb.Vasc.Biol. 2000; 20:1323-1329.
143. Brousseau ME, O'Connor JJ, Jr., Ordovas JM, Collins D, Otvos JD, Massov T, McNamara JR, Rubins HB, Robins SJ, Schaefer EJ. Cholesteryl ester transfer protein TaqI B2B2 genotype is associated with higher HDL cholesterol levels and lower risk of coronary heart disease end points in men with HDL deficiency: Veterans Affairs HDL Cholesterol Intervention Trial. Arterioscler.Thromb.Vasc.Biol. 2002; 22:1148-1154.
144. McCaskie PA, Beilby JP, Chapman CM, Hung J, McQuillan BM, Thompson PL, Palmer LJ. Cholesteryl ester transfer protein gene haplotypes, plasma high-density lipoprotein levels and the risk of coronary heart disease. Hum.Genet. 2007; 121:401-411.
145. Carlquist JF, Muhlestein JB, Horne BD, Hart NI, Bair TL, Molhuizen HO, Anderson JL. The cholesteryl ester transfer protein Taq1B gene polymorphism predicts clinical benefit of statin therapy in patients with significant coronary artery disease. Am.Heart J. 2003; 146:1007-1014.
146. de Grooth GJ, Zerba KE, Huang SP, Tsuchihashi Z, Kirchgessner T, Belder R, Vishnupad P, Hu B, Klerkx AH, Zwinderman AH, Jukema JW, Sacks FM, Kastelein JJ, Kuivenhoven JA. The cholesteryl ester transfer protein (CETP) TaqIB polymorphism in the cholesterol and recurrent events study: no interaction with the response to pravastatin therapy and no effects on cardiovascular outcome: a prospective analysis of the CETP TaqIB polymorphism on cardiovascular outcome and interaction with cholesterol-lowering therapy. J.Am.Coll.Cardiol. 2004; 43:854-857.
147. Mohrschladt MF, van der Sman-de Beer, Hofman MK, van der KM, Westendorp RG, Smelt AH. TaqIB polymorphism in CETP gene: the influence on incidence of cardiovascular disease in statin-treated patients with familial hypercholesterolemia. Eur.J.Hum.Genet. 2005; 13:877-882.
148. Borggreve SE, Hillege HL, Wolffenbuttel BH, de Jong PE, Zuurman MW, van der SG, Van Tol A, Dullaart RP. An increased coronary risk is paradoxically associated with common cholesteryl ester transfer protein gene variations that relate to higher high-density lipoprotein cholesterol: a population-based study. J.Clin.Endocrinol.Metab. 2006; 91:3382-3388.
149. Dullaart RP and Sluiter WJ. Common variation in the CETP gene and the implications for cardiovascular disease and its treatment: an updated analysis. Pharmacogenomics. 2008; 9:747-763.

150. Agellon LB, Walsh A, Hayek T, Moulin P, Jiang XC, Shelanski SA, Breslow JL, Tall AR. Reduced high density lipoprotein cholesterol in human cholesteryl ester transfer protein transgenic mice. J.Biol.Chem. 1991; 266:10796-10801.
151. Marotti KR, Castle CK, Boyle TP, Lin AH, Murray RW, Melchior GW. Severe atherosclerosis in transgenic mice expressing simian cholesteryl ester transfer protein. Nature. 1993; 364:73-75.
152. Plump AS, Masucci-Magoulas L, Bruce C, Bisgaier CL, Breslow JL, Tall AR. Increased atherosclerosis in ApoE and LDL receptor gene knock-out mice as a result of human cholesteryl ester transfer protein transgene expression. Arterioscler.Thromb.Vasc.Biol. 1999; 19:1105-1110.
153. Foger B, Chase M, Amar MJ, Vaisman BL, Shamburek RD, Paigen B, Fruchart-Najib J, Paiz JA, Koch CA, Hoyt RF, Brewer HB, Jr., Santamarina-Fojo S. Cholesteryl ester transfer protein corrects dysfunctional high density lipoproteins and reduces aortic atherosclerosis in lecithin cholesterol acyltransferase transgenic mice. J.Biol.Chem. 1999; 274:36912-36920.
154. Harder C, Lau P, Meng A, Whitman SC, McPherson R. Cholesteryl ester transfer protein (CETP) expression protects against diet induced atherosclerosis in SR-BI deficient mice. Arterioscler.Thromb.Vasc.Biol. 2007; 27:858-864.
