British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2012.02081.x
www.brjpharmacol.org

REVIEW

Cardiovascular disease risk reduction by raising HDL cholesterol – current therapies and future opportunities

K Mahdy Ali[1,4]*, A Wonnerth[1]*, K Huber[2] and J Wojta[1,3]

[1]*Department of Internal Medicine II, Medical University of Vienna,* [2]*3rd Medical Department for Cardiology and Emergency Medicine, Wilhelminenhospital,* [3]*Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, and* [4]*Department of Neurosurgery, Medical University of Graz, Graz, Austria*

Correspondence
Johann Wojta, Department of Internal Medicine II, Medical University of Vienna, Waehringer-Guertel 18-20, A-1090 Vienna, Austria. E-mail: johann.wojta@meduniwien.ac.at

*Both authors contributed equally to this review.

Keywords
High-density lipoprotein; function/dysfunction; coronary artery disease; pharmacology; niacin; fibrate; statin; cholesterol ester transfer protein (CETP); PPAR agonist; liver X-receptor agonist

Received
9 March 2012
Revised
31 May 2012
Accepted
4 June 2012

Since the first discovery of an inverse correlation between high-density lipoprotein-cholesterol (HDL-C) levels and coronary heart disease in the 1950s the life cycle of HDL, its role in atherosclerosis and the therapeutic modification of HDL-C levels have been major research topics. The Framingham study and others that followed could show that HDL-C is an independent cardiovascular risk factor and that the increase of HDL-C of only 10 mg·L^{-1} leads to a risk reduction of 2–3%. While statin therapy and therefore low-density lipoprotein-cholesterol (LDL-C) reduction could lower coronary heart disease considerably; cardiovascular morbidity and mortality still occur in a significant portion of subjects already receiving therapy. Therefore, new strategies and therapies are needed to further reduce the risk. Raising HDL-C was thought to achieve this goal. However, established drug therapies resulting in substantial HDL-C increase are scarce and their effect is controversial. Furthermore, it is becoming increasingly evident that HDL particle functionality is at least as important as HDL-C levels since HDL particles not only promote reverse cholesterol transport from the periphery (mainly macrophages) to the liver but also exert pleiotropic effects on inflammation, haemostasis and apoptosis. This review deals with the biology of HDL particles, the established and future therapeutic options to increase HDL-C and discusses the results and conclusions of the most important studies published in the last years. Finally, an outlook on future diagnostic tools and therapeutic opportunities regarding coronary artery disease is given.

Abbreviations

ABCA, ATP-binding cassette transporter A; ABCG, ATP-binding cassette transporter G; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; ApoC, apolipoprotein C; ApoC-III, apolipoprotein C-III; ApoE, apolipoprotein E; CAD, coronary artery disease; CETP, cholesterol ester transfer protein; CHD, coronary heart disease; CRP, C-reactive protein; FFA, free fatty acid; HDL(-C), high-density lipoprotein(-cholesterol); ICAM-1, intercellular cell adhesion molecule-1; IMT, intima-media thickness; IVUS, intravascular ultrasound; LCAT, lecithin-cholesterol acyltransferase; LDL(-C), low-density lipoprotein (-cholesterol); Lp(a), lipoprotein (a); LXR, liver X-receptor; LXRE, liver X-receptor response element; MCP-1, monocyte chemoattractant protein-1; MI, myocardial infarction; MPO, myeloperoxidase; NPC1, Niemann–Pick C1; NPC1L1, Niemann–Pick C1 like protein 1; oxLDL, oxidized low-density lipoprotein; PD1.prostaglandin D2 receptor subtype 1; PON1, paraoxonase-1; RCT, reverse cholesterol transfer; rHDL, reconstituted high-density lipoprotein; RXR, retinoid X-receptor; SR-BI, scavenger-receptor B-I; TC, total cholesterol; TG, triglyceride; TRL.TG-rich lipoprotein; TZD, thiazolidinediones; VCAM-1, vascular cell adhesion molecule-1; VLDL(-C), very low-density lipoprotein (-cholesterol)

Introduction

Coronary artery disease (CAD) is one of the major causes of death, worldwide (Yusuf *et al.*, 2001). Dyslipidaemia is characterized by elevated low-density lipoprotein cholesterol (LDL-C) and decreased high-density lipoprotein cholesterol (HDL-C) and is a known risk factor for development and progression of atherosclerosis in CAD (Arca *et al.*, 2007). In the past, therapeutic strategies were focused on lowering LDL-C, primarily by the use of statins. However, as CAD events seem not to be satisfyingly prevented by current treatment schemes (LaRosa *et al.*, 1999), therapeutic options to increase HDL-C stepped into spotlight, recently.

The role of HDL in atherosclerosis

Since the middle of the 20th century, research has been engaged with lipoproteins in health and in disease. In 1977, the Framingham study was the first large-scale study giving evidence that low levels of HDL-C is a major risk factor for CAD. The association between the incidence of CAD and HDL-C levels was stronger than for LDL levels (Gordon *et al.*, 1977). In a later re-evaluation of this same study, which included follow-up data of 12 years, low HDL-C levels were even associated with increased mortality (Wilson *et al.*, 1988). Jenkins *et al.* confirmed the correlation between HDL-C levels and CAD observed in epidemiological studies by performing coronary angiographies and found a significant association between HDL-C levels and the severity of atherosclerosis (Jenkins *et al.*, 1978). Some years later, Gordon *et al.* noted a 2–3% decrease in CAD risk with each increase by 10 $mg \cdot L^{-1}$ in HDL-C (Gordon *et al.*, 1989). A recent meta-analysis, including 302.430 subjects from 68 long-term prospective studies, supported the importance of HDL-C measurement in the risk assessment for CAD (Di Angelantonio *et al.*, 2009).

HDL metabolism and its atheroprotective properties

High-density lipoproteins are a heterogeneous group of particles that differ in size, shape, density, cholesterol and phospholipid content, as well as in apolipoprotein composition. The life cycle of HDL begins with apolipoprotein A-I (ApoA-I) being secreted by the liver. As ApoA-I binds circulating phospholipids and cholesterol, nascent discoid lipid-poor HDL particles are formed. These immature HDL particles trigger cholesterol efflux in subendothelial macrophages and fibroblasts and, via interactions with ATP-binding cassette transporter A1 (ABCA1), store the cholesterol in their core, after esterification by lecithin-cholesterol acyltransferase (LCAT). Such HDL particles obtain a spheric shape, resulting in the two main mature particles, HDL2 and HDL3. Subsequently, HDL deliver their cholesterol load either directly to the liver via scavenger-receptor B-I (SR-BI) or indirectly by shifting cholesterol to very low-density lipoprotein (VLDL) or LDL particles, which in turn are taken up by the liver via the LDL-receptor. This shift is carried out by cholesterol ester transfer protein (CETP), a protein associated with HDL. Either way, cholesterol finally gets excreted into the feces as neutral steroids or bile acids.

This process of cholesterol clearance was named 'reverse cholesterol transfer' (RCT) and has been the explanation for HDL's association with atheroprotection for a long time.

However, other anti-atherosclerotic properties of HDL have been discovered in recent years.

Anti-inflammatory effects of HDL

Atherosclerosis is an inflammatory disease. Adhesion and migration of immune cells into the vessel wall, as well as inflammatory cytokines and chemokines orchestrating these processes are essential (Ross, 1999b). *In vitro* studies have shown that HDL inhibits the expression of endothelial adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin (Cockerill *et al.*, 1995; 1999; Baker *et al.*, 1999). However, these observations could not be repeated in human aortic and coronary artery endothelial cells (Stannard *et al.*, 2001; Zhang *et al.*, 2002). Another anti-inflammatory effect of HDL is the inhibition of monocyte chemoattractant protein-1 (MCP-1) production, as demonstrated in human endothelial cells as well as murine vascular smooth muscle cells from the aorta (Mackness *et al.*, 2004; Tolle *et al.*, 2008). *In vivo* studies could confirm some of these *in vitro* observations. (Cockerill *et al.*, 2001) Nicholls *et al.* inserted a non-occlusive collar around carotid arteries in rabbits to imitate carotid stenosis and infused reconstituted HDL (rHDL). The treatment with rHDL resulted in the inhibition of VCAM-1, ICAM-1 and MCP-1 production, as well as in inhibition of leukocyte infiltration and the abolishment of reactive oxygen species production in the artery wall (Nicholls *et al.*, 2005).

Antioxidant effects of HDL

Oxidation of LDL in the arterial wall is one of the most crucial steps in the development of atherosclerotic lesions (Ross, 1999a). HDL is associated with several antioxidant enzymes, such as paraoxonase, platelet-activating factor acetylhydrolase, LCAT and reduced glutathione selenoperoxidase. In healthy subjects, HDL is able to inhibit the formation of mildly oxidized LDL (oxLDL). On the other hand, lipid hydroperoxides can be transfered from oxLDL to HDL by CETP. This oxidized HDL was shown to be cleared rapidly from circulation. Thus, HDL seems to be important for the physiological detoxification of oxLDL, as well (Garner *et al.*, 1998). However, HDL of patients with CAD seems to lack this ability (Navab *et al.*, 2000; 2001).

Anti-apoptotic effects of HDL

Cell death in response to endothelial injury is a constant process in atherosclerosis. The main stimulants are oxLDL, proinflammatory cytokines, as well as growth factor deprivation. In bovine aortic endothelial cells, Suc *et al.* demonstrated that HDL, especially ApoA-I, is able to prevent oxLDL-induced apoptosis by blocking intracellular signalling involved in apoptosis (Suc *et al.*, 1997). In other studies, TNF-α-induced apoptosis, as well as apoptosis induced by growth

factor deprivation, could be avoided by incubating the endothelial cells with HDL (Sugano *et al.*, 2000; Nofer *et al.*, 2001).

Anti-thrombotic effects of HDL

HDL seems to be implicated in haemostasis. On the one hand, it is able to regulate platelet adhesion by inhibiting platelet activation and aggregation (Conlan *et al.*, 1993; Cockerill *et al.*, 1999; Nofer *et al.*, 2010). On the other hand, HDL influences plasmatic coagulation. It was shown to inhibit thrombin-induced tissue factor expression in human endothelial cells (Viswambharan *et al.*, 2004), to inhibit the activation of factor X (Carson, 1981), and to enhance the activities of activated protein C and protein S, two important anticoagulants (Griffin *et al.*, 1999).

HDL composition in health and in disease

Despite all the earlier-mentioned findings, it was recently shown that HDL may malfunction in chronic inflammation (Natarajan *et al.*, 2010; Saemann *et al.*, 2010). As HDL particles are heterogeneous in their composition, scientists have questioned whether the observed impairment is due to a difference in protein assembly from one individual to another. Using shotgun proteomics, Vaisar *et al.* identified 48 HDL-associated proteins of which only 22 were linked to cholesterol and lipoprotein metabolism whereas 23 were linked to acute phase-response proteins and 3 to complement activation. Interestingly, HDL particles of healthy individuals differed in their composition with those of patients with CAD. Furthermore, HDL particles isolated from atherosclerotic lesions were very similar to the ones isolated from CAD patients' plasma (Vaisar *et al.*, 2007). Changes in HDL composition and function were also observed in other diseases. HDL of patients with diabetes, rheumatoid arthritis or chronic kidney disease displayed reduced antioxidant and anti-inflammatory properties as well as an altered protein cargo (Saemann *et al.*, 2010; Holzer *et al.*, 2011; Tolle *et al.*, 2012).

A very recently published work by Kar *et al.* demonstrates the ability of oxidized phosphlipids (Ox-PL) to destabilize HDL particles and alter their function. Furthermore, they could show that reconstituted HDL particles with high amounts of Ox-PL had less capacity to stimulate paraoxonase 1 (PON1), a protein that plays an integral role in the stimulation of reverse cholesterol transport from macrophages to HDL particles (Berrougui *et al.*, 2012; Kar *et al.*, 2012).

Established drug therapies

Statins

Statins (hydroxymethyl-glutaryl-coenzyme A reductase inhibitors) are the standard therapy in primary and secondary cardiovascular prevention. According to the Treating to New Targets (TNT) trial, high-dose treatment along with treatment goals of LDL-C below 1000 $mg \cdot L^{-1}$ are believed to achieve the best results in risk reduction (LaRosa *et al.*, 2005). High-dose statins are even beneficial in patients with normal LDL-C levels at baseline (Ridker *et al.*, 2009). In addition to effectively reducing LDL-C, statins are also able to increase HDL-C by 6–14.7% (Downs *et al.*, 1998; Simes *et al.*, 2002; Streja *et al.*, 2002; Athyros *et al.*, 2004; Nissen *et al.*, 2006).

Recently, a meta-analysis of 37 randomized studies, including 32 258 dyslipidemic patients, investigated the effect of statins on HDL-C. It was shown that all statins significantly raise HDL-C levels, Athough in a dose-dependent manner and not each statin to the same extent. Interestingly, changes in LDL-C and HDL-C concentrations were statistically independent from each other, no matter which statin was used (Barter *et al.*, 2010). However, the clinical importance of HDL-C concentrations in patients on statins is controversially discussed.

