Cholesteryl ester transfer protein: at the heart of the action of lipid-modulating therapy with statins, fibrates, niacin, and cholesteryl ester transfer protein inhibitors

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Received 5 March 2009; revised 6 July 2009; accepted 27 August 2009; online publish-ahead-of-print 12 October 2009

Subnormal plasma levels of high-density lipoprotein cholesterol (HDL-C) constitute a major cardiovascular risk factor; raising low HDL-C levels may therefore reduce the residual cardiovascular risk that frequently presents in dyslipidaemic subjects despite statin therapy. Cholesteryl ester transfer protein (CETP), a key modulator not only of the intravascular metabolism of HDL and apolipoprotein (apo) A-I but also of triglyceride (TG)-rich particles and low-density lipoprotein (LDL), mediates the transfer of cholesteryl esters from HDL to proatherogenic apoB-lipoproteins, with heterotransfer of TG mainly from very low-density lipoprotein to HDL. Cholesteryl ester transfer protein activity is elevated in the dyslipidaemias of metabolic disease involving insulin resistance and moderate to marked hypertriglyceridaemia, and is intimately associated with premature atherosclerosis and high cardiovascular risk. Cholesteryl ester transfer protein inhibition therefore presents a preferential target for elevation of HDL-C and reduction in atherosclerosis. This review appraises recent evidence for a central role of CETP in the action of current lipid-modulating agents with HDL-raising potential, i.e. statins, fibrates, and niacin, and compares their mechanisms of action with those of pharmacological agents under development which directly inhibit CETP. New CETP inhibitors, such as dalcetrapib and anacetrapib, are targeted to normalize HDL/apoA-I levels and anti-atherogenic activities of HDL particles. Further studies of these CETP inhibitors, in particular in long-term, large-scale outcome trials, will provide essential information on their safety and efficacy in reducing residual cardiovascular risk.

Keywords
- HDL
- Atherosclerosis
- Cholesteryl ester transfer protein
- Cholesteryl ester transfer protein inhibitor
- Triglycerides
- Reverse cholesterol transport

Introduction

Despite the widespread use of statin therapy, the incidence of cardiovascular morbidity and mortality remains elevated in many patients with dyslipidaemia, and particularly in those exhibiting metabolic disease and insulin resistance.1 In large landmark trials, reduction in low-density lipoprotein cholesterol (LDL-C) levels with statins has been shown to decrease the incidence of major cardiovascular events by 25–45%.2–4 Nonetheless, considerable residual cardiovascular risk, which includes a high frequency of recurrent events, remains even with an aggressive statin treatment regimen.5–9 New therapeutic options are clearly needed to further improve the treatment of atherogenic dyslipidaemia by reducing residual cardiovascular risk, especially with a view to reduction in lifetime risk.

Several cross-sectional and prospective epidemiological studies have demonstrated that high-density lipoprotein cholesterol (HDL-C) is a strong, independent, inverse predictor of risk of coronary heart disease (CHD).10–14 More recently, elevated circulating levels of the major apolipoproteins (apo) of HDL, apoA-I and
A recent meta-analysis suggested, however, that increasing HDL-C does not reduce the risk of cardiovascular events, and that such risk reduction is attributable to LDL-C raising alone. This finding is inconsistent with the weight of epidemiological and experimental evidence, and may reflect several major limitations in both design and methodology, including (i) the use of aggregated rather than individual subject data, (ii) lack of consideration of baseline triglyceride (TG) levels, (iii) inclusion of a majority of statin-driven studies in which differences between on-treatment and control levels of HDL-C were <3%, (iv) the risk of bias by confounding as this analysis describes an observational association, (v) insensitivity to measurement errors, and finally (vi) the combination of data from trials involving agents with significant distinctions in their action on HDL. Some prudence should therefore be applied when interpreting potentially spurious conclusions.

In contrast, a 16-year follow-up of the Bezafibrate Infarction Prevention Study demonstrated that HDL-C-raising therapy was associated with a reduction in risk of long-term mortality. Moreover, large-scale prospective clinical studies have shown that therapeutic raising of HDL-C levels is associated with attenuated progression of intima-media thickening in the carotid artery, slowed progression of coronary artery atherosclerosis, and reduced cardiovascular risk. It is equally relevant that infusion of the HDL mimetic ETC-216, a lipitated form of recombinant apoA-I Milano, induced regression of coronary atherosclerosis in a small cohort of patients with acute coronary syndromes as evaluated by intravascular ultrasound (IVUS). More recently, a single infusion of reconstituted HDL particles induced acute changes in plaque composition and structure in a placebo-controlled study in patients exhibiting symptomatic atherosclerotic vascular disease in the superficial femoral artery. Specifically, a 20% increment in HDL-C was associated with reduction in lipid content, macrophage size, and the intra-plaque expression of vascular cell adhesion molecule (VCAM-1; C21; P = 0.001), with no alteration of baseline triglyceride (TG) levels, (iv) inclusion of a majority of statin-driven studies in which differences between on-treatment and control levels of HDL-C were <3%, (v) the risk of bias by confounding as this analysis describes an observational association, (vi) insensitivity to measurement errors, and finally (vi) the combination of data from trials involving agents with significant distinctions in their action on HDL. Some prudence should therefore be applied when interpreting potentially spurious conclusions.

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HDL subfractions are distinct with respect to the degree of atheroprotection potentially conferred, although small, CE-poor, dense HDL3 are particularly active in vitro. Indeed, the hypothesis that all subfractions of HDL particles exert atheroprotection through one or more mechanisms appears both plausible and attractive at the present time.