155. Van Eck M, Hoekstra M, Hildebrand RB, Yaong Y, Stengel D, Kruijt JK, Sattler W, Tietge UJ, Ninio E, van Berkel TJ, Pratico D. Increased oxidative stress in scavenger receptor BI knockout mice with dysfunctional HDL. Arterioscler.Thromb.Vasc.Biol. 2007; 27:2413-2419.
156. Hayek T, Masucci-Magoulas L, Jiang X, Walsh A, Rubin E, Breslow JL, Tall AR. Decreased early atherosclerotic lesions in hypertriglyceridemic mice expressing cholesteryl ester transfer protein transgene. J.Clin.Invest. 1995; 96:2071-2074.
157. Cazita PM, Berti JA, Aoki C, Gidlund M, Harada LM, Nunes VS, Quintao EC, Oliveira HC. Cholesteryl ester transfer protein expression attenuates atherosclerosis in ovariectomized mice. J.Lipid Res. 2003; 44:33-40.
158. MacLean PS, Bower JF, Vadlamudi S, Osborne JN, Bradfield JF, Burden HW, Bensch WH, Kauffman RF, Barakat HA. Cholesteryl ester transfer protein expression prevents diet-induced atherosclerotic lesions in male db/db mice. Arterioscler.Thromb.Vasc.Biol. 2003; 23:1412-1415.
159. Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, Devchand P, Wahli W, Willson TM, Lenhard JM, Lehmann JM. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. Proc.Natl.Acad.Sci.U.S.A. 1997; 94:4318-4323.
160. Forman BM, Chen J, Evans RM. Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. Proc.Natl.Acad.Sci.U.S.A. 1997; 94:4312-4317.
161. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan receptors to drug discovery. J.Med.Chem. 2000; 43:527-550.
162. Beaven SW and Tontonoz P. Nuclear receptors in lipid metabolism: targeting the heart of dyslipidemia. Annu.Rev.Med. 2006; 57:313-29.:313-329.
163. Chen W, Wang LL, Liu HY, Long L, Li S. Peroxisome proliferator-activated receptor delta-agonist, GW501516, ameliorates insulin resistance, improves dyslipidaemia in monosodium L-glutamate metabolic syndrome mice. Basic Clin.Pharmacol.Toxicol. 2008; 103:240-246.
164. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. J.Clin.Invest. 2002; 109:1125-1131.

165. Joseph SB and Tontonoz P. LXRs: new therapeutic targets in atherosclerosis? Curr.Opin.Pharmacol. 2003; 3:192-197.
166. Edwards PA, Kast HR, Anisfeld AM. BAREing it all: the adoption of LXR and FXR and their roles in lipid homeostasis. J.Lipid Res. 2002; 43:2-12.
167. Terasaka N, Hiroshima A, Koieyama T, Ubukata N, Morikawa Y, Nakai D, Inaba T. T-0901317, a synthetic liver X receptor ligand, inhibits development of atherosclerosis in LDL receptor-deficient mice. FEBS Lett. 2003; 536:6-11.
168. Kovanen PT and Pentikainen MO. Pharmacological evidence for a role of liver X receptors in atheroprotection. FEBS Lett. 2003; 536:3-5.
169. Moreau A, Vilarem MJ, Maurel P, Pascussi JM. Xenoreceptors CAR and PXR activation and consequences on lipid metabolism, glucose homeostasis, and inflammatory response. Mol.Pharm. 2008; 5:35-41.
170. Endo A, Kuroda M, Tanzawa K. Competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by ML-236A and ML-236B fungal metabolites, having hypocholesterolemic activity. FEBS Lett. 1976; 72:323-326.
171. Istvan ES and Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. Science. 2001; 292:1160-1164.
172. Arad Y, Ramakrishnan R, Ginsberg HN. Effects of lovastatin therapy on very-low-density lipoprotein triglyceride metabolism in subjects with combined hyperlipidemia: evidence for reduced assembly and secretion of triglyceride-rich lipoproteins. Metabolism. 1992; 41:487-493.
173. Bilheimer DW, Grundy SM, Brown MS, Goldstein JL. Mevinolin and colestipol stimulate receptor-mediated clearance of low density lipoprotein from plasma in familial hypercholesterolemia heterozygotes. Proc.Natl.Acad.Sci.U.S.A. 1983; 80:4124-4128.
174. Le NA, Innis-Whitehouse W, Li X, Bakker-Arkema R, Black D, Brown WV. Lipid and apolipoprotein levels and distribution in patients with hypertriglyceridemia: effect of triglyceride reductions with atorvastatin. Metabolism. 2000; 49:167-177.
175. Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. JAMA. 2007; 298:786-798.