Some studies published data in favour of HDL-C and its role in disease prevention. In the GREACE study, a mean 3 year therapy with atorvastatin increased HDL-C by 7% and a hazard ratio of 0.85 for every 40 $mg \cdot L^{-1}$ (0.1 $mmol \cdot L^{-1}$) increase was calculated, independent of LDL-C lowering (Athyros *et al.*, 2004). It is important to mention though that this study was planned in a 'Real Life' setting. Thus, the group receiving atorvastatin was treated in cardiology clinics whereas the control group was treated by general practitioners according to 'usual' medical care. In ASTEROID, rosuvastatin therapy led to an HDL-C increase of 14.7% accompanied by a significant regression in atherosclerosis. However, LDL-C was simultaneously reduced by 53.2% and no information was given whether LDL-C and HDL-C had an independent impact. (Nissen *et al.*, 2006)

Conversely, results of the primary prevention trial JUPITER showed no predictive power of HDL-C for the end points first non-fatal myocardial infarction (MI) and stroke in patients already on a high-dose statin treatment. Consequently, the authors, although still supporting HDL-C measurements in the initial risk assessment, question the necessity of measurements during adequate statin therapy (Ridker *et al.*, 2010). However, critics point out that HDL-C levels at baseline have been quite high in the JUPITER population. Referring to results from the VOYAGER meta-analysis, saying that the extent of HDL-C increase is dependent on HDL-C levels at baseline (low HDL-C levels are associated with a higher increase during statin treatment) the observations made in JUPITER could therefore lead to false conclusions (Barter *et al.*, 2010).

Niacin

Niacin (nicotinic acid) is the oldest and most effective agent in increasing HDL-C. Discovered in the 1950s (Altschul *et al.*, 1955), it caught interest primarily because of its ability to decrease LDL-C, but with the implementation of statin therapy in standard care, it slowly disappeared. Decades later, niacin reappeared in clinical use as a potential substance to increase HDL-C. Many clinical trials have been evaluating its benefit on atherosclerotic disease, in monotherapy or in combination with other drugs. However, these trials were rather small.

The Coronary Drug Project assessed niacin monotherapy in a randomized, placebo-controlled clinical trial in 3906 patients with previous MI. Niacin was shown to decrease the

occurrence of MI at 6 years (The Coronary Drug Project Research Group, 1975) as well as total mortality at 15 years significantly (Canner *et al.*, 1986).

In the Cholesterol Lowering Atherosclerosis Study, niacin was combined with colestipol, a bile-acid sequestrant, and change in atherosclerosis was quantified by coronary angiography in 162 men with previous coronary bypass surgery. After 2 years, drug-treated subjects showed a 37% increase in HDL-C levels, a 43% reduction in LDL-C and a 26% reduction in total cholesterol (TC). Atherosclerosis regression was seen in significantly more drug-treated than in placebo-treated subjects (Blankenhorn *et al.*, 1987). At 4 years, these results remained significant. Furthermore, significantly fewer drug-treated subjects developed new lesions in native coronary arteries and bypass grafts. (Cashin-Hemphill *et al.*, 1990)

The combination of niacin with statin therapy was evaluated in HATS and the ARBITER studies. The first included 180 patients with CAD, normal LDL-C and low HDL-C levels. After 3 years, the combination of simvastatin and niacin compared with placebo lead to a significant regression of coronary stenosis. LDL-C was reduced by 42% and HDL-C increased by 26% (Brown *et al.*, 2001). The ARBITER 2 study included 167 patients with the same characteristics, but already on a current statin therapy and either niacin or placebo was added for 1 year. The primary endpoint was change in carotid intima-media thickness (IMT). In the niacin group, HDL-C increased by 21%. The placebo group had a significant increase in IMT, whereas the IMT of niacin-treated patients remained the same. However, there was no significant overall difference in IMT progression between the two groups (Taylor *et al.*, 2004). As the ARBITER group did not want to dismiss on niacin, a subsequent study followed, in which a longer treatment period was tested (ARBITER 3). After 2 years of application, niacin-treated patients presented with a significant regression of IMT compared with the placebo group, and changes in HDL-C were independently associated with this arterial improvement (Taylor *et al.*, 2006). Recently, the same group published the results of the ARBITER 6 study, which compared treatment with niacin versus ezetimibe added to a background statin therapy. Once again, niacin could prove its ability to significantly reduce IMT, whereas ezetimibe could not. (Villines *et al.*, 2010)

The large-scale AIM-HIGH trial was scheduled to present further results regarding the effect of niacin plus statin on therapy of cardiovascular disease in 2012; however, the study was terminated prematurely due to a lack of effect (more on that in the conclusions section; Brown, 2005).

In 2010, a meta-analysis of 11 randomized controlled trials, also including the ones mentioned earlier, evaluated the influence of niacin therapy on cardiovascular outcome. A therapeutic strategy including niacin was shown to significantly reduce major coronary events by 25%, stroke by 26%, and all cardiovascular events by 27%. Unfortunately, due to lack of well-powered studies on niacin monotherapy, the effect of niacin alone could not be assessed (Bruckert *et al.*, 2010).

While two receptors for niacin were discovered a few years ago (HM74 and HM74A), it is not quite clear how niacin leads to an increase in HDL-C levels. Various theories have been discussed (Soudijn *et al.*, 2007). One rationale is based on niacin influencing CETP (Hernandez *et al.*, 2007; van der Hoorn *et al.*, 2008), supported by the observation of an inverse correlation between trigyleride (TG) levels and HDL-C levels (Geurian *et al.*, 1992). Another one is based on niacin's inhibitory involvement in HDL-C catabolism (Shepherd *et al.*, 1979; Bodor and Offermanns, 2008). At last, niacin was also shown to have pleiotropic effects apart from lipid modification, such as increasing the expression of PPAR-γ in macrophages and the endothelium (Vosper, 2009b).

Niacin has one significant flaw causing prostaglandin-mediated vasodilation, a phenomenon called flushing (Kamanna *et al.*, 2009). This skin reaction makes the implementation of niacin in patient care very difficult as it leads to low compliance and treatment discontinuation. A promising strategy to avoid flushing without altering niacin's impact on lipid metabolism is the combination with an antagonist of the prostaglandin D2 receptor subtype 1 (PD1), that is laropiprant (Parhofer, 2009). In 2008, Merck's Tredaptive™, which combines extended-release niacin with laropiprant, has been approved for marketing in the European Union, Iceland and Norway, but failed to enter the US market (known as Cordaptive™ in the United States). The randomized, placebo-controlled, double-blind study HPS2-THRIVE due in 2013 will hopefully provide answers on the efficacy and safety of niacin plus laropiprant in cardiovascular disease (Armitage *et al.*, 2007).

Fibrates

Fibrates (fibric acid derivates) are synthetic ligands for PPAR-α. The hallmarks of fibrate therapy are a substantial decrease of plasma TG levels ranging from 30 to 50% and a moderate increase of HDL-C levels ranging from 5 to 15% (Goldenberg *et al.*, 2008).

Activation of PPAR-α leads to β-oxidation of free fatty acids (FFA) in the liver reducing the availability of fatty acids for VLDL synthesis and secretion. Furthermore, the expression of the gene coding for lipoprotein lipase is increased and apolipoprotein C-III (ApoC-III) expression in the liver is decreased. This leads to a reduced synthesis and simultaneously increased hydrolysis of triglyceride-rich lipoproteins. HDL-C increase results from raising the expression of apolipoproteins A-I and A-II decreasing CETP-mediated transfer of cholesterol from HDL to VLDL and enhancing cell cholesterol efflux via the induction of ABCA 1 and the decrease of SR-B1 in the liver (Berger *et al.*, 2005; Farnier, 2008).

Fibrates also reduce plasma LDL-C levels. This effect, however, is variable. A considerably more important effect on LDL is the ability to change particle size from smaller, more atherogenic particles to larger, less atherogenic particles. (Goldenberg *et al.*, 2008)

Besides the effects on the lipid profile, fibrates also exert other pleiotropic functions via PPAR-α by modulating platelet aggregation and endothelial dysfunction as well as by acting anti-inflammatory through the inhibition of the transcription factor NF-κB, thereby reducing levels of IL-6 and C-reactive protein (CRP). Furthermore, fibrates have been shown to reduce levels of fibrinogen and to increase fibrinolysis (Goldenberg *et al.*, 2008; Moutzouri *et al.*, 2010).

Fibrates have been in use for over four decades, with clofibrate being the first fibrate used in the clinical setting. However, a trial conducted by the World Health Organization

revealed increased mortality rates in patients treated with clofibrate (Report from the Committee of Principal Investigators, 1978).

Although all fibrates have been shown to increase HDL-C significantly, their beneficial effect on all-cause mortality and cardiac mortality remains controversial (Saha *et al.*, 2007).

In the Helsinki Heart Study, a placebo-controlled study including over 4000 men, gemfibrozil was able to raise HDL-C levels by 11%. The incidence of coronary heart disease (CHD) after 5 years was reduced by 34%, non-fatal MI was reduced by 37%. All-cause mortality remained unchanged after 5 years as well as after 18 years of follow-up (Frick *et al.*, 1987; Tenkanen *et al.*, 2006). In the Veterans Affairs HDL Intervention Trial, 2531 men with established CHD and low HDL-C (<400 mg·L^{-1}) were randomized to gemfibrozil or placebo. HDL-C levels were increased by 6%, but more strikingly the risk for non-fatal MI or CHD mortality decreased by 22% (Rubins *et al.*, 1999).

In the Bezafibrate Infarction Prevention study, 3090 patients were randomized to bezafibrate or placebo. HDL-C increased by 14% in those receiving bezafibrate but the coronary event rate could not be reduced significantly. *Post hoc* analysis, however, revealed that in some subgroups bezafibrate therapy could influence the outcome beneficially: patients with high baseline triglyceride levels (>2000 mg·L^{-1}) showed a 39.2% reduction in the cumulative probability of the primary end points CHD mortality and non-fatal MI. In a long-term follow-up, cardiac mortality was significantly reduced dependent on the magnitude of change in HDL-C levels. Especially patients with metabolic syndrome benefited from bezafibrate showing a 56% reduction of cardiac mortality during an 8 year follow-up. In addition, bezafibrate was able to significantly delay onset of diabetes (Goldenberg *et al.*, 2008).

The newest fibrate to be admitted to the market, fenofibrate, has been studied extensively. In the largest trial, the-FIELD trial, 9795 diabetic patients were randomized to micronized fenofibrate or placebo. HDL-C increased only moderately in those treated with fenofibrate, albeit the difference to those receiving placebo was significant. The investigators of the FIELD study could detect a significant decrease of non-fatal MI in fenofibrate-treated patients, but the primary composite end point, CHD death, was not different in the two groups. However, total cardiovascular disease events decreased significantly in the fenofibrate treatment arm (Keech *et al.*, 2005; Abourbih *et al.*, 2009; Moutzouri *et al.*, 2010).

Recently, results from the ACCORD lipid study led to similar conclusions; 5518 patients with type 2 diabetes, who were treated with open-label simvastatin, were assigned to either fenofibrate or placebo. After a mean follow-up of 4.7 years, no significant difference in secondary outcome (non-fatal MI, non-fatal stroke, cardiovascular death) could be observed. Consequently, the routine use of fenofibrate in combination with simvastatin to reduce cardiovascular risk in high-risk patients with type 2 diabetes could not be recommended by the ACCORD study group. (Ginsberg *et al.*, 2010; Tenenbaum and Fisman, 2010)

In conclusion, different types of fibrates have been under evaluation up until now. While some were shown to be potent agents in the treatment for dyslipidaemia in cardiovascular disease, others failed to do so and cannot be recommended in standard care. In general, fibrates were shown to be more potent in triglyceride reduction than in alteration of HDL-C and LDL-C levels. Therefore, fibrates should mostly be used in treatment of patients with hypertriglyceridaemia and low HDL-C levels, which is a common feature in type 2 diabetes and the metabolic syndrome (Figure 1).

Future therapeutic options

PPAR agonists

PPAR-α, -γ and -δ play essential roles in glucose and lipid metabolism. Regarded as 'master' transcriptional regulators of nutrient metabolism, these three nuclear receptors form heterodimers with the retinoid X-receptor (RXR) and bind to peroxisome proliferator responsive elements (Berger *et al.*, 2005; Ogata *et al.*, 2009).

PPAR-α is found mainly in the liver, kidney, heart and skeletal muscle. It up-regulates genes responsible for the oxidation of fatty acids, lipolysis and HDL metabolism while down-regulating VLDL synthesis and cholesterol esterification and inhibiting inflammation (Ogata *et al.*, 2009).

PPAR-γ is present in adipocytes, skeletal muscle, the heart and monocytes. It plays an important role in adipocyte differentiation and lipid storage and improves insulin sensitivity. PPAR-γ activation increases lipid uptake into the adipose tissue, thus attenuating lipolysis and FFA release leading to a decline in circulating FFAs. Activation also leads to reduced pro-inflammatory cytokine and chemokine levels. In macrophages activation induces lipid efflux while in vitro vascular smooth muscle cell proliferation was blocked and apoptosis was increased. (Berger *et al.*, 2005; Ogata *et al.*, 2009)

The mechanism of action for PPAR-δ is less elucidated. Expressed ubiquitously, this receptor seems to protect against hyperlipidaemia and obesity while also acting anti-inflammatorily (Berger *et al.*, 2005; Ogata *et al.*, 2009).