The clinical benefits of raising low HDL-C levels observed in lipid intervention trials and the limitations of available therapies have stimulated the search to identify new, more efficacious HDL-raising agents. The marked increase in HDL-C associated with human deficiency of CETP suggested CETP inhibition as a novel and potentially effective approach to elevate HDL-C. Indeed, we interpret available evidence from prospective and cross-sectional epidemiological studies to support the overall contention that reduction of CETP activity, particularly when supranormal as typically occurs in dyslipidaemic subjects at high cardiovascular risk, constitutes a potential strategy for decreasing atherosclerosis and cardiovascular disease.

This critical and timely review provides an integrated view of the role of CETP in cholesterol homeostasis and metabolism in man, identifies CETP as a central actor in the mechanisms of action of the major anti-dyslipidaemic agents which are currently available, and finally compares the principal features of pharmacological agents in development that directly target CETP. To ensure thorough identification of relevant publications, the PubMed database was searched (2002–present) using pre-defined keywords: cholesteryl ester transfer protein, CETP inhibitor, reverse cholest-erol transport, TGs, HDL, statins, and fibrates.

The role of high-density lipoprotein and cholesteryl ester transfer protein in cholesterol metabolism

Although HDL exhibits a number of anti-atherosclerotic activities that appear to contribute to the cardiovascular benefits afforded by raising HDL levels, the major contribution is thought to be due to the key role of HDL particles in the atheroprotective reverse cholesterol transport (RCT) process. This anti-atherogenic pathway has been reviewed extensively and is summarized schematically in Figure 1. It involves the HDL-mediated efflux of cholesterol from peripheral tissues, including cholesterol-loaded monocyte-derived macrophages and foam cells in the arterial wall, with subsequent transport to the liver either for excretion as biliary cholesterol and bile acids, or for recycling.

A major quantitative route for delivery of cholesterol to the liver is represented by the CETP-mediated transfer of CE from HDL to apoB-containing particles, mainly very low-density lipoprotein (VLDL) and LDL, with subsequent uptake primarily by hepatic LDL receptors. This pathway is frequently referred to as the indirect RCT pathway and accounts for some 70% of CE delivery to the liver in man (Figure 1). Cholesteryl ester transfer protein is secreted primarily by the liver and adipose tissue, and circulates in plasma associated principally with HDL. It promotes the transfer of CE from HDL to VLDL and LDL, in exchange for TG which moves in the opposite direction (Figure 2); the endogenous plasma activity of CETP is modulated to a major degree by the magnitude of triglyceridaemia. Indeed the rapid intravascular turnover of VLDL (half-life <30 min) is consistent with maintenance of a non-steady state in the plasma CE pool, with net mass transfer of CE from HDL to VLDL by CETP.

Critically, CETP may exert both pro-atherogenic and anti-atherogenic actions. In its pro-atherogenic dimension, CETP-mediated transfer of CE may effectively reduce the flux of cholesterol through HDL to hepatic scavenger receptor B1 (SR-B1) and LDL receptors in the direct RCT pathway, concomitantly enhancing the mass of cholesterol transported by atherogenic VLDL, intermediate-density lipoprotein (IDL), remnants, and LDL. In this way, the cholesterol burden of these particles is increased, potentially resulting in enhanced deposition in peripheral tissues and the arterial wall. As we and others have proposed, this mechanism may be of special relevance in the post-prandial state.

In moderate to marked hypertriglyceridaemia, a second major CETP-mediated, pro-atherogenic pathway is of critical importance. Thus, under such conditions, elevated levels of apoB-containing acceptor particles for CETP drive enhanced transfer of TG from VLDL to HDL, leading to TG enrichment of HDL with abnormal intravascular metabolism involving reduction in particle size and fall in HDL-C and apoA-I levels due to accelerated renal catabolism (see below).

In contrast, however, CETP may exert anti-atherogenic impact as it promotes the flux of CE to the liver via indirect RCT, with hepatic CE uptake predominantly through the anti-atherogenic LDL receptor pathway. Furthermore, CETP is critical to optimization of LDL particle structure and apoB100 conformation for high affinity binding to LDL receptors.

As indicated above, CETP is centrally implicated in post-prandial hypertriglyceridaemia, an independent risk factor for CHD. The post-prandial state is characterized by the transient accumulation of intestine-derived chylomicrons (CM) and hepatically derived VLDL and their remnants, which may infiltrate and undergo retention in the arterial wall. During the lipolytic process, surface components (mainly phospholipids and free cholesterol) of CM and VLDL are sequestered to HDL due to the action of phospholipid transfer protein (PLTP). In post-prandial hypertriglyceridaemia, CETP-mediated transfer of CE and TG between plasma lipoprotein particles is accelerated as a direct consequence both of increase in the absolute number of apoB-containing acceptor particles for CE, and of major increase in the cumulative surface area under the curve for these particles during the 8 h post-prandial phase, thereby favouring CE enrichment of TG-rich lipoproteins with concomitant transformation of CE-enriched HDL into TG-rich HDL particles (Figure 2). Triglyceride enrichment of HDL is deleterious, as it leads to a loss of apoA-I from the HDL particle; in addition, hepatic lipase-mediated hydrolysis of HDL phospholipids and TG leads to reduction in HDL particle size. Accelerated catabolism of HDL and apoA-I ensues via the renal pathway, with decrease in plasma levels of both HDL-C and apoA-I.