176. Lagrost L, Athias A, Lemort N, Richard JL, Desrumaux C, Chatenet-Duchene L, Courtois M, Farnier M, Jacotot B, Braschi S, Gambert P. Plasma lipoprotein distribution and lipid transfer activities in patients with type IIb hyperlipidemia treated with simvastatin. Atherosclerosis. 1999; 143:415-425.
177. Guerin M, Lassel TS, Le Goff W, Farnier M, Chapman MJ. Action of atorvastatin in combined hyperlipidemia : preferential reduction of cholesteryl ester transfer from HDL to VLDL1 particles. Arterioscler.Thromb.Vasc.Biol. 2000; 20:189-197.
178. Ahnadi CE, Berthezene F, Ponsin G. Simvastatin-induced decrease in the transfer of cholesterol esters from high density lipoproteins to very low and low density lipoproteins in normolipidemic subjects. Atherosclerosis 1993; 99:219-228.
179. Guerin M, Dolphin PJ, Talussot C, Gardette J, Berthezene F, Chapman MJ. Pravastatin modulates cholesteryl ester transfer from HDL to apoB-containing lipoproteins and lipoprotein subspecies profile in familial hypercholesterolemia. Arterioscler.Thromb.Vasc.Biol. 1995; 15:1359-1368.
180. Guerin M, Egger P, Soudant C, Le Goff W, Van Tol A, Dupuis R, Chapman MJ. Dose-dependent action of atorvastatin in type IIB hyperlipidemia: preferential and progressive reduction of atherogenic apoB-containing lipoprotein subclasses (VLDL-2, IDL, small dense LDL) and stimulation of cellular cholesterol efflux. Atherosclerosis. 2002; 163:287-296.

181. Davignon J and Laaksonen R. Low-density lipoprotein-independent effects of statins. Curr.Opin.Lipidol. 1999; 10:543-559.
182. Wilt TJ, Bloomfield HE, MacDonald R, Nelson D, Rutks I, Ho M, Larsen G, McCall A, Pineros S, Sales A. Effectiveness of statin therapy in adults with coronary heart disease. Arch.Intern.Med. 2004; 164:1427-1436.
183. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005; 366:1267-1278.
184. Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR. The role of fibrates in the prevention of cardiovascular disease--a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am.Heart J. 2007; 154:943-953.
185. Remick J, Weintraub H, Setton R, Offenbacher J, Fisher E, Schwartzbard A. Fibrate therapy: an update. Cardiol.Rev. 2008; 16:129-141.
186. Heller F and Harvengt C. Effects of clofibrate, bezafibrate, fenofibrate and probucol on plasma lipolytic enzymes in normolipaemic subjects. Eur.J.Clin.Pharmacol. 1983; 25:57-63.
187. Staels B, Vu-Dac N, Kosykh VA, Saladin R, Fruchart JC, Dallongeville J, Auwerx J. Fibrates downregulate apolipoprotein C-III expression independent of induction of peroxisomal acyl coenzyme A oxidase. A potential mechanism for the hypolipidemic action of fibrates. J.Clin.Invest. 1995; 95:705-712.
188. Malmendier CL, Lontie JF, Delcroix C, Dubois DY, Magot T, De Roy L. Apolipoproteins C-II and C-III metabolism in hypertriglyceridemic patients. Effect of a drastic triglyceride reduction by combined diet restriction and fenofibrate administration. Atherosclerosis. 1989; 77:139-149.
189. Schoonjans K, Staels B, Auwerx J. The peroxisome proliferator activated receptors (PPARS) and their effects on lipid metabolism and adipocyte differentiation. Biochim.Biophys.Acta. 1996; 1302:93-109.
190. Schoonjans K, Watanabe M, Suzuki H, Mahfoudi A, Krey G, Wahli W, Grimaldi P, Staels B, Yamamoto T, Auwerx J. Induction of the acyl-coenzyme A synthetase gene by fibrates and fatty acids is mediated by a peroxisome proliferator response element in the C promoter. J.Biol.Chem. 1995; 270:19269-19276.
191. Martin G, Schoonjans K, Lefebvre AM, Staels B, Auwerx J. Coordinate regulation of the expression of the fatty acid transport protein and acyl-CoA synthetase genes by PPARalpha and PPARgamma activators. J.Biol.Chem. 1997; 272:28210-28217.
192. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 1998; 98:2088-2093.
193. Birjmohun RS, Hutten BA, Kastelein JJ, Stroes ES. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. J.Am.Coll.Cardiol. 2005; 45:185-197.
194. Berthou L, Duverger N, Emmanuel F, Langouet S, Auwerx J, Guillouzo A, Fruchart JC, Rubin E, Denefle P, Staels B, Branellec D. Opposite regulation of human versus mouse apolipoprotein A-I by fibrates in human apolipoprotein A-I transgenic mice. J.Clin.Invest 1996; 97:2408-2416.