All three receptors increase transcription of ABCA1, which mediates the efflux of cholesterol from cells to nascent HDL particles (Ogata *et al.*, 2009).

Interestingly, all PPARs are dependent on the PPAR-α promoter activity and the liver X-receptor (LXR) to exert their actions. siRNA mediated downregulation of LXRα was shown to attenuate any effects of PPAR agonists. In PPAR-α (–/–) cells, the effects of PPAR agonists were reduced while the effect was completely abolished when the PPAR-α promoter was mutated (Ogata *et al.*, 2009).

There are several drugs acting as PPAR agonists to increase HDL-C. Some of them are in use for decades such as fibric acid derivatives while the effect of others such as thiazolidinediones (TZDs) or dual PPAR-α/γ agonists, PPAR-δ agonists and novel PPAR-α agonists are controversial or are currently under investigation, respectively.

PPAR-α agonists. In recent years the mechanisms of action and the binding specificities of fibrates to PPARs have been uncovered. While fibrates mainly bind to PPAR-α, most fibrates were also found to bind to at least PPAR-γ as well, which might explain the delay of onset of diabetes caused by bezafibrate in the BIP study (via the insulin sensitizing ability

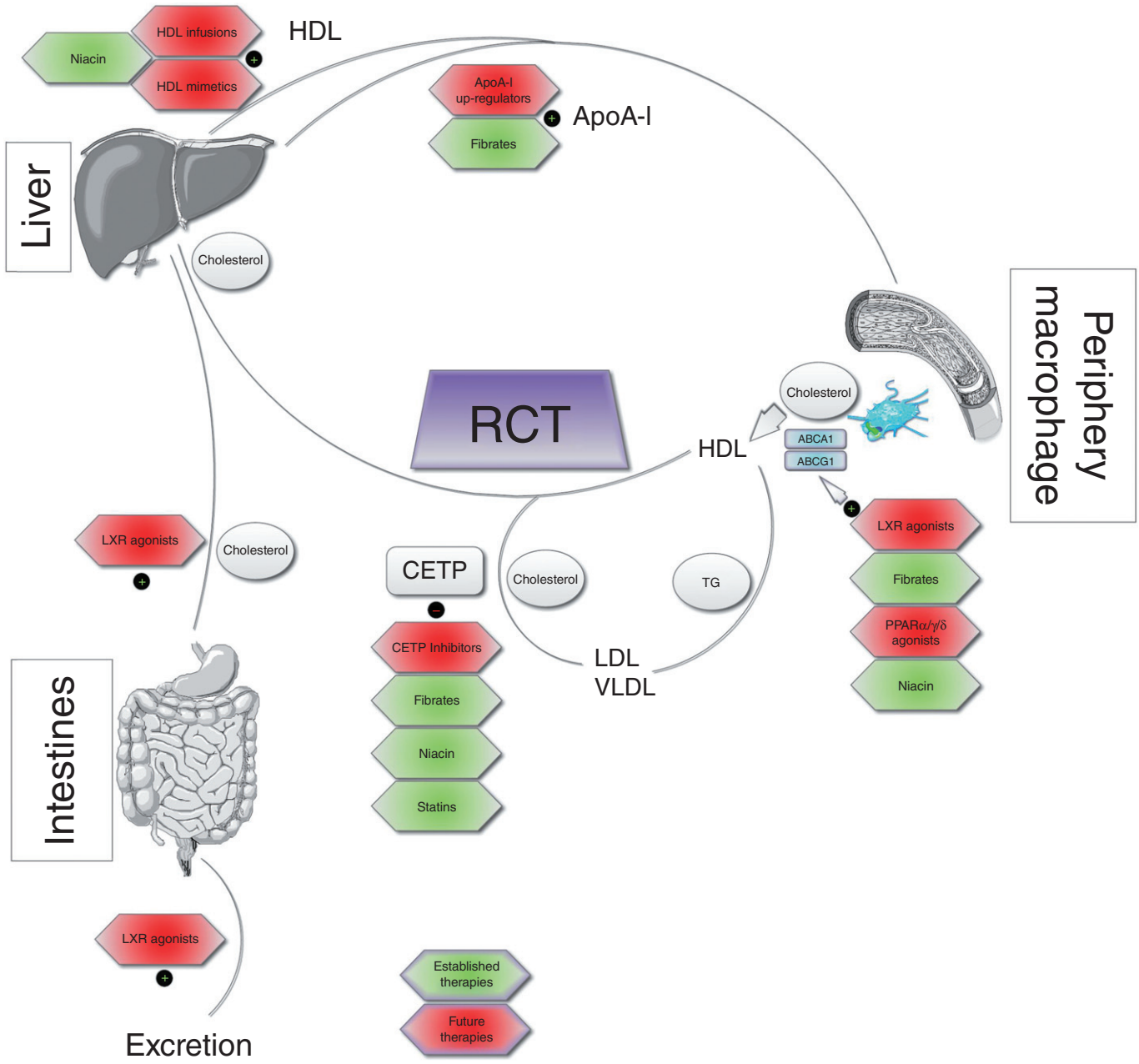

Figure 1

An overview of the HDL life cycle and where the therapeutic options mentioned earlier come into action. Statins raise HDL-C levels mainly by inhibiting CETP. Fibrates induce RCT via ABCA1 and ABCG1 up-regulation, inhibit CETP and induce ApoA-I production. Niacin induces RCT via ABCA1 and ABCG1, block CETP and inhibit clearance of HDL particles in the liver. PPARα/γ/δ agonists mainly raise HDL-C through ABCA1 and ABCG1 and consecutive induction of RCT. LXR agonists activate RCT via ABCA1 and ABCG1, promote transport of cholesterol esters from the liver to the intestines, inhibit intestinal cholesterol absorption and up-regulate excretion of cholesterol.

of PPAR-γ binding; Goldenberg *et al.*, 2009; Tenenbaum and Fisman, 2010).

Fibrates have been in use for several decades now. Therefore, numerous studies dealt with the mechanisms of action and the effects of fibrate therapy. Thus the effects of fibrates are discussed in a separate chapter of this review (see earlier).

Several novel PPAR-α agonists were discovered or designed that exhibit a greater PPAR-α binding potency and specificity than fibrates. Potent agonists such as LY518674 or CP-778 875 could lower TG levels and raise HDL-C levels in humans in lower doses than fibrates. The highly selective agonists BMS-687453 and BMS-711939 were also able to raise HDL-C and ApoA-I levels in human ApoA-I transgenic mice as well as lower TG and LDL-C levels in fat-fed hamsters. While the LDL-C lowering ability was greater than that of fenofibrate, the influences on TG and HDL-C

levels were comparable with fenofibrate (Mukherjee *et al.*, 2008).

In diabetic cynomolgus monkeys, the potent agonist CP-900691 not only improved plasma lipid levels significantly by lowering TG, VLDL-C and LDL-C levels, increasing HDL-C and ApoA-I levels, but also ameliorated insulin sensitivity, reduced body weight and CRP levels and raised adiponectin levels. While all other aforementioned novel agonists were not superior to fibrate controls in animals and humans, CP-900691 could be an exciting alternative by tackling both, the glycaemic and the lipidaemic status simultaneously (Wagner *et al.*, 2010).

TZDs. The two TZDs currently on the market, rosiglitazone (except in Europe) and pioglitazone, are mainly agonists of PPAR-γ, although pioglitazone and even rosiglitazone are said to bind to PPAR-α as well, and are mostly recognized for their ability to increase insulin sensitivity. Rosiglitazone has been taken from the European market because its use was associated with an increased risk for MI (Nissen *et al.*, 2007a; Shah *et al.*, 2010).

The beneficial effect of TZDs on the lipid profile and on HDL-C levels is controversial. While there are studies showing an HDL-C increase of 14–18% in diabetic populations treated with TZDs, other studies only show a marginal or even adverse effect on lipid parameters. Pioglitazone has been shown to increase ApoA-I levels and rosiglitazone increases ApoA-II levels, whereby an increase of ApoA-I levels is controversial. However, the mechanisms by which these glitazones are able to influence HDL-C levels are not completely understood yet. (van Wijk *et al.*, 2003; Carreon-Torres *et al.*, 2009; Millar *et al.*, 2010)

Dual PPAR-α/γ agonists. PPAR-α agonists are known to influence the lipid profile beneficially and PPAR-γ agonists improve insulin sensitivity. Thus, there have been attempts to design new, dual PPAR agonists that combine both effects to treat patients more effectively, because many diabetic patients also suffer from dyslipidaemia and dyslipidemic patients frequently develop type 2 diabetes or at least an impaired glucose tolerance.

New glitazars like tesaglitazar and muraglitazar bind to both PPAR-α and PPAR-γ and did show favourable effects in animal models increasing insulin sensitivity and improving dyslipidaemia. Both drugs even entered phase III trials, but both were withdrawn due to serious patient safety reasons as the risk for serious adverse cardiovascular events was increased in the respective studies. Other dual PPAR-α/γ agonists are being tested for efficacy and safety in animals and a new glitazone, namely aleglitazar, is even being tested in a phase II trial. However, it seems as if the activation of PPARs and in particular the balance between PPAR-α and PPAR-γ binding, is more delicate than expected (Nissen *et al.*, 2005; Tenenbaum *et al.*, 2005; Kendall *et al.*, 2006; Zadelaar *et al.*, 2006; Kim *et al.*, 2008; Casimiro-Garcia *et al.*, 2009; Henry *et al.*, 2009; van der Hoorn *et al.*, 2009; Hansen *et al.*, 2011).

PPAR-δ agonists. One of the key components of PPAR-δ activation is the induction of skeletal muscle fatty acid oxidation, which can also be observed in response to physical exercise. Physical exercise leads to PPAR-δ up-regulation and subsequently to increased lipolysis and activity of SR-B1 and ABCA1. Thus, it can be hypothesized that upon PPAR-δ activation TG should decrease while HDL-C levels should increase. Several PPAR-δ agonists were designed and tested in recent years but the effect on HDL-C levels remained controversial. In a study with human subjects, the agonist GW501516 was shown to decrease TG and increase HDL-C levels. These effects were comparable with those seen in animal models with this agonist (Sprecher *et al.*, 2007).

In another study with moderately overweight individuals, the same agonist could not raise HDL-C levels significantly; however, fasting and postprandial plasma TG, LDL-C and ApoB levels were decreased significantly and liver fat content could also be lowered. (Riserus *et al.*, 2008)

The agonist GW0742 did influence neither HDL-C production nor catabolism but promoted macrophage-to-feces reverse cholesterol transport via the reduction of Niemann–Pick C1 like protein 1 (NPC1L1) expression (Briand *et al.*, 2009).

CETP Inhibitors

CETP is a high molecular weight protein secreted by the liver and adipose tissue and is mainly found in association with HDL. CETP stimulates the transfer of cholesterol ester from HDL to TG-rich lipoproteins (TRL), such as VLDL and LDL. It is hypothesized that this cholesterol increase in TRL leads to enhanced cholesterol deposition into the peripheral arterial wall. Furthermore, CETP transfers triglycerides from VLDL or LDL to HDL. (Tall, 1993) TG-rich HDL particles get more easily hydrolysed by hepatic lipase, which leads to a destabilization of HDL and decreasing plasma concentrations due to enhanced renal catabolism. (Lamarche *et al.*, 1999) Consequently, many scientists have considered CETP to be a culprit in dyslipidaemia and atherogenesis. This hypothesis was further supported by findings regarding altered CETP activity and CETP serum levels in these diseases.

CETP activity was shown to be elevated in CAD, in diabetes and in the metabolic syndrome. (Hibino *et al.*, 1996; Riemens *et al.*, 1998; Gomez Rosso *et al.*, 2008; Park *et al.*, 2010) Gene mutations in CETP leading to CETP deficiency were shown to result in increased HDL-C and ApoA-I lipoprotein as well as decreased LDL-C levels. (Inazu *et al.*, 1990) The Framingham Offspring Study examined the TaqI polymorphism leading to decreased CETP activity. The phenotype leading to significantly lower CETP activity, lower CETP levels and higher HDL-C levels, could be associated with a decreased risk for CHD, although statistical significance could not be sustained after adjustment for common cardiovascular risk factors and was only seen in men (Ordovas *et al.*, 2000). Two years later, VA-HIT presented similar results (Brousseau *et al.*, 2002). CETP serum levels were also associated with atherosclerosis and were able to predict future CAD in apparently healthy men and women with high TG concentrations. (Boekholdt *et al.*, 2004) In subjects with familial hypercholesterolaemia, CETP levels were positively associated with progression of atherosclerosis, determined by IMT. In this same study, statins were shown to decrease CETP and atherogenic lipid levels. Still, in a subgroup of subjects with high CETP, statins were not able to sufficiently normalize lipid abnormalities (de Grooth *et al.*, 2004). These results illustrate the need for medication affecting CETP activity specifically.

Several strategies have been pursued in order to counteract CETP, including vaccination(Rittershaus *et al.*, 2000), antisense deoxynucleotides (Sugano *et al.*, 1998) and small molecule inhibitors of CETP. Three compounds have found their way into clinical trials so far, namely torcetrapib, dalcetrapib and anacetrapib.