The action of CETP during the post-prandial phase has been shown to differ in normolipidaemic subjects when compared with that in patients with the mixed dyslipidaemic phenotype.
typical of premature coronary artery disease, type 2 diabetes, and the metabolic syndrome. In the post-prandial phase, CETP-mediated net CE transfer flux from HDL to potentially atherogenic TG-rich lipoproteins (especially large VLDL1) is markedly enhanced in mixed (type IIB) dyslipidaemia compared with normolipidaemic controls (Figure 2); such enhanced CE mass transfer occurs concomitantly with elevated levels of TG-rich particles which are maintained over the 8 h post-prandial phase and act as preferential acceptors of CE. In contrast, the area under the curve for triglyceridaemia is up to four-fold lower over the post-prandial phase in normolipidaemic controls, who typically display peak TG levels at 2–4 h of less than ~150 mg/dL.

The nature of the assay employed for evaluation of CETP activity in plasma is of special relevance to the above discussion; indeed, in vitro assays of CETP activity provide contrasting data depending on whether endogenous or exogenous substrate(s) are employed. Assays involving the addition of exogenous HDL or LDL particles containing apoE or apoA-I to plasma samples result in the transfer of CE from HDL to LDL particles, whereas assays employing endogenous HDL particles do not. This is because CETP has a higher affinity for exogenous substrates than for endogenous HDL particles. Therefore, the results of in vitro assays of CETP activity should be interpreted with caution, as they may not accurately reflect the in vivo activity of CETP.

Figure 1 Pathways of reverse cholesterol transport in man. The reverse cholesterol transport system involves lipoprotein-mediated transport of cholesterol from peripheral, extra-hepatic tissues, and arterial tissue (potentially including cholesterol-loaded foam cells/macrophages) to the liver for excretion, either in the form of bile acids or biliary cholesterol. The ATP-binding cassette transporters, ABCA1 and ABCG1, and the scavenger receptor B1, are all implicated in cellular cholesterol efflux mechanisms to specific apoA-I/HDL acceptors. The progressive action of lecithin:cholesterol acyltransferase on free cholesterol in lipid-poor, apolipoprotein A-I-containing nascent high-density lipoprotein, including pre-β-HDL, gives rise to the formation of a spectrum of mature, spherical high-density lipoproteins with a neutral lipid core of cholesteryl ester and triglyceride. Mature high-density lipoproteins consist of two major subclasses, large cholesteryl ester-rich HDL2 and small cholesteryl ester-poor, protein-rich HDL3 particles; the latter represent the intravascular precursors of HDL2. The reverse cholesterol transport system involves two key pathways: (a) the direct pathway (blue lines), in which the cholesteryl ester content (and potentially some free cholesterol) of mature high-density lipoprotein particles is taken up primarily by a selective uptake process involving the hepatic scavenger receptor B1, and: (b) an indirect pathway (red lines) in which cholesteryl ester originating in high-density lipoprotein is deviated to potentially atherogenic very low-density lipoprotein, intermediate-density lipoprotein, and low-density lipoprotein particles by cholesteryl ester transfer protein. Both the cholesteryl ester and free cholesterol content of these particles are taken up by the liver predominantly via the low-density lipoprotein receptor which binds their apoB100 component. This latter pathway may represent up to 70% of cholesteryl ester delivered to the liver per day. The hepatic low-density lipoprotein receptor is also responsible for the direct uptake of high-density lipoprotein particles containing apoA-I; apoE may be present as a component of both HDL2 and HDL3 particles, and may be derived either by transfer from triglyceride-rich lipoproteins, or from tissue sources (principally liver and monocyte-macrophages). Whereas high-density lipoprotein uptake by the low-density lipoprotein receptor results primarily in lysosomal-mediated degradation of both lipids and apolipoproteins, interaction of high-density lipoprotein with scavenger receptor B1 regenerates lipid-poor apoA-I and cholesterol-depleted high-density lipoproteins, both of which may re-enter the HDL/apoA-I cycle. LPL, lipoprotein lipase; PL, phospholipids; HDL-R, holo HDL receptor; HL, hepatic lipase.
measure the net mass transfer of CE from HDL to acceptor VLDL and LDL particles at their plasma concentrations; such endogenous activity is modulated primarily by the relative concentrations of CE donor and acceptor particles, their lipid and protein composition, circulating CETP protein levels, and finally, the plasma half-life of the respective particles. For clinical studies of CETP activity, when the status of the integrated CETP system in the plasma of a given subject is to be evaluated, then the endogenous assay is most appropriate, as it uniquely respects endogenous levels of all the components of the CETP system in the sample.45

**Figure 2** Comparison of pathways of cholesteryl ester transfer protein-mediated heterotransfer of neutral core lipids between lipoprotein particles in normotriglyceridaemia vs. mixed dyslipidaemia involving moderate to marked hypertriglyceridaemia and subnormal levels of triglyceride-enriched high-density lipoprotein. In normotriglyceridaemia, net cholesteryl ester transfer from high-density lipoprotein to low-density lipoprotein predominates, with minor transfer to triglyceride-rich lipoproteins. In hypertriglyceridaemic states, increased numbers of very low-density lipoprotein particles constitute preferential cholesteryl ester acceptors giving rise to elevated acceptor capacity for cholesteryl ester transfer protein; high net mass transfer rates of cholesteryl ester from high-density lipoprotein to triglyceride-rich lipoproteins and of triglyceride from triglyceride-rich lipoproteins to both high- and low-density lipoproteins result. Triglyceride enrichment of both high- and low-density lipoproteins by this mechanism gives rise to formation of small dense low-density lipoprotein and small dense high-density lipoprotein.45 Modified from Barter et al.49 (with permission from Lippincott Williams and Wilkins).