195. Guerin M, Bruckert E, Dolphin PJ, Turpin G, Chapman MJ. Fenofibrate reduces plasma cholesteryl ester transfer from HDL to VLDL and normalizes the atherogenic, dense LDL profile in combined hyperlipidemia. Arterioscler.Thromb.Vasc.Biol. 1996; 16:763-772.
196. Knopp RH. Drug treatment of lipid disorders. N.Engl.J.Med. 1999; 341:498-511.

197. Bays HE, Davidson M, Jones MR, Abby SL. Effects of colesevelam hydrochloride on low-density lipoprotein cholesterol and high-sensitivity C-reactive protein when added to statins in patients with hypercholesterolemia. Am.J.Cardiol. 2006; 97:1198-1205.
198. Hunninghake D, Insull W, Jr., Toth P, Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. Atherosclerosis. 2001; 158:407-416.
199. Altmann SW, Davis HR, Jr., Zhu LJ, Yao X, Hoos LM, Tetzloff G, Iyer SP, Maguire M, Golovko A, Zeng M, Wang L, Murgolo N, Graziano MP. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science. 2004; 303:1201-1204.
200. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N.Engl.J.Med. 2008; 358:1431-1443.
201. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR, Jr., Bangdiwala S, Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989; 79:8-15.
202. Shepherd J, Packard CJ, Patsch JR, Gotto AM, Jr., Taunton OD. Effects of nicotinic acid therapy on plasma high density lipoprotein subfraction distribution and composition and on apolipoprotein A metabolism. J.Clin.Invest. 1979; 63:858-867.
203. Paolini JF, Mitchel YB, Reyes R, Kher U, Lai E, Watson DJ, Norquist JM, Meehan AG, Bays HE, Davidson M, Ballantyne CM. Effects of laropiprant on nicotinic acid-induced flushing in patients with dyslipidemia. Am.J.Cardiol. 2008; 101:625-630.
204. Bodor ET and Offermanns S. Nicotinic acid: an old drug with a promising future. Br.J.Pharmacol. 2008; 153 Suppl 1:S68-75.
205. Jin FY, Kamanna VS, Kashyap ML. Niacin accelerates intracellular ApoB degradation by inhibiting triacylglycerol synthesis in human hepatoblastoma (HepG2) cells. Arterioscler.Thromb.Vasc.Biol. 1999; 19:1051-1059.
206. Ganji SH, Tavintharan S, Zhu D, Xing Y, Kamanna VS, Kashyap ML. Niacin noncompetitively inhibits DGAT2 but not DGAT1 activity in HepG2 cells. J.Lipid Res. 2004; 45:1835-1845.
207. Hernandez M, Wright SD, Cai TQ. Critical role of cholesterol ester transfer protein in nicotinic acid-mediated HDL elevation in mice. Biochem.Biophys.Res.Commun. 2007; 355:1075-1080.
208. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J.Am.Coll.Cardiol. 1986; 8:1245-1255.
209. Wang X, Driscoll DM, Morton RE. Molecular cloning and expression of lipid transfer inhibitor protein reveals its identity with apolipoprotein F. J.Biol.Chem. 1999; 274:1814-1820.
210. He Y, Greene DJ, Kinter M, Morton RE. Control of cholesteryl ester transfer protein activity by sequestration of lipid transfer inhibitor protein in an inactive complex. J.Lipid Res. 2008; 49:1529-1537.
211. Gaynor BJ, Sand T, Clark RW, Aiello RJ, Bamberger MJ, Moberly JB. Inhibition of cholesteryl ester transfer protein activity in hamsters alters HDL lipid composition. Atherosclerosis. 1994; 110:101-109.
212. Whitlock ME, Swenson TL, Ramakrishnan R, Leonard MT, Marcel YL, Milne RW, Tall AR. Monoclonal antibody inhibition of cholesteryl ester transfer protein activity

in the rabbit. Effects on lipoprotein composition and high density lipoprotein cholesteryl ester metabolism. J.Clin.Invest. 1989; 84:129-137.
213. Abbey M and Calvert GD. Effects of blocking plasma lipid transfer protein activity in the rabbit. Biochim.Biophys.Acta. 1989; 1003:20-29.
214. Sugano M and Makino N. Changes in plasma lipoprotein cholesterol levels by antisense oligodeoxynucleotides against cholesteryl ester transfer protein in cholesterol-fed rabbits. J.Biol.Chem. 1996; 271:19080-19083.