Despite promising results in phase I and II studies (Brousseau *et al.*, 2004; Davidson *et al.*, 2006), in the large-scale phase III study, ILLUMINATE, torcetrapib therapy led to an increase in all-cause mortality and cardiovascular events, although it was able to increase HDL-C by 72% and decrease LDL-C by 25% (Barter *et al.*, 2007). Correspondent results came from several imaging studies, in which torcetrapib failed to halt atherosclerosis progression in patients with mixed dyslipidaemia as well as in patients with coronary disease. (Bots *et al.*, 2007; Nissen *et al.*, 2007b) In patients with familial hypercholesterolaemia, torcetrapib therapy even led to a significant progression in IMT of the common carotid artery compared with the control group (Kastelein *et al.*, 2007). As increases in systolic blood pressure, a decrease in serum potassium and an increase in serum sodium, bicarbonate and aldosterone were observed in these trials, subsequent analyses addressed the question whether the negative outcome results were due to CETP inhibition or compound-specific off-target effects. The conclusion was drawn that the off-target toxicity contributed to the observed adverse events and that CETP inhibition, by means of raising HDL-C and lowering LDL-C levels, had no impact (Kastelein, 2007; Barter, 2009). Finally, the concept of CETP inhibition was not dropped, and new compounds have been designed that differ from torcetrapib in certain molecular structures, thus avoiding off-target effects.

Dalcetrapib (JTT-705) was tested in patients with dyslipidaemia, CAD or CAD risk equivalent in several phase II studies. Dalcetrapib was generally well tolerated and successfully increased HDL-C with no clinically relevant changes in blood pressure, laboratory parameters including aldosterone, or electrocardiograms (Stein *et al.*, 2009; 2010). Results from Dal-PLAQUE were published in September 2011. In this phase IIb, study with a follow-up of 24 months, 130 patients with CAD or at high risk for CAD were given either 600 mg of dalcetrapib or placebo. Primary end points were MRI-assessed structural changes in the arterial wall or (^{18}FDG)PET/CT-assessed changes in arterial inflammation. Under dalcetrapib, HDL-C increased by 31% and CETP activity decreased. In contrast to placebo use, neither significant plaque progression (at 24 months) nor an increased inflammatory response in the vessel wall (at 6 months) was seen in the dalcetrapib group. There were no significant differences in adverse events between the two groups.

Interestingly, high-sensitive CRP increased by 33% in the dalcetrapib group whereas no change was seen in the placebo group. According to the authors, this disparity between local and systemic inflammation was already observed in other studies and raises the question whether general blood biomarkers provide the same information as local imaging biomarkers. (Fayad *et al.*, 2011)

Phase III studies are ongoing to elucidate whether dalcetrapib is able to prevent cardiovascular events and mortality. Dal-PLAQUE2 started in January 2010 and is designed to evaluate dalcetrapib's power to prevent atherosclerotic progression using IMT and intravascular ultrasound (IVUS) techniques. Follow-up is planned at 24 months (Tardif *et al.*, 2011).

Dal-OUTCOMES, testing a dosage of 600 mg dalcetrapib in patients with recent ACS, is scheduled to be complete in 2013 and will give information about dalcetrapib's clinical efficacy to reduce coronary events in secondary prevention. (Schwartz *et al.*, 2009)

Anacetrapib (MK-0859) was shown to be even more potent than the other CETP inhibitors. Eight weeks of anacetrapib therapy increased HDL-C by 139% and decreased LDL-C by 40%. (Bloomfield *et al.*, 2009) There was no significant difference in blood pressure compared with placebo, and anacetrapib was well tolerated. The phase III study DEFINE will examine anacetrapib's effect in patients with CAD or CAD risk equivalents on a background statin therapy (Cannon *et al.*, 2009; 2010).

In addition, new compounds are constantly developed and are being tested in their ability to inhibit CETP (Kuo *et al.*, 2009; Schmeck *et al.*, 2010; Wang *et al.*, 2010).

HDL infusions and HDL mimetics

In contrast to increasing HDL-C indirectly by interfering in the HDL metabolism, the concept was developed to directly increase HDL-C, by infusing reconstituted or recombinant HDL particles into the circulation.

One of these compounds is recombinant ApoA-IMilano. ApoA-IMilano is an apolipoprotein variant that was naturally found in inhabitants of a little village in Northern Italy. Despite strikingly low HDL-C concentrations, it was quite suprising that the carriers showed no increased risk for atherosclerosis (Franceschini *et al.*, 1985; Sirtori *et al.*, 2001). After recombinant ApoA-IMilano has proved itself safe and efficient in several *in vitro* and *in vivo* models (Shah *et al.*, 1998; 2001; Chiesa *et al.*, 2002), results of a randomized, placebo-controlled IVUS trial on a recombinant ApoA-IMilano/phospholipid complex, called ETC-216, in patients with recent ACS were published in 2003. Although the authors reported a significant regression of coronary atherosclerosis, it is noteworthy that this significance was only calculated within groups, without comparing the atheroma changes in the treated versus the placebo group (Nissen *et al.*, 2003). A few years later Nicholls *et al.* (2006) presented similar results. Another reconstituted HDL compound is CSL-111, consisting of ApoA-I from human plasma combined with soybean phosphatidylcholine. Four weekly infusions of CSL-111 in 111 patients proved to be well tolerated and, compared with baseline, there was significant lesion regression. However, there was no significant reduction in atheroma volume, as measured by IVUS, compared with the placebo group. (Tardif *et al.*, 2007)

Soon after the ILLUMINATE results were published, the scientific community started to wonder whether the sole therapeutic increase in HDL-C was enough to prevent atherosclerosis. As torcetrapib failed to have a beneficial impact on lesions despite significant changes in HDL-C concentrations, it was suggested that HDL quality, that is function, was more important than quantity. Human ApoA-I consists of 243 amino acids and is organized in a helix bundle domain comprising the N-terminal, central α-helices and a strongly lipid binding C-terminal domain (Vedhachalam *et al.*, 2004). Labo-

ratories have designed short peptides that do not share sequence homology, but mimic ApoA-I function. As the first mimetics were able to bind lipids, but failed to change atherosclerotic lesions, emphasis was set on finding new mimetics with preserved anti-inflammatory properties (Navab *et al.*, 2010). The peptide 4F is the most promising mimetic so far. The 4F peptide synthesized from D-amino acids (D-4F) proved stable in the circulation *in vivo*. In ApoE-null mice, oral D-4F rendered HDL anti-inflammatory, enhanced reverse cholesterol transport from macrophages as much as the formation of pre-β HDL (Navab *et al.*, 2004). A dose-dependent formation of pre-β HDL particles could also be confirmed in human plasma (Troutt *et al.*, 2008). Recently, an *in vitro* study confirmed 4F's anti-inflammatory properties in human cells. 4F was shown to induce cholesterol efflux in human monocyte-derived macrophages, significantly reduced LPS-triggered production of pro-inflammatory cytokines, and significantly decreased monocyte adhesion to human endothelial cells as well as transendothelial migration (Smythies *et al.*, 2010). It was, however, not evident if these anti-inflammatory actions would also affect the development of atherosclerotic lesions. Navab *et al*. administered 4F orally to LDL receptor-null mice on a Western diet. Lesions decreased by 79% and LDL was protected from oxidation (Navab *et al.*, 2002). In rabbits, D-4F also induced a significant regression of atherosclerotic lesions and improved the HDL-inflammatory index. Interestingly, these changes were independent of TC or HDL-C levels (Van Lenten *et al.*, 2007). Subsequently, D-4F was tested in a phase I study in patients with CHD or at equivalent risk. Five groups of 8 people received 30, 100, 300, 500 mg of unformulated D-4F, or placebo, respectively. There were no alterations in lipid or lipoportein concentrations, but 4 h after administration of 300 mg and 2 h after administration of 500 mg, the HDL-inflammatory index improved significantly, suggesting an anti-inflammatory effect of D-4F in humans. (Bloedon *et al.*, 2008)

Another ApoA-I mimetic peptide, 5A, was recently shown to inhibit inflammation and oxidative stress in a carotid artery stenosis model in rabbits. These effects were also seen in human coronary artery endothelial cells *in vitro* and were shown to be dependent on ABCA1 (Tabet *et al.*, 2010).

ApoA-I Up-regulators

A novel approach to increase HDL and to improve its function is to stimulate the synthesis of ApoA-I, thus, stimulating the first step in HDL life cycle. RVX-208, a stimulator of ApoA-I gene expression is a promising compound in that respect. RVX-208 was shown to induce ApoA-I synthesis in HepG2 cells. In monkeys, it also led to an increase in serum ApoA-I and HDL-C concentrations (60 and 97%, respectively), as well as to ABCA1-, ABCG1- and SR-B1-dependent cholesterol efflux. In humans, administered orally for 1 week, RVX-208 significantly increased ApoA-I, pre-β HDL and HDL functionality (Bailey *et al.*, 2010). However, further trials are needed to address whether the upregulation of ApoA-I by compounds, such as RVX-208, have atheroprotective effects in cardiovascular diseases.

LXR agonists

Belonging to a large family of nuclear receptors, LXRs bind to the regulatory regions of target genes and stimulate their transcription. Initially, LXRs were isolated from the cDNA library of a human liver as orphan receptors because their ligands were not identified at the time of characterization. It is now evident that oxidized cholesterol derivatives, also known as oxysterols, are specific ligands for LXRs. Currently, two LXR isoforms, LXRα and LXRβ, which share 80% homology have been characterized. The former is expressed mainly in the liver, intestine, kidney, spleen and adipose tissue, while the latter is expressed ubiquitously (Wojcicka *et al.*, 2007).

Both receptor types form heterodimers with the RXR, which can then be activated by either LXR agonists or 9-cis retinoic acid (a specific RXR ligand) to bind to an LXR response element (LXRE) in the promoter regions of target genes (Wojcicka *et al.*, 2007).

The primary role of LXRs is to act as intracellular cholesterol sensors. LXRs sense excess cholesterol (cholesterol and oxysterol levels correlate with each other, thus if oxysterol levels are high cholesterol levels will be high as well) and activate several mechanisms to protect the cell from cholesterol overload. LXRs are therefore able to stimulate the reverse cholesterol transport, from the removal of cholesterol from the cell, to the transport of cholesterol to the liver to its biliary excretion. Of lesser importance is the inhibition of intestinal cholesterol uptake as well as cholesterol synthesis (Wojcicka *et al.*, 2007).

In macrophages LXRs up-regulate the expression of ABCA1 and ABCG1. ABCA1 is also involved in the formation of nascent HDL particles in the liver and small intestine. LXRs also stimulate the expression of Niemann–Pick C1 (NPC1) and C2 (NPC2), which redistribute cholesterol from the endosomal compartment to the plasma membrane. Furthermore, hepatic SR-B1, essential for the delivery of cholesterol from HDL particles to hepatocytes, is up-regulated by LXRs *in vitro* (Wojcicka *et al.*, 2007; Beltowski, 2008).

LXRs also decrease the expression NPC1L1, which is present in the apical membrane of enterocytes to absorb cholesterol from the intestinal lumen. Simultaneously, ABCA1 in the small intestine is up-regulated leading to the formation of HDL particles and the transport of cholesterol to ApoA-I. Hepatic ABCG5 and ABCG8, responsible for the cholesterol transport to the bile, thus leading to an increased faecal cholesterol extraction are up-regulated by LXRs as well (Wojcicka *et al.*, 2007; Beltowski, 2008).

However, LXRs stimulate hepatic lipogenesis leading to hepatic and plasma hypertriglyceridaemia, leading to partially severe liver steatosis and dysfunction. This effect is mediated by the sterol regulatory element binding protein-1c (SREBP-1c) Knockout studies have revealed that SREBP-1c is influenced by LXRα rather than LXRβ (Jamroz-Wisniewska *et al.*, 2007; Wojcicka *et al.*, 2007; Beltowski, 2008).

As of now, LXR agonists are being developed and tested in animal models for their effects. Several synthetically engineered LXR agonists have been tested extensively, namely T0901317, GW3965, AZ876 and ATI-111. They all show a high potency regarding the interaction with the receptors, but none of them show an exclusive selectivity for either of the two variants (Groot *et al.*, 2005; Honzumi *et al.*, 2010; Peng *et al.*, 2011; Srivastava, 2011; van der Hoorn *et al.*, 2011).

Based on the fact that LXRs are potent activators of RCT, one might suppose that agonists like T0901317 should

increase HDL-C levels. However, LXRs and their agonists not only activate RCT, but also CETP leading to a cholesterol transfer from HDL to LDL and VLDL particles. Therefore, studies regarding the influence of LXR agonists on the lipid profile have to be interpreted with care because several studies were performed in mice, which apparently lack CETP. Thus, T0901317 is able to elevate HDL-C levels in wild-type mice while CETP transgenic C57BL/6J mice and cynomolgus monkeys show an increase in non-HDL cholesterol levels and decreased HDL-C levels upon treatment with T0901317 (Jamroz-Wisniewska *et al.*, 2007; Wojcicka *et al.*, 2007; Beltowski, 2008; Honzumi *et al.*, 2010).