**Lipid-modulating agents that act to modify the atherogenic lipid profile via indirect or direct action on cholesteryl ester transfer protein**

Abundant evidence from in vivo and in vitro studies reveals that the current pharmacological agents (i.e. statins, fibrates, and niacin) commonly used in the treatment of atherogenic dyslipidaemia share the characteristic that their mechanisms of action involve—to varying degrees—direct and/or indirect reduction in plasma CETP activity. Such pharmacologically mediated modulation of CETP typically occurs either through reduction in numbers of apoB-containing lipoprotein acceptor particles (CM, VLDL, remnants, and LDL) for CETP-mediated CE transfer during the fasting and/or post-prandial phases, or through effects on CETP gene expression with resulting alteration in circulating concentrations of CETP protein, or both. These effects are especially relevant to the atherogenic lipid profile typical of type 2 diabetes and metabolic syndrome; such dysmetabolic states not only feature the atherogenic lipid triad, i.e. elevated levels of TG-rich lipoproteins and small dense LDL, together with subnormal levels of HDL-C, but also elevated levels of endogenous CETP activity, a key driver of this lipid phenotype.3,45 Indeed, supranormal CETP activity equally favours the qualitative abnormalities in HDL particles discussed above, which are intimately associated with defective anti-atherogenic function.3,27

**Statins**

In all common forms of atherogenic dyslipidaemia, notably hypercholesterolaemia and mixed dyslipidaemia, therapy to attenuate atherosclerosis and cardiovascular risk is firmly focused on marked reduction of circulating concentrations of atherogenic
lipoproteins (LDL, VLDL, and remnants) with inhibitors of endogenous cholesterol synthesis, i.e. statins. A number of clinical trials have however revealed that statins typically induce modest and sustained elevation in HDL-C of up to 16%–67 most frequently, such elevations are in the range of 5–10% as revealed in the recent VOYAGER meta-analysis. The mechanism(s) underlying the statin-mediated increase in HDL-C is unclear, but appears to be multiple. Significantly, both *in vitro* and *in vivo* studies, in addition to post hoc analyses from large statin-related outcomes studies, have identified key factors which may contribute to the HDL response and facilitate deduction of putative mechanisms. In sum, these studies have revealed that statins reduce supranormal rates of endogenous CETP-mediated CE transfer from HDL to atherogenic particles in dyslipidaemic subjects. This effect, whether in normolipidaemic or dyslipidaemic subjects, or in animal models, involves several mechanisms which include reduction in the number of apoB-containing lipoprotein particles available to accept CE from HDL, and down-regulation of hepatic CETP mRNA expression with subsequent reduction of circulating plasma CETP concentration. As the absolute degree of reduction in baseline levels of apoB-containing particles by statins is largely dose-dependent for each statin, it is predictable that incremental statin-mediated reduction in atherogenic lipoprotein acceptor levels drives concomitant reduction in CETP activity (Table 1). Thus, the most potent statin, rosuvastatin, at its highest dose (40 mg/day), induced decrements of 12 and 59%, respectively, in CETP activity in hypercholesterolaemic and in mixed dyslipidaemic subjects, together with reductions in plasma CETP mass of 33–37%. The superior reduction in CETP activity seen in mixed dyslipidaemia reflects potent reduction in TG-rich lipoproteins, notably the VLDL1 subfraction (–46%), the most avid CE acceptor particle. Indeed, earlier studies with atorvastatin (10 mg/day) in a similar mixed lipid phenotype revealed that decrease in CETP activity was significantly correlated with statin-mediated reduction in VLDL1 levels. Clearly then, the effects of statins on lipoprotein profile and CETP activity are intimately related and are at least in part dependent on baseline lipid phenotype. Statins equally appear to moderately enhance hepatic apoA-I production (10–15%) and reduce CETP gene expression by inhibiting cholesterol biosynthesis in the liver; the cholesterol response element in the promoter of the CETP gene presumably underlies this latter effect. Finally, statin-induced increase in HDL-C may in part be attributable to enhanced peroxisome proliferator-activated receptor (PPAR) α activity, which may stimulate both hepatic apoA-I synthesis and HDL formation.

Further lines of evidence support an effect of statins on CETP activity; first, the degree of change in HDL-C is directly related to the degree of reduction in TG and LDL-C; and secondly, a shift in the HDL particle distribution towards larger, relatively cholesterol- and apoA-I-rich HDL particles typical of HDL2 observed in statin-treated populations, including patients displaying heterozygous familial hypercholesterolaemia. Furthermore, lifestyle factors known to influence plasma CETP activity, such as alcohol intake, body mass index, and reduction in plasma TG, are also independent contributors to statin-induced change in HDL-C.

The activity of hepatic lipase, an enzyme which hydrolyses both lipoprotein phospholipids and TG, may be moderately attenuated (up to –22%) on a dose-dependent basis by statin treatment. This effect favours maintenance of HDL/apoA-I lipidation—and thus prolonged apoA-I plasma residence time—and may indeed amplify the effect of statins in up-regulating apoA-I production. Further studies are needed, however, not only to determine how the above mechanisms mutually interact to favour elevation in circulating HDL-C and apoA-I levels, but also to establish whether statin-mediated effects on CETP activity, HDL-C, and apoA-I levels independently contribute to cardiovascular benefit in dyslipidaemic patients.