215. Sugano M, Makino N, Sawada S, Otsuka S, Watanabe M, Okamoto H, Kamada M, Mizushima A. Effect of antisense oligonucleotides against cholesteryl ester transfer protein on the development of atherosclerosis in cholesterol-fed rabbits. J.Biol.Chem. 1998; 273:5033-5036.
216. Rittershaus CW, Miller DP, Thomas LJ, Picard MD, Honan CM, Emmett CD, Pettey CL, Adari H, Hammond RA, Beattie DT, Callow AD, Marsh HC, Ryan US. Vaccine-induced antibodies inhibit CETP activity in vivo and reduce aortic lesions in a rabbit model of atherosclerosis. Arterioscler.Thromb.Vasc.Biol. 2000; 20:2106-2112.
217. Okamoto H, Yonemori F, Wakitani K, Minowa T, Maeda K, Shinkai H. A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits. Nature. 2000; 406:203-207.
218. Huang Z, Inazu A, Nohara A, Higashikata T, Mabuchi H. Cholesteryl ester transfer protein inhibitor (JTT-705) and the development of atherosclerosis in rabbits with severe hypercholesterolaemia. Clin.Sci.(Lond). 2002; 103:587-594.
219. Clark RW, Ruggeri RB, Cunningham D, Bamberger MJ. Description of the torcetrapib series of cholesteryl ester transfer protein inhibitors, including mechanism of action. J.Lipid Res. 2006; 47:537-552.
220. Morehouse LA, Sugarman ED, Bourassa PA, Sand TM, Zimetti F, Gao F, Rothblat GH, Milici AJ. Inhibition of CETP activity by torcetrapib reduces susceptibility to diet-induced atherosclerosis in New Zealand White rabbits. J.Lipid Res. 2007; 48:1263-1272.
221. de Grooth GJ, Kuivenhoven JA, Stalenhoef AF, de Graaf J, Zwinderman AH, Posma JL, Van Tol A, Kastelein JJ. Efficacy and safety of a novel cholesteryl ester transfer protein inhibitor, JTT-705, in humans: a randomized phase II dose-response study. Circulation 2002; 105:2159-2165.
222. Clark RW, Sutfin TA, Ruggeri RB, Willauer AT, Sugarman ED, Magnus-Aryitey G, Cosgrove PG, Sand TM, Wester RT, Williams JA, Perlman ME, Bamberger MJ. Raising high-density lipoprotein in humans through inhibition of cholesteryl ester transfer protein: an initial multidose study of torcetrapib. Arterioscler.Thromb.Vasc.Biol. 2004; 24:490-497.
223. Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, Clark RW, Mancuso JP, Rader DJ. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. N.Engl.J.Med. 2004; 350:1505-1515.
224. Brousseau ME, Diffenderfer MR, Millar JS, Nartsupha C, Asztalos BF, Welty FK, Wolfe ML, Rudling M, Bjorkhem I, Angelin B, Mancuso JP, Digenio AG, Rader DJ, Schaefer EJ. Effects of cholesteryl ester transfer protein inhibition on high-density lipoprotein subspecies, apolipoprotein A-I metabolism, and fecal sterol excretion. Arterioscler.Thromb.Vasc.Biol. 2005; 25:1057-1064.
225. Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ, Revkin JH, Grobbee DE, Riley WA, Shear CL, Duggan WT, Bots ML. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. N.Engl.J.Med. 2007; 356:1620-1630.

226. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, Ruzyllo W, Bachinsky WB, Lasala GP, Tuzcu EM. Effect of torcetrapib on the progression of coronary atherosclerosis. N.Engl.J.Med. 2007; 356:1304-1316.
227. Bots ML, Visseren FL, Evans GW, Riley WA, Revkin JH, Tegeler CH, Shear CL, Duggan WT, Vicari RM, Grobbee DE, Kastelein JJ. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. Lancet. 2007; 370:153-160.
228. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B. Effects of torcetrapib in patients at high risk for coronary events. N.Engl.J.Med. 2007; 357:2109-2122.
229. Krishna R, Anderson MS, Bergman AJ, Jin B, Fallon M, Cote J, Rosko K, Chavez-Eng C, Lutz R, Bloomfield DM, Gutierrez M, Doherty J, Bieberdorf F, Chodakewitz J, Gottesdiener KM, Wagner JA. Effect of the cholesteryl ester transfer protein inhibitor, anacetrapib, on lipoproteins in patients with dyslipidaemia and on 24-h ambulatory blood pressure in healthy individuals: two double-blind, randomised placebo-controlled phase I studies. Lancet. 2007; 370:1907-1914.