An earlier study showed similar results in male Syrian gold hamsters treated with either GW3965 or SB742881, respectively. In such treated hamsters, LDL-C and VLDL-C levels rose significantly while HDL-C levels decreased significantly. Also, TG levels increased considerably (Groot *et al.*, 2005).

ATI-111 an LXR agonist showing preference for the LXRα isoform and higher potency than T0901317 was shown to not increase TG, VLDL-C or LDL-C levels in male LDLR–/– mice after 8 weeks of treatment. However, HDL-C levels also did not rise significantly (Peng *et al.*, 2011).

A study in APOE*3 Leiden mice evaluating the effects of the LXR agonist AZ876 could show a decreased TC level while HDL-C levels increased. However, TG levels also rose considerably leading to a steatosis of the liver and significant liver dysfunction. (van der Hoorn *et al.*, 2011)

Considering all these results, the effect of LXR agonists on HDL-C plasma levels seems quite disappointing. Moreover, considering the dramatic rise of TG levels after treatment with some LXR agonists their usefulness regarding the lipid profile modifying effect has to be evaluated quite critically. However, the same studies showing no or a negligible positive effect on plasma lipid levels in general and HDL-C plasma levels could specifically show a clear anti-atherogenic and anti-inflammatory effect.

LXR agonists were shown to decrease atherosclerotic plaque size in mouse models (T0901317, GW3965, AZ876, ATI-111) significantly. Some of them were able to reduce the number of lesions (AZ876, GW3965), alter the composition of plaques towards more stable lesions (T09013117) or even prevent lesion development (AZ876, GW3965) (Jamroz-Wisniewska *et al.*, 2007; Beltowski, 2008; Peng *et al.*, 2011; Srivastava, 2011; van der Hoorn *et al.*, 2011).

In mice and rats administration of T0901317 or GW3965 led to decreased levels of inflammatory cytokines and other key mediators in the development of atherosclerosis such as TNF-α, IL-1β, IL-6, IFN-γ, MMP-9 and ICAM-1 (Jamroz-Wisniewska *et al.*, 2007; Beltowski, 2008; van der Hoorn *et al.*, 2011).

Interestingly, tri-butyltin chloride, an organotin widely used in agricultural and chemical industries and known to induce adipogenesis and reduce fertility in mammals, was shown to induce ABCA1 expression and ApoA-I-mediated cellular cholesterol efflux via the activation of the LXRα/RXR heterodimer (Cui *et al.*, 2011).

While LXR agonists do not seem to be suitable to increase HDL-C levels they could represent an exciting class of new anti-atherosclerotic drugs as they were shown to in part lower atherosclerotic plaque size dramatically. Some of these molecules were even able to completely prevent the formation of atherosclerotic lesions. However, these studies were conducted in animal models. The next step has to be to try to translate these highly interesting findings into the clinical setting. It should also be noted that LXRα and LXRβ use different signalling pathways (Jamroz-Wisniewska *et al.*, 2007; Wojcicka *et al.*, 2007). Currently, no exclusively specific agonists for either isoform of the receptor are available so that unwanted side effects of LXR signalling such as liver steatosis jeopardize the beneficial anti-inflammatory and anti-atherosclerotic effects of these compounds. Thus, the design of drugs activating either LXR isoform exclusively or drugs displaying tissue selectivity would provide exciting opportunities for the treatment of patients (Figure 1).

Conclusion

The Framingham Study was the first to suggest that positively influencing HDL-C levels may lead to a decrease in cardiovascular mortality (Gordon *et al.*, 1977). Since then, other studies have confirmed this statement. Currently, optimal statin treatment manages to achieve a risk reduction for cardiovascular mortality of about 25–35% (Boden *et al.*, 2011; Brooks *et al.*, 2010; Davidson and Rosenson, 2009). Considering that cardiovascular disease can be held accountable for about 50% of all deaths a risk reduction of 25–35% cannot be enough (Greenow *et al.*, 2005).

Raising HDL-C was seen as a viable and promising way to further reduce the risk of cardiovascular mortality. However, things are not as easy as they seem with HDL-C (Asztalos *et al.*, 2006; Freund *et al.*, 1993; Gordon *et al.*, 1977; 1989; Kannel and McGee, 1985; Wilson *et al.*, 1988).

Firstly, raising HDL-C was proven to be a daunting task. Of the currently available drugs only niacin has the potential to raise HDL-C levels substantially (approximately 25%) (Carlson, 2005; Brooks *et al.*, 2010). Dietary and lifestyle changes as well as statin therapy can help raise HDL-C levels by 5–10% (Downs *et al.*, 1998; Streja *et al.*, 2002; Varady and Jones, 2005; Nissen *et al.*, 2006; Hausenloy and Yellon, 2009). Fibrate treatment manages to raise HDL-C by 10–15% (Frick *et al.*, 1987; Goldenberg *et al.*, 2008). But studies examining the effect of fibrates on cardiovascular mortality yielded disappointing results (Keech *et al.*, 2005; Abourbih *et al.*, 2009; Ginsberg *et al.*, 2010; Tenenbaum and Fisman, 2010).

Niacin seems to be neglected in dyslipidaemia treatment because it frequently provokes flushing. This side effect is certainly stressful for patients, but it is harmless. However, while earlier studies indicated that niacin had a favourable effect on cardiovascular mortality, the recently published results of AIM-HIGH were sobering at first. AIM-HIGH could not show any benefit for niacin treatment in combination with statin therapy. But, as outlined by Nicholls, the results of this study have to be interpreted with caution (Nicholls, 2012).

The verdict on niacin is still open at least until the results of the HPS2-THRIVE study are published.

Secondly, there has been increasing evidence that the quality and not the quantity of HDL is important. HDL particles are in large part responsible for reverse cholesterol transport, the mechanism that can reverse atheroma formation. HDL particles take up cholesterol from foam cells and

thus reduce the risk of cholesterol oxidation and further foam cell formation. This way, the vicious circle can be broken and arterial wall inflammation is halted. HDL particles are also able to normalize endothelial cell function, inducing nitric oxide (NO) production (leading to vasodilation) and inhibiting inflammation, chemotaxis and thrombosis. So, to influence atherosclerosis proper HDL particle function is of utmost importance. (Tall, 2008; Singh *et al*., 2010)

Studies showed that in a state of chronic inflammation (as is the case with atherosclerosis, chronic renal disease, diabetes or several forms of arthritis), reverse cholesterol transport is interrupted. Furthermore, HDL particles do not act as antioxidative agents, they rather support oxidation of cholesterol, fuelling the inflammatory process. Moreover, other pleiotropic effects of HDL are hampered (Natarajan *et al*., 2010; Saemann *et al*., 2010).

One study could show that when the protease chymase is present, reverse cholesterol transport via ABCA1 is severely impaired, thus indicating that the altered environment in an atherosclerotic vessel wall may severely impact the functionality of HDL particles (Favari *et al*., 2004).

ApoA-I is a specific target for myeloperoxidase (MPO) an agent found mainly in neutrophils and monocytes and playing an important role in microorganism eradication. MPO, which is found in high amounts in human atheroma lesions is able to alter the protein structure of HDL particles rendering them less able to remove cholesterol from macrophages. MPO was even able to alter the functionality of reconstituted HDL (Smith, 2010a,b). Considering the fact that statins (rosuvastatin in particular) are able to lower MPO levels *in vivo* their role in HDL metabolism seems to be preserving HDL function by creating a less inflamed environment rather than to simply increase HDL-C levels (Andreou *et al*., 2010).

Drugs like torcetrapib (ILLUSTRATE, ILLUMINATE, RADIANCE) and niacin (AIM-HIGH) could raise HDL-C levels by 25–60%. (Barter, 2009) Still, no change in cardiovascular mortality was detected. In addition the atheroma size was not affected which could support the notion that raising HDL-C levels may not be as beneficial as once thought. (Singh *et al*., 2010) One meta-regression analysis, studying the association between change in HDL-C levels and CAD morbidity and mortality could not even detect a significant reduction of CAD risk upon elevation of HDL-C levels while the reduction of LDL-C levels had significant beneficial effect (Briel *et al*., 2009).

The proper function of HDL particles seems to be the crucial factor leading to the favourable effects. Supporting this hypothesis is the fact that people expressing ApoA-IMilano have low levels of HDL-C, yet are not more at risk of suffering from cardiovascular disease than the normal population. ApoA-IMilano infusions much rather helped lower the atheroma burden via reverse cholesterol transport. (Joy and Hegele, 2008; Tall, 2008; Vergeer *et al*., 2010)

Thirdly, HDL-C may be a suboptimal parameter for assessing cardiovascular risk. Several studies have shown that a low HDL-C level is a risk factor for cardiovascular disease. But HDL-C levels, which are acquired by ultracentrifugation determining the amount of cholesterol in HDL particles per 100 mL of plasma, give no hint on the composition of HDL particles nor their functionality (deGoma *et al*., 2008). HDL particles differ in their ways of action (e.g. large cholesterol rich particles activate reverse cholesterol transport via SR-B1, while the smaller preβ-HDL particles use ABCA1). Simply measuring HDL-C levels does not provide enough information on an otherwise highly complex and dynamic system. New, inexpensive and easily applicable assays are needed to assess the functional capacity of HDL particles in cardiovascular disease patients to better understand the pathophysiology of atherosclerosis and to be able to identify the specific therapeutic needs for every patient (deGoma *et al*., 2008; Vergeer *et al*., 2010). Interestingly, study groups were recently able to show how drug treatment is able to alter HDL composition. Sorrentino *et al*. published results of the effect of extended-release niacin therapy on HDL in diabetic patients. Three months of niacin (1500 mg daily) versus placebo led to a significant improvement of HDL function in the drug-treated group. Niacin stimulated endothelial NO production, endothelial progenitor cell-mediated endothelial repair and reduced superoxide production, all properties which are impaired in diabetics compared with healthy controls (Sorrentino *et al*., 2010). In CAD subjects, 1 year of extended-release niacin (2000 mg daily) plus atorvastatin therapy modified HDL in a way that protein composition resembled more closely that of healthy control subjects indicating improved RCT (Green *et al*., 2008).

Page *et al*. found out that mifepristone, a glucocorticoid and progestin antagonist currently under investigation for the treatment of Cushing's syndrome, did lower HDL-C levels in 30 healthy postmenopausal females by approximately 25%, but that HDL-C mediated cholesterol efflux from cultured macrophages did only decrease by 12%, thus supporting the hypothesis that HDL-C levels are not necessarily directly correlated to HDL particle function (Page *et al*., 2012).

With the predictive ability of HDL-C levels and the efficacy of HDL-C raising drugs being critically discussed some new parameters were presented that might be better suited to predict cardiovascular mortality (Table 1).

On the one hand, the ratio of ApoB/ApoA-I has been proposed to correlate well, even better than LDL-C levels, with cardiovascular risk. Several studies (AMORIS, INTERHEART) could show that the ratio of ApoB/ApoA-I is better suited to predict cardiovascular risk than LDL-C levels with the risk increasing the higher the ratio is (Yusuf *et al*., 2004; Walldius and Jungner, 2006).

Another molecule worth noting as a potential biomarker and risk factor in cardiovascular disease is lipoprotein (a) [Lp(a)]. Consisting of a cholesterol rich LDL particle with one molecule of apolipoprotein B100 and one molecule of apolipoprotein A this molecule acts prothrombotic as it shares structural homology with plasminogen and plasmin without their fibrinolytic activity. Additionally, it nurtures atherosclerotic plaques with the deposition of Lp(a)-cholesterol. Elevated Lp(a) levels have been shown to correlate with increased cardiovascular risk being independent from levels of other lipid molecules or age. Statins and niacin are able to lower Lp(a) levels significantly, however, no randomized, controlled intervention trials selectively aiming at reducing CAD via the reduction of Lp(a) levels have been designed. Such studies will be necessary to recognize and accept Lp(a) as

Table 1

List of the relevant established HDL-C raising substance classes and their therapeutic effects

Substance class	HDL-C raising potential	Effects on other lipid parameters	Important pleiotropic effects
Statins	5–10% (Streja *et al.*, 2002; Nissen *et al.*, 2006)	**LDL-C** ↓ TG ↓ Lp (a) ↓	Anti-inflammatory (Liao, 2002) Anti-thrombotic (Liao, 2002) Improvement of endothelial function (Liao, 2002) Plaque stabilization (Liao, 2002) Reduction of cerebrovascular events (Liao, 2002)
Fibrates	10–15% (Frick *et al.*, 1987; Goldenberg *et al.*, 2008)	LDL-C↓ **TG** ↓	Increase of insulin sensitivity (Abourbih *et al.*, 2009) Anti-inflammatory (Goldenberg *et al.*, 2008) Anti-thrombotic (Goldenberg *et al.*, 2008)
Niacin	>25% (Carlson, 2005; Brooks *et al.*, 2010)	VLDL-C ↓ TG ↓ **Lp (a)** ↓	Improvement of endothelial function (Vosper, 2009a) Reduction of carotid intima-media thickness (Carlson, 2005)

a potential risk factor which can be targeted in the treatment of cardiovascular disease. (Nordestgaard *et al.*, 2010)

Finally, the quest for further lowering the risk for cardiovascular mortality beyond the use of statins and the reduction of LDL-C levels has lead to an intense examination of the role of HDL particles in the biology of atherosclerosis. As a result, the mechanisms of established drugs, which induce an increase of HDL-C levels, were discovered and new drugs that aim for higher HDL-C levels were designed.