**Fibrates**

Early prospective trials of fibrates and of niacin promoted the concept that raising HDL-C levels by therapeutic means would translate into clinical benefit in dyslipidaemic patients at high cardiovascular risk. Fibrates are a chemically heterogeneous class of agents, among which the most widely clinically used, fenofibrate, is primarily a PPARα agonist of moderate affinity. Fibrates bind to PPARα by mimicking the structure of free fatty acids and may increase HDL-C by up to 20% as a function of baseline lipid phenotype. Fibrates appear to increase HDL-C levels in part by reducing plasma CETP activity, an action associated primarily with the potent ability of these agents to lower levels of TG-rich acceptor lipoproteins for CE, mainly VLDL, in both the fasting and post-prandial phases (Table 1). The capacity of fibrates to reduce (endogenous) plasma CETP concentration by up to –26% in patients with mixed dyslipidaemia appears related at least in part to CETP gene expression, suggesting that fibrates may modulate CETP gene expression through activation of PPARα. Reduction in VLDL, and specifically in the VLDL1 subfraction, following treatment with fenofibrate or ciprofibrate in patients with mixed dyslipidaemia was associated with a significant decrease (up to –35%) in the CETP-mediated transfer and targeting of CE from HDL to these particles. Reduction in the CETP-mediated flux of CE from HDL to VLDL therefore represents a common feature of the impact of statins and fibrates on the perturbed intravascular cholesterol metabolism characteristic of mixed dyslipidaemia.

Fibrates also mediate modification in qualitative features of HDL and LDL particles. Thus, fenofibrate induced increases in the mass of light HDL subspecies at the expense of dense HDL3 particles in mixed dyslipidaemia, and equally shifted the dense LDL profile to a normalized distribution in which particles of lower density predominated; reduction in CETP activity is readily implicated in each of these effects. Fibrates preferentially enhance concentrations of apoA-I plus apoA-II-containing HDL particles with physicochemical properties intermediate between those of large HDL2 and small dense HDL3. Such action is in contrast to that of statins, however, which induce increase in the apoA-I-rich HDL subpopulation of largest size (x1-HDL particles). The effect of fibrates on HDL particle subspecies result in part from fibrate-mediated up-regulation of apoA-I and apoA-II gene expression, although the increment in their plasma
Table 1 Effect of statins and fibrates on endogenous plasma cholesteryl ester transfer protein activity, cholesteryl ester transfer protein mass, and the atherogenic lipid profile in dyslipidaemic subjects

| Lipid-lowering agent | Lipid phenotype | Patient status | TG (mg/dL) | VLDL-C (mg/dL) | LDL-C (mg/dL) | HDL-C (mg/dL) | ApoB (mg/dL) | ApoA-I (mg/dL) | Reduction in CE transfer rates from HDL to apoB-lipoproteins (µg CE/h/mL plasma) | CETP mass (µg/mL) |
|----------------------|-----------------|----------------|------------|----------------|---------------|---------------|--------------|---------------|---------------------------------------------------------------------------------|------------------|
| **Statins**          |                 |                |            |                |               |               |              |               |                                                                                  |                  |
| Pravastatin 40 mg/day | HFH             | Baseline       | 108        | 10             | 258           | 52            | 192          | 149           | −18%                                                                             | ND                |
|                      |                 | On-treatment   | 71 (−34%)  | 10 (0%)        | 167 (−35%)    | 52 (0%)       | 133 (−31%)   | 139 (−7%)     | ND                                                                                | ND                |
| Atorvastatin 10 mg/day | Mixed (combined) hyperlipidaemia (IIb) | Baseline       | 197        | 46             | 175           | 46            | 144          | 132           | −21%                                                                             | ND                |
|                      |                 | On-treatment   | 144 (−27%) | 26 (−43%)      | 111 (−37%)    | 46 (0%)       | 99 (−31%)    | 135 (+2%)     | ND                                                                                | ND                |
| Rosuvastatin 40 mg/day | Hypercholesterolaemia (IIa) | Baseline       | 121        | 15             | 172           | 57            | 127          | 125           | −12%                                                                             | 1.8               |
|                      | Mixed (combined) hyperlipidaemia (IIb) | On-treatment   | 89 (−26%)  | 10 (−36%)      | 68 (−60%)     | 62 (+9%)      | 65 (−49%)    | 144 (+15%)    | 1.2 (−33%)                                                                       | 1.9               |
|                      |                 | On-treatment   | 234        | 36             | 164           | 42            | 134          | 124           | −59%                                                                             | ND                |
|                      |                 |                | 157 (−33%) | 18 (−50%)      | 72 (−56%)     | 46 (+11%)     | 69 (−49%)    | 133 (+7%)     | 1.2 (−37%)                                                                       | ND                |
| **Fibrates**         |                 |                |            |                |               |               |              |               |                                                                                  |                  |
| Fenofibrate 200 mg/day | Mixed (combined) hyperlipidaemia (IIb) | Baseline       | 289        | 48             | 185           | 37            | 157          | 132           | −30%                                                                             | ND                |
|                      |                 | On-treatment   | 161 (−44%) | 23 (−52%)      | 159 (−14%)    | 44 (+19%)     | 133 (−15%)   | 148 (+12%)    | ND                                                                                | ND                |
| Clofibrate 100 mg/day | Mixed (combined) hyperlipidaemia (IIb) | Baseline       | 198        | 43             | 186           | 37            | 147          | 150           | −25%                                                                             | ND                |
|                      |                 | On-treatment   | 108 (−45%) | 25 (−42%)      | 149 (−20%)    | 42 (+14%)     | 109 (−26%)   | 156 (+5%)     | ND                                                                                | ND                |

Mixed (combined) hyperlipidaemia is alternatively referred to as mixed or combined dyslipidaemia. Apo, apolipoprotein; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; HFH, heterozygous familial hypercholesterolaemia; ND, not determined; TG, triglyceride; VLDL-C, very low-density lipoprotein cholesterol.
levels of apoA-I is minor as their fractional catabolic rate in the plasma compartment is accelerated.90