In recent years, the importance of HDL-C levels and HDL particles in atherosclerosis has often been questioned. Increase of HDL-C levels has led to conflicting results regarding cardiovascular risk. New therapeutic options are being developed and analysed for their therapeutic potential.

Additionally, there are new biomarkers and risk factors being proposed for future use and targeting.

So, while raising HDL-C has not yet met the initially lofty expectations it still should be a viable therapeutic option for those remaining at a high cardiovascular risk especially because the results of the Framingham study and others that followed cannot be ignored.

Conflicts of interest

None.

References

Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P *et al.* (2009). Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. Am J Med 122: 962. e961-968.

Altschul R, Hoffer A, Stephen JD (1955). Influence of nicotinic acid on serum cholesterol in man. Arch Biochem Biophys 54: 558–559.

Andreou I, Tousoulis D, Miliou A, Tentolouris C, Zisimos K, Gounari P *et al.* (2010). Effects of rosuvastatin on myeloperoxidase levels in patients with chronic heart failure: a randomized placebo-controlled study. Atherosclerosis 210: 194–198.

Arca M, Montali A, Valiante S, Campagna F, Pigna G, Paoletti V *et al.* (2007). Usefulness of atherogenic dyslipidemia for predicting cardiovascular risk in patients with angiographically defined coronary artery disease. Am J Cardiol 100: 1511–1516.

Armitage J, Baigent C, Chen Z, Landray M (2007). Treatment of HDL to reduce the incidence of vascular events HPS2-THRIVE. Available at http://www.controlled-trials.com/mrct/trial/393479/HPS393472-THRIVE.

Asztalos BF, Demissie S, Cupples LA, Collins D, Cox CE, Horvath KV *et al.* (2006). LpA-I, LpA-I:A-II HDL and CHD-risk: the framingham offspring study and the veterans affairs HDL intervention trial. Atherosclerosis 188: 59–67.

Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Mercouris BR, Pehlivanidis A *et al.* (2004). Effect of atorvastatin on high density lipoprotein cholesterol and its relationship with coronary events: a subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) Study. Curr Med Res Opin 20: 627–637.

Bailey D, Jahagirdar R, Gordon A, Hafiane A, Campbell S, Chatur S *et al.* (2010). RVX-208: a small molecule that increases apolipoprotein A-I and high-density lipoprotein cholesterol in vitro and in vivo. J Am Coll Cardiol 55: 2580–2589.

Baker PW, Rye KA, Gamble JR, Vadas MA, Barter PJ (1999). Ability of reconstituted high density lipoproteins to inhibit cytokine-induced expression of vascular cell adhesion molecule-1 in human umbilical vein endothelial cells. J Lipid Res 40: 345–353.

Barter P (2009). Lessons learned from the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial. Am J Cardiol 104 (Suppl.): 10E–15E.

Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M *et al.* (2007). Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 357: 2109–2122.

Barter PJ, Brandrup-Wognsen G, Palmer MK, Nicholls SJ (2010). Effect of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER Database. J Lipid Res 51: 1546–1553.

Beltowski J (2008). Liver X receptors (LXR) as therapeutic targets in dyslipidemia. Cardiovasc Ther 26: 297–316.

Berger JP, Akiyama TE, Meinke PT (2005). PPARs: therapeutic targets for metabolic disease. Trends Pharmacol Sci 26: 244–251.

Berrougui H, Loued S, Khalil A (2012). Purified human paraoxonase-1 interacts with plasma membrane lipid rafts and mediates cholesterol efflux from macrophages. Free Radic Biol Med 52: 1372–1381.

Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L (1987). Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 257: 3233–3240.

Bloedon LT, Dunbar R, Duffy D, Pinell-Salles P, Norris R, DeGroot BJ *et al.* (2008). Safety, pharmacokinetics, and pharmacodynamics of oral apoA-I mimetic peptide D-4F in high-risk cardiovascular patients. J Lipid Res 49: 1344–1352.

Bloomfield D, Carlson GL, Sapre A, Tribble D, McKenney JM, Littlejohn TW, 3rd *et al.* (2009). Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients. Am Heart J 157: 352–360. e352.

Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K *et al.* (2011). Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 365: 2255–2267.

Bodor ET, Offermanns S (2008). Nicotinic acid: an old drug with a promising future. Br J Pharmacol 153 (Suppl. 1): S68–S75.

Boekholdt SM, Kuivenhoven JA, Wareham NJ, Peters RJ, Jukema JW, Luben R *et al.* (2004). Plasma levels of cholesteryl ester transfer protein and the risk of future coronary artery disease in apparently healthy men and women: the prospective EPIC (European Prospective Investigation into Cancer and nutrition)-Norfolk population study. Circulation 110: 1418–1423.

Bots ML, Visseren FL, Evans GW, Riley WA, Revkin JH, Tegeler CH *et al.* (2007). Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. Lancet 370: 153–160.

Briand F, Naik SU, Fuki I, Millar JS, Macphee C, Walker M *et al.* (2009). Both the peroxisome proliferator-activated receptor delta agonist, GW0742, and ezetimibe promote reverse cholesterol transport in mice by reducing intestinal reabsorption of HDL-derived cholesterol. Clin Transl Sci 2: 127–133.

Briel M, Ferreira-Gonzalez I, You JJ, Karanicolas PJ, Akl EA, Wu P *et al.* (2009). Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. BMJ 338: b92.

Brooks EL, Kuvin JT, Karas RH (2010). Niacin's role in the statin era. Expert Opin Pharmacother 11: 2291–2300.

Brousseau ME, O'Connor JJ Jr, Ordovas JM, Collins D, Otvos JD, Massov T *et al.* (2002). 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 22: 1148–1154.

Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, Clark RW *et al.* (2004). Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. N Engl J Med 350: 1505–1515.

Brown BG (2005). AIM HIGH: Niacin Plus Statin to Prevent Vascular Events. Available at http://www.controlled-trials.com/mrct/trial/436557/AIM+HIGH.

Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS *et al.* (2001). Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 345: 1583–1592.

Bruckert E, Labreuche J, Amarenco P (2010). Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. Atherosclerosis 210: 353–361.

Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ *et al.* (1986). Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol 8: 1245–1255.

Cannon CP, Dansky HM, Davidson M, Gotto AM Jr, Brinton EA, Gould AL *et al.* (2009). Design of the DEFINE trial: determining the EFficacy and tolerability of CETP INhibition with AnacEtrapib. Am Heart J 158: 513–519. e513.

Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AM *et al.* (2010). Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med 363: 2406–2415.

Carlson LA (2005). Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. J Intern Med 258: 94–114.

Carreon-Torres E, Rendon-Sauer K, Monter-Garrido M, Toledo-Ibelles P, Gamboa R, Menjivar M *et al.* (2009). Rosiglitazone modifies HDL structure and increases HDL-apo AI synthesis and catabolic rates. Clin Chim Acta 401: 37–41.

Carson SD (1981). Plasma high density lipoproteins inhibit the activation of coagulation factor X by factor VIIa and tissue factor. FEBS Lett 132: 37–40.

Cashin-Hemphill L, Mack WJ, Pogoda JM, Sanmarco ME, Azen SP, Blankenhorn DH (1990). Beneficial effects of colestipol-niacin on coronary atherosclerosis. A 4-year follow-up. JAMA 264: 3013–3017.

Casimiro-Garcia A, Bigge CF, Davis JA, Padalino T, Pulaski J, Ohren JF *et al.* (2009). Synthesis and evaluation of novel alpha-heteroaryl-phenylpropanoic acid derivatives as PPARalpha/gamma dual agonists. Bioorg Med Chem 17: 7113–7125.

Chiesa G, Monteggia E, Marchesi M, Lorenzon P, Laucello M, Lorusso V *et al.* (2002). Recombinant apolipoprotein A-I(Milano) infusion into rabbit carotid artery rapidly removes lipid from fatty streaks. Circ Res 90: 974–980.

Cockerill GW, Rye KA, Gamble JR, Vadas MA, Barter PJ (1995). High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arterioscler Thromb Vasc Biol 15: 1987–1994.

Cockerill GW, Saklatvala J, Ridley SH, Yarwood H, Miller NE, Oral B *et al.* (1999). High-density lipoproteins differentially modulate cytokine-induced expression of E-selectin and cyclooxygenase-2. Arterioscler Thromb Vasc Biol 19: 910–917.

Cockerill GW, Huehns TY, Weerasinghe A, Stocker C, Lerch PG, Miller NE *et al.* (2001). Elevation of plasma high-density lipoprotein concentration reduces interleukin-1-induced expression of E-selectin in an in vivo model of acute inflammation. Circulation 103: 108–112.

Conlan MG, Folsom AR, Finch A, Davis CE, Sorlie P, Marcucci G *et al.* (1993). Associations of factor VIII and von Willebrand factor with age, race, sex, and risk factors for atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) Study. Thromb Haemost 70: 380–385.

Cui H, Okuhira K, Ohoka N, Naito M, Kagechika H, Hirose A *et al.* (2011). Tributyltin chloride induces ABCA1 expression and apolipoprotein A-I-mediated cellular cholesterol efflux by activating LXRalpha/RXR. Biochem Pharmacol 81: 819–824.

Davidson MH, Rosenson RS (2009). Novel targets that affect high-density lipoprotein metabolsim: the next frontier. Am J Cardiol 104: 52E–57E.

Davidson MH, McKenney JM, Shear CL, Revkin JH (2006). Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below-average high-density lipoprotein cholesterol levels. J Am Coll Cardiol 48: 1774–1781.

Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A *et al.* (2009). Major lipids, apolipoproteins, and risk of vascular disease. JAMA 302: 1993–2000.

Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA *et al.* (1998). Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 279: 1615–1622.

Farnier M (2008). Update on the clinical utility of fenofibrate in mixed dyslipidemias: mechanisms of action and rational prescribing. Vasc Health Risk Manag 4: 991–1000.

Favari E, Lee M, Calabresi L, Franceschini G, Zimetti F, Bernini F *et al.* (2004). Depletion of pre-beta-high density lipoprotein by human chymase impairs ATP-binding cassette transporter A1- but not scavenger receptor class B type I-mediated lipid efflux to high density lipoprotein. J Biol Chem 279: 9930–9936.

Fayad ZA, Mani V, Woodward M, Kallend D, Abt M, Burgess T *et al.* (2011). Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. Lancet 378: 1547–1559.

Franceschini G, Sirtori CR, Bosisio E, Gualandri V, Orsini GB, Mogavero AM *et al.* (1985). Relationship of the phenotypic expression of the A-IMilano apoprotein with plasma lipid and lipoprotein patterns. Atherosclerosis 58: 159–174.

Freund KM, Belanger AJ, D'Agostino RB, Kannel WB (1993). The health risks of smoking. The Framingham Study: 34 years of follow-up. Ann Epidemiol 3: 417–424.

Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P *et al.* (1987). Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 317: 1237–1245.

Garner B, Waldeck AR, Witting PK, Rye KA, Stocker R (1998). Oxidation of high density lipoproteins. II. Evidence for direct reduction of lipid hydroperoxides by methionine residues of apolipoproteins AI and AII. J Biol Chem 273: 6088–6095.

Geurian K, Pinson JB, Weart CW (1992). The triglyceride connection in atherosclerosis. Ann Pharmacother 26: 1109–1117.

Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P *et al.* (2010). Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 362: 1563–1574.

Goldenberg I, Benderly M, Goldbourt U (2008). Update on the use of fibrates: focus on bezafibrate. Vasc Health Risk Manag 4: 131–141.

Goldenberg I, Benderly M, Sidi R, Boyko V, Tenenbaum A, Tanne D *et al.* (2009). Relation of clinical benefit of raising high-density lipoprotein cholesterol to serum levels of low-density lipoprotein cholesterol in patients with coronary heart disease (from the Bezafibrate Infarction Prevention Trial). Am J Cardiol 103: 41–45.

deGoma EM, deGoma RL, Rader DJ (2008). Beyond high-density lipoprotein cholesterol levels evaluating high-density lipoprotein function as influenced by novel therapeutic approaches. J Am Coll Cardiol 51: 2199–2211.

Gomez Rosso L, Benitez MB, Fornari MC, Berardi V, Lynch S, Schreier L *et al.* (2008). Alterations in cell adhesion molecules and other biomarkers of cardiovascular disease in patients with metabolic syndrome. Atherosclerosis 199: 415–423.

Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD *et al.* (1989). High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 79: 8–15.

Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR (1977). High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med 62: 707–714.

Green PS, Vaisar T, Pennathur S, Kulstad JJ, Moore AB, Marcovina S *et al.* (2008). Combined statin and niacin therapy remodels the high-density lipoprotein proteome. Circulation 118: 1259–1267.

Greenow K, Pearce NJ, Ramji DP (2005). The key role of apolipoprotein E in atherosclerosis. J Mol Med 83: 329–342.

Griffin JH, Kojima K, Banka CL, Curtiss LK, Fernandez JA (1999). High-density lipoprotein enhancement of anticoagulant activities of plasma protein S and activated protein C. J Clin Invest 103: 219–227.