Other documented effects of fibrates on HDL metabolism result from PPARα-mediated up-regulation of lipoprotein lipase activity with enhanced lipolysis of CM and VLDL, resulting in release of surface fragments containing phospholipid and free cholesterol that sequester to the HDL pool under the action of PLTP; this latter effect may be amplified by PPARα-mediated attenuation of the hepatic synthesis and production of apoC-III.89,91,92 The potent TG-lowering action of fibrates is of course central to the attenuation of elevated basal levels of CETP activity in dyslipidaemic subjects, as it effects marked reduction in numbers of TG-rich particle acceptors with high avidity for CETP. Finally, enhanced cholesterol efflux from macrophages to HDL/apoA-I acceptors subsequent to PPARα-mediated up-regulation of SR-B1 and ABCA1 expression may impact on plasma HDL-C levels to a minor degree.93

As emphasized earlier, the impact of fibrates is largely a function of baseline lipid levels;40-91,93 the effects of both gemfibrozil and fenofibrate on plasma HDL-C levels are most pronounced when fasting levels of TG and TG-rich lipoproteins are elevated, and when baseline HDL-C levels are low.91,94 As with statins, the question can be legitimately raised as to the relative contribution of HDL-raising to cardiovascular benefit by fibrates, particularly given the wide range of anti-inflammatory actions of these agents.91,92

In regard to the impact of fibrates on cardiovascular disease, fenofibrate reduced angiographic progression of CHD in patients with type 2 diabetes,95,96 whereas gemfibrozil significantly reduced the frequency of non-fatal myocardial infarction or death attributable to CHD by 22% relative to placebo in the VA-HIT Trial.83 The FIELD trial, however, failed to show this in type 2 diabetes patients in a primary prevention context.97 In the Helsinki Heart Study, the observed reduction in major coronary events in subjects without CHD, but with non-HDL-C > 200 mg/dL, was attributed in part to the gemfibrozil-induced increase in HDL-C.92 Similarly, in men with known CHD and low HDL-C in the VA-HIT study, cardiovascular event reduction was shown to be inversely related to HDL-C level, and particularly that of HDL3, but not to change in either TG or LDL-C.91,93 It is noteworthy, however, that absolute increments in HDL-C in these studies were 11% and 6%, respectively, and that reductions in TG levels were at least three-fold greater (35 and 31%, respectively).

Importantly, a pooled meta-analysis of long-term randomized placebo-controlled clinical trials with fibrates has revealed that these agents significantly reduce the occurrence of non-fatal myocardial infarction, but are without significant effect on other adverse cardiovascular outcomes.98 Recent subgroup analyses have however revealed that subjects displaying the lipid triad in conjunction with a metabolic syndrome phenotype appear to benefit significantly from fibrate therapy; the mechanistic basis of such findings is indeterminate, but suggests that in addition to their effects on the lipid profile, fibrates may beneficially attenuate vascular and systemic inflammation due to PPARα-mediated down-regulation of a wide spectrum of pro-inflammatory genes.99,100

In summary, statins and fibrates act in part by similar mechanisms to attenuate supranormal CETP activity in atherogenic dyslipidaemia by reducing acceptor particle numbers for HDL CE. Other aspects of the actions of fibrates which influence the concentrations and qualitative aspects of HDL particles (notably those focused on TG-rich particles involving the lipolytic pathway) appear to be distinct from those not only of statins, but also of niacin and CETP inhibitors (see below).

**Niacin**

The broad spectrum action and efficacy of niacin (nicotinic acid; vitamin B3) in markedly lowering elevated concentrations of TG-rich lipoproteins, IDL, LDL, and Lp(a), together with its capacity to raise HDL-C, are especially notable. Indeed, niacin is presently the most effective agent available for raising HDL-C, typically increasing levels by up to 30% on a dose-dependent basis.3,7,24,33,101 The clinical benefits associated with niacin treatment, both as monotherapy or in combination with a statin, feature attenuation of atherosclerosis progression and/or induction of plaque regression in addition to reduction in cardiovascular risk, and have been reviewed elsewhere.25 The mechanisms underlying the action of niacin in reducing plasma VLDL, LDL, and apoB levels in vivo involve enhanced clearance of TG-rich lipoproteins containing either apoB100 or B48,102 although evidence is equally available to support decreased rates of VLDL production; such discrepancies may depend upon the metabolic background.103 Only recently has attention been focused on delineating the mechanisms which underlie the HDL-raising action of niacin.102,104,105 Four key processes are considered to contribute to niacin-mediated elevation in apoA-I and HDL-C levels: (i) up-regulation of apoA-I production (+24%) relative to placebo without change in fractional catabolic rate,102 with no change in either the concentration of or kinetic parameters for apoA-II; (ii) the ability of niacin to exert transient inhibition of hormone-sensitive TG lipase in adipose tissue and attenuate liberation of free fatty acids via TG lipolysis, with consequent reduction in hepatic VLDL-TG production, plasma VLDL levels, and thence in CETP-mediated depletion of HDL-C; (iii) reduction in plasma CETP activity as a result of the combined effect of reduction in hepatic CETP gene expression, plasma CETP mass, and numbers of apoB-containing acceptor particles available for HDL-C (see below);104,106 and (iv) reduction in the hepatic uptake of HDL, potentially by the holo-particle uptake pathway.107,108 Considered together, these processes would feasibly increase the plasma residence time of HDL and apoA-I and thus increase HDL-C levels. Such action is entirely consistent with recent findings in low HDL-C human subjects with established CAD who were treated with a niacin/statin combination, and in whom abnormalities in the HDL proteome were partially reversed.109 Finally, the potential role of niacin in enhancing cholesterol efflux via ABCA1 from macrophages to HDL acceptors, with positive impact on HDL-C levels, cannot be excluded.110 The above observations concur to place CETP firmly at the centre of the processes mediated by niacin treatment which directly lead to efficacious elevation of both HDL-C and apoA-I.

**Cholesteryl ester transfer protein inhibitors**

Several efficacious chemical CETP inhibitors have been identified; these include torcetrapib (Pfizer, New York, NY, USA), dalcetrapib...
The adverse outcome in ILLUMINATE. These trials used coid excess in patients administered torcetrapib contributed to levels, supporting the contention that an off-target mineralocorticoid mechanism mediates changes in blood pressure and aldosterone level, revealing that torcetrapib raised blood pressure with concomitant increase in expression of component genes of the renin–angiotensin–aldosterone system (RAAS) in adrenal tissue. Structure—activity investigations have provided further evidence that the hypertension effects of torcetrapib are unrelated to HDL-raising. Studies in rats support a relationship between torcetrapib-mediated changes in blood pressure and aldosterone level, revealing that torcetrapib raised blood pressure with concomitant increase in expression of component genes of the renin–angiotensin–aldosterone system (RAAS) in adrenal tissue. Structure—activity investigations have provided further evidence that the hypertension effects of torcetrapib are unrelated to HDL-raising.

Three prospective clinical trials of torcetrapib reported increments in systolic blood pressure of 2.8–5.4 mmHg; a pooled analysis of two of the trials reported elevation in plasma sodium and bicarbonate levels and reduction in potassium levels, supporting the contention that an off-target mineralocorticoid excess in patients administered torcetrapib contributed to the adverse outcome in ILLUMINATE. These trials used imaging modalities to evaluate atherosclerosis progression (ILLUSTRATE) and carotid intima-media thickening (CIMT; RADIANCE 1, RADIANCE 2). Although substantial increases in HDL-C (54–63%) and reductions in LDL-C (18–20%) from baseline were observed, torcetrapib plus atorvastatin failed to diminish maximum CIMT in patients with familial hypercholesterolaemia and in mixed dyslipidaemia; equally, this combination did not significantly decrease IVUS-assessed atheroma volume in patients with CHD. Although overall findings in the ILLUSTRATE trial did not reveal a beneficial impact of torcetrapib treatment on the progression of coronary atheroma, a post hoc analysis showed that patients exhibiting the greatest HDL-raising response (HDL-C > 87 mg/dL) displayed the lowest rate of progression of per cent atheroma volume (–0.7 vs. +0.7%, P = 0.0003).

It has nonetheless been hypothesized that HDL function may be impaired by torcetrapib, either by a direct mechanism or indirectly by CETP inhibition. Torcetrapib-associated HDL dysfunction might result directly from the formation of non-productive complexes in which torcetrapib binds to CETP in a 1:1 ratio, forming a larger complex with HDL particles. However, calculation shows that for plasma concentrations of HDL 6–10 μM, and CETP 20–60 nM, only up to 1% of HDL particles could contain a single molecule of torcetrapib bound to CETP—at this level potential HDL particle dysfunction resulting from direct binding of torcetrapib would be undetectable unless inactive complexes were purified; in addition, any torcetrapib in excess of that bound to CETP–HDL complexes appears to partition preferentially into TG-rich lipoproteins (R. Clark, personal communication).

Equally, CETP inhibition could potentially result in the generation of HDL particles with deficient anti-atherogenic properties despite absence of bound torcetrapib; for example, large HDL particles enriched in apoA-I and CE might exert deleterious effects on the direct or indirect RCT pathways and on steroid metabolism. Further evidence for the functionality of HDL particles formed under torcetrapib treatment has recently been reported in mixed dyslipidaemic subjects with low HDL-C and elevated TG levels at baseline; CETP inhibition favoured modification towards normalization of the abnormally low neutral core lipid ratio (CE/TG) in all HDL particles including HDL2 and HDL3 subfractions. These findings support the contention that selective CETP inhibition favourably modulates the abnormal physicochemical properties of HDL2 and HDL3 particles in mixed dyslipidaemia, concomitantly enhancing both cholesterol efflux and selective hepatic uptake of HDL-C (Figure 1).

In summary, available evidence indicates that torcetrapib-mediated inhibition of CETP does not induce dysfunction in HDL particles, but rather modifies their metabolism, structure, and physicochemical properties favouring normalization of anti-atherogenic functionality.

Dalcetrapib
Dalcetrapib is distinct from torcetrapib in the nature of its interaction with the CETP protein. Indeed, depending on the assay used, IC50 values for CETP activity have been estimated to be 0.4–10 μM for dalcetrapib compared with 19–79 nM for torcetrapib, clearly suggesting that plasma concentrations reached in clinical studies with dalcetrapib are unlikely to achieve complete inhibition of CETP. Dalcetrapib interacts with cysteine 13 residue in CETP, with high specificity for CETP over other SH-containing enzymes. Furthermore, unlike torcetrapib, dalcetrapib does not appear to induce the formation of a CETP–HDL complex at therapeutic plasma concentrations.