Groot PH, Pearce NJ, Yates JW, Stocker C, Sauermelch C, Doe CP *et al.* (2005). Synthetic LXR agonists increase LDL in CETP species. J Lipid Res 46: 2182–2191.

de Grooth GJ, Smilde TJ, Van Wissen S, Klerkx AH, Zwinderman AH, Fruchart JC *et al.* (2004). The relationship between cholesteryl ester transfer protein levels and risk factor profile in patients with familial hypercholesterolemia. Atherosclerosis 173: 261–267.

Hansen BC, Tigno XT, Benardeau A, Meyer M, Sebokova E, Mizrahi J (2011). Effects of aleglitazar, a balanced dual peroxisome proliferator-activated receptor alpha/gamma agonist on glycemic and lipid parameters in a primate model of the metabolic syndrome. Cardiovasc Diabetol 10: 7.

Hausenloy DJ, Yellon DM (2009). Enhancing cardiovascular disease risk reduction: raising high-density lipoprotein levels. Curr Opin Cardiol 24: 473–482.

Henry RR, Lincoff AM, Mudaliar S, Rabbia M, Chognot C, Herz M (2009). Effect of the dual peroxisome proliferator-activated receptor-alpha/gamma agonist aleglitazar on risk of cardiovascular disease in patients with type 2 diabetes (SYNCHRONY): a phase II, randomised, dose-ranging study. Lancet 374: 126–135.

Hernandez M, Wright SD, Cai TQ (2007). Critical role of cholesterol ester transfer protein in nicotinic acid-mediated HDL elevation in mice. Biochem Biophys Res Commun 355: 1075–1080.

Hibino T, Sakuma N, Sato T (1996). Higher level of plasma cholesteryl ester transfer activity from high-density lipoprotein to apo B-containing lipoproteins in subjects with angiographically detectable coronary artery disease. Clin Cardiol 19: 483–486.

Holzer M, Birner-Gruenberger R, Stojakovic T, El-Gamal D, Binder V, Wadsack C *et al.* (2011). Uremia alters HDL composition and function. J Am Soc Nephrol 22: 1631–1641.

Honzumi S, Shima A, Hiroshima A, Koieyama T, Ubukata N, Terasaka N (2010). LXRalpha regulates human CETP expression in vitro and in transgenic mice. Atherosclerosis 212: 139–145.

van der Hoorn J, Linden D, Lindahl U, Bekkers M, Voskuilen M, Nilsson R *et al.* (2011). Low dose of the liver X receptor agonist, AZ876, reduces atherosclerosis in APOE*3Leiden mice without affecting liver or plasma triglyceride levels. Br J Pharmacol 162: 1553–1563.

van der Hoorn JW, de Haan W, Berbee JF, Havekes LM, Jukema JW, Rensen PC *et al.* (2008). Niacin increases HDL by reducing hepatic expression and plasma levels of cholesteryl ester transfer protein in APOE*3Leiden.CETP mice. Arterioscler Thromb Vasc Biol 28: 2016–2022.

van der Hoorn JW, Jukema JW, Havekes LM, Lundholm E, Camejo G, Rensen PC *et al.* (2009). The dual PPARalpha/gamma agonist tesaglitazar blocks progression of pre-existing atherosclerosis in APOE*3Leiden.CETP transgenic mice. Br J Pharmacol 156: 1067–1075.

Inazu A, Brown ML, Hesler CB, Agellon LB, Koizumi J, Takata K *et al.* (1990). Increased high-density lipoprotein levels caused by a common cholesteryl-ester transfer protein gene mutation. N Engl J Med 323: 1234–1238.

Jamroz-Wisniewska A, Wojcicka G, Horoszewicz K, Beltowski J (2007). Liver X receptors (LXRs). Part II: non-lipid effects, role in pathology, and therapeutic implications. Postepy Hig Med Dosw (Online) 61: 760–785.

Jenkins PJ, Harper RW, Nestel PJ (1978). Severity of coronary atherosclerosis related to lipoprotein concentration. Br Med J 2: 388–391.

Joy T, Hegele RA (2008). Is raising HDL a futile strategy for atheroprotection? Nat Rev Drug Discov 7: 143–155.

Kamanna VS, Ganji SH, Kashyap ML (2009). The mechanism and mitigation of niacin-induced flushing. Int J Clin Pract 63: 1369–1377.

Kannel WB, McGee DL (1985). Epidemiology of sudden death: insights from the Framingham Study. Cardiovasc Clin 15: 93–105.

Kar S, Patel MA, Tripathy RK, Bajaj P, Survankar U, Pande AH (2012). Oxidized phospholipid content destabilizes the structure of reconstituted high density lipoprotein particles and changes their function. Biochim Biophys Acta 1821: 1200–1210.

Kastelein JJ (2007). Refocusing on use of cholesteryl ester transfer protein inhibitors. Am J Cardiol 100: n47–n52.

Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ *et al.* (2007). Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. N Engl J Med 356: 1620–1630.

Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR *et al.* (2005). Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 366: 1849–1861.

Kendall DM, Rubin CJ, Mohideen P, Ledeine JM, Belder R, Gross J *et al.* (2006). Improvement of glycemic control, triglycerides, and HDL cholesterol levels with muraglitazar, a dual (alpha/gamma) peroxisome proliferator-activated receptor activator, in patients with type 2 diabetes inadequately controlled with metformin monotherapy: A double-blind, randomized, pioglitazone-comparative study. Diabetes Care 29: 1016–1023.

Kim MK, Chae YN, Son MH, Kim SH, Kim JK, Moon HS *et al.* (2008). PAR-5359, a well-balanced PPARalpha/gamma dual agonist, exhibits equivalent antidiabetic and hypolipidemic activities in vitro and in vivo. Eur J Pharmacol 595: 119–125.

Kuo GH, Rano T, Pelton P, Demarest KT, Gibbs AC, Murray WV *et al.* (2009). Design, synthesis, and biological evaluation of (2R,alphaS)-3,4-dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluorome thoxy)-phenyl]-alpha-(trifluoromethyl)-1(2H)-quinolineethanol as potent and orally active cholesteryl ester transfer protein inhibitor. J Med Chem 52: 1768–1772.

Lamarche B, Uffelman KD, Carpentier A, Cohn JS, Steiner G, Barrett PH *et al.* (1999). Triglyceride enrichment of HDL enhances in vivo metabolic clearance of HDL apo A-I in healthy men. J Clin Invest 103: 1191–1199.

LaRosa JC, He J, Vupputuri S (1999). Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 282: 2340–2346.

LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC *et al.* (2005). Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 352: 1425–1435.

Liao JK (2002). Beyond lipid lowering: the role of statins in vascular protection. Int J Cardiol 86: 5–18.

Mackness B, Hine D, Liu Y, Mastorikou M, Mackness M (2004). Paraoxonase-1 inhibits oxidised LDL-induced MCP-1 production by endothelial cells. Biochem Biophys Res Commun 318: 680–683.

Millar JS, Ikewaki K, Bloedon LT (2010). The effect of rosiglitazone on HDL metabolism in subjects with metabolic syndrome and low HDL. J Lipid Res 52: 136–142.

Moutzouri E, Kei A, Elisaf MS, Milionis HJ (2010). Management of dyslipidemias with fibrates, alone and in combination with statins: role of delayed-release fenofibric acid. Vasc Health Risk Manag 6: 525–539.

Mukherjee R, Locke KT, Miao B, Meyers D, Monshizadegan H, Zhang R *et al.* (2008). Novel peroxisome proliferator-activated receptor alpha agonists lower low-density lipoprotein and triglycerides, raise high-density lipoprotein, and synergistically increase cholesterol excretion with a liver X receptor agonist. J Pharmacol Exp Ther 327: 716–726.

Natarajan P, Ray KK, Cannon CP (2010). High-density lipoprotein and coronary heart disease: current and future therapies. J Am Coll Cardiol 55: 1283–1299.

Navab M, Hama SY, Anantharamaiah GM, Hassan K, Hough GP, Watson AD *et al.* (2000). Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: steps 2 and 3. J Lipid Res 41: 1495–1508.

Navab M, Berliner JA, Subbanagounder G, Hama S, Lusis AJ, Castellani LW *et al.* (2001). HDL and the inflammatory response induced by LDL-derived oxidized phospholipids. Arterioscler Thromb Vasc Biol 21: 481–488.

Navab M, Anantharamaiah GM, Hama S, Garber DW, Chaddha M, Hough G *et al.* (2002). Oral administration of an Apo A-I mimetic Peptide synthesized from D-amino acids dramatically reduces atherosclerosis in mice independent of plasma cholesterol. Circulation 105: 290–292.

Navab M, Anantharamaiah GM, Reddy ST, Hama S, Hough G, Grijalva VR *et al.* (2004). Oral D-4F causes formation of pre-beta high-density lipoprotein and improves high-density lipoprotein-mediated cholesterol efflux and reverse cholesterol transport from macrophages in apolipoprotein E-null mice. Circulation 109: 3215–3220.

Navab M, Shechter I, Anantharamaiah GM, Reddy ST, Van Lenten BJ, Fogelman AM (2010). Structure and function of HDL mimetics. Arterioscler Thromb Vasc Biol 30: 164–168.

Nicholls SJ (2012). Is niacin ineffective? Or did AIM-HIGH miss its target? Cleve Clin J Med 79: 38–43.

Nicholls SJ, Dusting GJ, Cutri B, Bao S, Drummond GR, Rye KA *et al.* (2005). Reconstituted high-density lipoproteins inhibit the acute pro-oxidant and proinflammatory vascular changes induced by a periarterial collar in normocholesterolemic rabbits. Circulation 111: 1543–1550.

Nicholls SJ, Tuzcu EM, Sipahi I, Schoenhagen P, Crowe T, Kapadia S *et al.* (2006). Relationship between atheroma regression and change in lumen size after infusion of apolipoprotein A-I Milano. J Am Coll Cardiol 47: 992–997.

Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M *et al.* (2003). Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA 290: 2292–2300.

Nissen SE, Wolski K, Topol EJ (2005). Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA 294: 2581–2586.

Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM *et al*. (2006). Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 295: 1556–1565.

Nissen SE, Nicholls SJ, Wolski K, Howey DC, McErlean E, Wang MD *et al*. (2007a). Effects of a potent and selective PPAR-alpha agonist in patients with atherogenic dyslipidemia or hypercholesterolemia: two randomized controlled trials. JAMA 297: 1362–1373.

Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT *et al*. (2007b). Effect of torcetrapib on the progression of coronary atherosclerosis. N Engl J Med 356: 1304–1316.

Nofer JR, Levkau B, Wolinska I, Junker R, Fobker M, von Eckardstein A *et al*. (2001). Suppression of endothelial cell apoptosis by high density lipoproteins (HDL) and HDL-associated lysosphingolipids. J Biol Chem 276: 34480–34485.

Nofer JR, Brodde MF, Kehrel BE (2010). High density lipoproteins (HDL), platelets and the pathogenesis of atherosclerosis. Clin Exp Pharmacol Physiol 37: 726–735.

Nordestgaard BG, Chapman MJ, Ray K (2010). Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J 31: 2844–2853.

Ogata M, Tsujita M, Hossain MA, Akita N, Gonzalez FJ, Staels B *et al*. (2009). On the mechanism for PPAR agonists to enhance ABCA1 gene expression. Atherosclerosis 205: 413–419.

Ordovas JM, Cupples LA, Corella D, Otvos JD, Osgood D, Martinez A *et al*. (2000). 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 20: 1323–1329.

Page ST, Krauss RM, Gross C, Ishida B, Heinecke JW, Tang C *et al*. (2012). Impact of Mifepristone, a Glucocorticoid/Progesterone Antagonist, on HDL Cholesterol, HDL Particle Concentration, and HDL Function. J Clin Endocrinol Metab 97: 1598–1605.

Parhofer KG (2009). Review of extended-release niacin/laropiprant fixed combination in the treatment of mixed dyslipidemia and primary hypercholesterolemia. Vasc Health Risk Manag 5: 901–908.

Park KH, Shin DG, Kim JR, Hong JH, Cho KH (2010). The functional and compositional properties of lipoproteins are altered in patients with metabolic syndrome with increased cholesteryl ester transfer protein activity. Int J Mol Med 25: 129–136.

Peng D, Hiipakka RA, Xie JT, Dai Q, Kokontis JM, Reardon CA *et al*. (2011). A novel potent synthetic steroidal liver X receptor agonist lowers plasma cholesterol and triglycerides and reduces atherosclerosis in LDLR(-/-) mice. Br J Pharmacol 162: 1792–1804.

Report from the Committee of Principal Investigators (1978). A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Br Heart J 40: 1069–1118.

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ *et al*. (2009). Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 373: 1175–1182.

Ridker PM, Genest J, Boekholdt SM, Libby P, Gotto AM, Nordestgaard BG *et al*. (2010). HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. Lancet 376: 333–339.

Riemens S, van Tol A, Sluiter W, Dullaart R (1998). Elevated plasma cholesteryl ester transfer in NIDDM: relationships with apolipoprotein B-containing lipoproteins and phospholipid transfer protein. Atherosclerosis 140: 71–79.

Riserus U, Sprecher D, Johnson T, Olson E, Hirschberg S, Liu A *et al*. (2008). Activation of peroxisome proliferator-activated receptor (PPAR)delta promotes reversal of multiple metabolic abnormalities, reduces oxidative stress, and increases fatty acid oxidation in moderately obese men. Diabetes 57: 332–339.

Rittershaus CW, Miller DP, Thomas LJ, Picard MD, Honan CM, Emmett CD *et al*. (2000). Vaccine-induced antibodies inhibit CETP activity in vivo and reduce aortic lesions in a rabbit model of atherosclerosis. Arterioscler Thromb Vasc Biol 20: 2106–2112.

Ross R (1999a). Atherosclerosis – an inflammatory disease. N Engl J Med 340: 115–126.

Ross R (1999b). Atherosclerosis – an inflammatory disease. N Engl J Med 340: 115–126.

Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB *et al*. (1999). Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 341: 410–418.

Saemann MD, Poglitsch M, Kopecky C, Haidinger M, Horl WH, Weichhart T (2010). The versatility of HDL: a crucial anti-inflammatory regulator. Eur J Clin Invest 40: 1131–1143.

Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR (2007). 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 154: 943–953.

Schmeck C, Gielen-Haertwig H, Vakalopoulos A, Bischoff H, Li V, Wirtz G *et al*. (2010). Novel tetrahydrochinoline derived CETP inhibitors. Bioorg Med Chem Lett 20: 1740–1743.

Schwartz GG, Olsson AG, Ballantyne CM, Barter PJ, Holme IM, Kallend D *et al*. (2009). Rationale and design of the dal-OUTCOMES trial: efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome. Am Heart J 158: 896–901. e893.

Shah ND, Montori VM, Krumholz HM, Tu K, Alexander GC, Jackevicius CA (2010). Responding to an FDA warning–geographic variation in the use of rosiglitazone. N Engl J Med 363: 2081–2084.

Shah PK, Nilsson J, Kaul S, Fishbein MC, Ageland H, Hamsten A *et al*. (1998). Effects of recombinant apolipoprotein A-I(Milano) on aortic atherosclerosis in apolipoprotein E-deficient mice. Circulation 97: 780–785.

Shah PK, Yano J, Reyes O, Chyu KY, Kaul S, Bisgaier CL *et al*. (2001). High-dose recombinant apolipoprotein A-I(milano) mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein e-deficient mice. Potential implications for acute plaque stabilization. Circulation 103: 3047–3050.

Shepherd J, Packard CJ, Patsch JR, Gotto AM Jr, Taunton OD (1979). Effects of nicotinic acid therapy on plasma high density lipoprotein subfraction distribution and composition and on apolipoprotein A metabolism. J Clin Invest 63: 858–867.

Simes RJ, Marschner IC, Hunt D, Colquhoun D, Sullivan D, Stewart RA *et al*. (2002). Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? Circulation 105: 1162–1169.

Singh V, Sharma R, Kumar A, Deedwania P (2010). Low high-density lipoprotein cholesterol: current status and future strategies for management. Vasc Health Risk Manag 6: 979–996.

Sirtori CR, Calabresi L, Franceschini G, Baldassarre D, Amato M, Johansson J *et al.* (2001). Cardiovascular status of carriers of the apolipoprotein A-I(Milano) mutant: the Limone sul Garda study. Circulation 103: 1949–1954.

Smith JD (2010a). Dysfunctional HDL as a diagnostic and therapeutic target. Arterioscler Thromb Vasc Biol 30: 151–155.

Smith JD (2010b). Myeloperoxidase, inflammation, and dysfunctional high-density lipoprotein. J Clin Lipidol 4: 382–388.

Smythies LE, White CR, Maheshwari A, Palgunachari MN, Anantharamaiah GM, Chaddha M *et al.* (2010). Apolipoprotein A-I mimetic 4F alters the function of human monocyte-derived macrophages. Am J Physiol Cell Physiol 298: C1538–C1548.

Sorrentino SA, Besler C, Rohrer L, Meyer M, Heinrich K, Bahlmann FH *et al.* (2010). Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. Circulation 121: 110–122.

Soudijn W, Wijngaarden IAP IV, Ijzerman AP (2007). Nicotinic acid receptor subtypes and their ligands. Med Res Rev 27: 417–433.

Sprecher DL, Massien C, Pearce G, Billin AN, Perlstein I, Willson TM *et al.* (2007). Triglyceride:high-density lipoprotein cholesterol effects in healthy subjects administered a peroxisome proliferator activated receptor delta agonist. Arterioscler Thromb Vasc Biol 27: 359–365.

Srivastava RA (2011). Evaluation of anti-atherosclerotic activities of PPAR-alpha, PPAR-gamma, and LXR agonists in hyperlipidemic atherosclerosis-susceptible F(1)B hamsters. Atherosclerosis 214: 86–93.

Stannard AK, Khan S, Graham A, Owen JS, Allen SP (2001). Inability of plasma high-density lipoproteins to inhibit cell adhesion molecule expression in human coronary artery endothelial cells. Atherosclerosis 154: 31–38.

Stein EA, Stroes ES, Steiner G, Buckley BM, Capponi AM, Burgess T *et al.* (2009). Safety and tolerability of dalcetrapib. Am J Cardiol 104: 82–91.

Stein EA, Roth EM, Rhyne JM, Burgess T, Kallend D, Robinson JG (2010). Safety and tolerability of dalcetrapib (RO4607381/JTT-705): results from a 48-week trial. Eur Heart J 31: 480–488.

Streja L, Packard CJ, Shephard J, Cobbe S, Ford I (2002). Factors affecting low-density lipoprotein and high-density lipoprotein cholesterol response to pravastatin in the West of Scotland Primary Prevention Study (WOSCOPS). Am J Cardiol 90: 731–736.

Suc I, Escargueil-Blanc I, Troly M, Salvayre R, Negre-Salvayre A (1997). HDL and ApoA prevent cell death of endothelial cells induced by oxidized LDL. Arterioscler Thromb Vasc Biol 17: 2158–2166.

Sugano M, Makino N, Sawada S, Otsuka S, Watanabe M, Okamoto H *et al.* (1998). Effect of antisense oligonucleotides against cholesteryl ester transfer protein on the development of atherosclerosis in cholesterol-fed rabbits. J Biol Chem 273: 5033–5036.

Sugano M, Tsuchida K, Makino N (2000). High-density lipoproteins protect endothelial cells from tumor necrosis factor-alpha-induced apoptosis. Biochem Biophys Res Commun 272: 872–876.

Tabet F, Remaley AT, Segaliny AI, Millet J, Yan L, Nakhla S *et al.* (2010). The 5A apolipoprotein A-I mimetic peptide displays antiinflammatory and antioxidant properties in vivo and in vitro. Arterioscler Thromb Vasc Biol 30: 246–252.

Tall AR (1993). Plasma cholesteryl ester transfer protein. J Lipid Res 34: 1255–1274.

Tall AR (2008). Cholesterol efflux pathways and other potential mechanisms involved in the athero-protective effect of high density lipoproteins. J Intern Med 263: 256–273.

Tardif JC, Grégoire J, L'Allier PL, Ibrahim R, Lespérance J, Heinonen TM *et al.* (2007). Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA 297: 1675–1682.

Tardif JC, Lesage F, Harel F, Romeo P, Pressacco J (2011). Imaging biomarkers in atherosclerosis trials. Circ Cardiovasc Imaging 4: 319–333.

Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA (2004). 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 110: 3512–3517.

Taylor AJ, Lee HJ, Sullenberger LE (2006). The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. Curr Med Res Opin 22: 2243–2250.

Tenenbaum A, Fisman EZ (2010). 'If it ain't broke, don't fix it': a commentary on the positive-negative results of the ACCORD Lipid study. Cardiovasc Diabetol 9: 24–28.

Tenenbaum A, Motro M, Fisman EZ (2005). Dual and pan-peroxisome proliferator-activated receptors (PPAR) co-agonism: the bezafibrate lessons. Cardiovasc Diabetol 4: 14.

Tenkanen L, Manttari M, Kovanen PT, Virkkunen H, Manninen V (2006). Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. Arch Intern Med 166: 743–748.

The Coronary Drug Project Research Group (1975). Clofibrate and niacin in coronary heart disease. JAMA 231: 360–381.

Tolle M, Pawlak A, Schuchardt M, Kawamura A, Tietge UJ, Lorkowski S *et al.* (2008). HDL-associated lysosphingolipids inhibit NAD(P)H oxidase-dependent monocyte chemoattractant protein-1 production. Arterioscler Thromb Vasc Biol 28: 1542–1548.

Tolle M, Huang T, Schuchardt M, Jankowski V, Prufer N, Jankowski J *et al.* (2012). High-density lipoprotein loses its anti-inflammatory capacity by accumulation of pro-inflammatory-serum amyloid A. Cardiovasc Res 94: 154–162.

Troutt JS, Alborn WE, Mosior MK, Dai J, Murphy AT, Beyer TP *et al.* (2008). An apolipoprotein A-I mimetic dose-dependently increases the formation of prebeta1 HDL in human plasma. J Lipid Res 49: 581–587.

Vaisar T, Pennathur S, Green PS, Gharib SA, Hoofnagle AN, Cheung MC *et al.* (2007). Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL. J Clin Invest 117: 746–756.

Van Lenten BJ, Wagner AC, Navab M, Anantharamaiah GM, Hama S, Reddy ST *et al.* (2007). Lipoprotein inflammatory properties and serum amyloid A levels but not cholesterol levels predict lesion area in cholesterol-fed rabbits. J Lipid Res 48: 2344–2353.

Varady KA, Jones PJ (2005). Combination diet and exercise interventions for the treatment of dyslipidemia: an effective preliminary strategy to lower cholesterol levels? J Nutr 135: 1829–1835.

Vedhachalam C, Liu L, Nickel M, Dhanasekaran P, Anantharamaiah GM, Lund-Katz S *et al*. (2004). Influence of ApoA-I structure on the ABCA1-mediated efflux of cellular lipids. J Biol Chem 279: 49931–49939.

Vergeer M, Holleboom AG, Kastelein JJ, Kuivenhoven JA (2010). The HDL hypothesis: does high-density lipoprotein protect from atherosclerosis? J Lipid Res 51: 2058–2073.

Villines TC, Stanek EJ, Devine PJ, Turco M, Miller M, Weissman NJ *et al*. (2010). The ARBITER 6-HALTS Trial (arterial biology for the investigation of the treatment effects of reducing cholesterol 6-HDL and LDL treatment strategies in atherosclerosis) final results and the impact of medication adherence, dose, and treatment duration. J Am Coll Cardiol 55: 2721–2726.

Viswambharan H, Ming XF, Zhu S, Hubsch A, Lerch P, Vergeres G *et al*. (2004). Reconstituted high-density lipoprotein inhibits thrombin-induced endothelial tissue factor expression through inhibition of RhoA and stimulation of phosphatidylinositol 3-kinase but not Akt/endothelial nitric oxide synthase. Circ Res 94: 918–925.

Vosper H (2009a). Niacin: a re-emerging pharmaceutical for the treatment of dyslipidaemia. Br J Pharmacol 158: 429–441.

Vosper H (2009b). Niacin: a re-emerging pharmaceutical for the treatment of dyslipidaemia. Br J Pharmacol 158: 429–441.

Wagner JD, Shadoan MK, Zhang L, Ward GM, Royer LJ, Kavanagh K *et al*. (2010). A selective peroxisome proliferator-activated receptor alpha agonist, CP-900691, improves plasma lipids, lipoproteins, and glycemic control in diabetic monkeys. J Pharmacol Exp Ther 333: 844–853.

Walldius G, Jungner I (2006). The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy–a review of the evidence. J Intern Med 259: 493–519.

Wang A, Prouty CP, Pelton PD, Yong M, Demarest KT, Murray WV *et al*. (2010). Synthesis and discovery of 2,3-dihydro-3,8-diphenylbenzo[1,4]oxazines as a novel class of potent cholesteryl ester transfer protein inhibitors. Bioorg Med Chem Lett 20: 1432–1435.

van Wijk JP, de Koning EJ, Martens EP, Rabelink TJ (2003). Thiazolidinediones and blood lipids in type 2 diabetes. Arterioscler Thromb Vasc Biol 23: 1744–1749.

Wilson PW, Abbott RD, Castelli WP (1988). High density lipoprotein cholesterol and mortality. The Framingham Heart Study. Arteriosclerosis 8: 737–741.

Wojcicka G, Jamroz-Wisniewska A, Horoszewicz K, Beltowski J (2007). Liver X receptors (LXRs). Part I: structure, function, regulation of activity, and role in lipid metabolism. Postepy Hig Med Dosw (Online) 61: 736–759.

Yusuf S, Reddy S, Ounpuu S, Anand S (2001). Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 104: 2746–2753.

Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F *et al*. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364: 937–952.

Zadelaar AS, Boesten LS, Jukema JW, van Vlijmen BJ, Kooistra T, Emeis JJ *et al*. (2006). Dual PPARalpha/gamma agonist tesaglitazar reduces atherosclerosis in insulin-resistant and hypercholesterolemic ApoE*3Leiden mice. Arterioscler Thromb Vasc Biol 26: 2560–2566.

Zhang WJ, Stocker R, McCall MR, Forte TM, Frei B (2002). Lack of inhibitory effect of HDL on TNFalpha-induced adhesion molecule expression in human aortic endothelial cells. Atherosclerosis 165: 241–249.