The efficacy of dalcetrapib was initially demonstrated in cholesterol-fed rabbits. After 6-month treatment, dalcetrapib (mean dose 255 mg/kg/day) significantly increased HDL-C...
(+90%), with elevation in HDL2-C (+170%), HDL3-C (+59%), and apoA-I (+78%) (P < 0.01 for comparison of on-treatment levels vs. baseline). In addition, dalcetrapib treatment effected a 70% reduction in aortic arch lesions compared with controls.\textsuperscript{129} In a subsequent similar study, dalcetrapib elevated HDL-C levels but atheromatous area was not correlated with HDL-C levels or CETP activity.\textsuperscript{130}

A Phase II, placebo-controlled, randomized study evaluated the efficacy and safety of dalcetrapib in 198 healthy subjects with mild hyperlipidaemia (HDL-C ≤ 60 mg/dL and TG ≤ 400 mg/dL).\textsuperscript{131} After 4 weeks, dalcetrapib (900 mg/day) significantly reduced CETP activity (−37%, P < 0.0001), increased HDL-C (+34%, P < 0.0001), and decreased LDL-C (−7%, P = 0.02), and in addition exerted a non-significant effect on apoA-I (+16%). Dalcetrapib was well tolerated, with no clinically significant changes in blood pressure. The efficacy and safety of dalcetrapib at doses of 300 and 600 mg/day were also assessed in a randomized, Phase II study conducted in 155 patients with type II hypercholesterolaemia (LDL-C > 160 mg/dL, HDL-C < 60 mg/dL, and TG < 400 mg/dL) receiving pravastatin (40 mg/day).\textsuperscript{132} After 4 weeks, dalcetrapib (600 mg/day) significantly reduced CETP activity by 30%, compared with baseline (P < 0.001). Significant increases in HDL2-C and HDL3-C relative to baseline (P < 0.001).\textsuperscript{132} The combination of agents was well tolerated, with no clinically significant changes in blood pressure. Furthermore, in a recent analysis of four 4-week Phase IIa studies (including the two studies mentioned above) and one 12-week Phase IIb study in patients with type II hyperlipidaemia, CHD, or CHD risk equivalents, dalcetrapib was generally well tolerated and was not associated with clinically relevant elevations in blood pressure or cardiovascular adverse events at the doses studied.\textsuperscript{133} Finally, in a CETP-deficient rat model, dalcetrapib did not increase blood pressure or expression of RAAS-related genes.\textsuperscript{138}

Several clinical trials are ongoing with the objective of evaluating the clinical efficacy and safety of dalcetrapib. One of these, dal-VESSEL, is focused on modulation of vascular function by CETP inhibition and will shed further light on the mechanisms implicated in the improved endothelial function which was recently observed in hypercholesterolaemic subjects with low baseline HDL-C subsequent to dalcetrapib treatment.\textsuperscript{134} The impact of dalcetrapib on atherosclerotic plaque development (dal-PLAQUE) has been initiated in some 100 patients with CHD using positron emission tomography/computed tomography and magnetic resonance imaging.\textsuperscript{135} Finally, in order to evaluate the effects of dalcetrapib on mortality and morbidity, >15 600 high-risk CHD patients considered to have stable disease after a recent acute coronary syndrome event will be recruited into the ongoing dal-OUTCOMES trial.\textsuperscript{136} Patients will receive dalcetrapib on a background of optimized therapy for LDL-C reduction; importantly, no inclusion criterion for HDL-C level was set in this trial, thereby allowing assessment of the potential clinical benefit of HDL raising via CETP inhibition to be evaluated across a range of baseline HDL-C levels (Table 2).

### Anacetrapib

Anacetrapib, like torcetrapib, induces tight reversible binding of CETP to HDL, with IC\textsubscript{50} values for CETP of 15–57 nM.\textsuperscript{137} A Phase I randomized, placebo-controlled study assessed the efficacy and safety of anacetrapib in 50 patients with dyslipidaemia (LDL-C, 100–190 mg/dL).\textsuperscript{138} After 28-day treatment, anacetrapib produced dose-dependent lipid-altering effects; at the maximal

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**Table 2** Overview of the dal-OUTCOMES trial: a randomized, double-blind, placebo-controlled study assessing the effect of RO4607381 (dalcetrapib) 600 mg/d on cardiovascular mortality and morbidity in clinically stable patients with a recent acute coronary syndrome\textsuperscript{135}

| Design                        | Criteria                                                                 | Main outcomes                                                                 |
|-------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| **Phase III**                 | Inclusion                                                               | Primary<br>Time to first occurrence of any component of the composite cardiovascular event, cardiovascular mortality/morbidity (event driven) |
| Treatment (interventional)    | Male/female adult patients ≥ 45 years of age                             | Secondary<br>Composite endpoint: all-cause mortality (event driven)            |
| Randomized                    | Recently hospitalized for acute coronary syndrome                         | Change from baseline in blood lipids and lipoprotein levels (throughout study) |
| Double-blind (subject, investigator) | Clinically stable            | Adverse events, laboratory safety, vital signs, ECG (throughout study)        |
| Placebo controlled            | Receiving evidence-based medical and dietary management of dyslipidaemia |                                                                               |
| Parallel assignment           | Exclusion                                                               |                                                                               |
| International                 | Uncontrolled diabetes                                                   |                                                                               |
|                               | Clinically unstable                                                     |                                                                               |
|                               | Severe anaemia                                                          |                                                                               |
|                               | Uncontrolled hypertension                                               |                                                                               |
|                               | Concomitant treatment with any other                                    |                                                                               |
|                               | HDL-C-raising drug (e.g. niacin, fibrate)                                |                                                                               |
|                               | Healthy volunteers                                                       |                                                                               |

ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol.
dose tested, anacetrapib (300 mg/day) induced marked increments in HDL-C and apoA-I levels (+129 and +47%, respectively), with significant reduction in LDL-C (−38%) compared with placebo. In a second Phase I study of the effects of anacetrapib on 24 h ambulatory blood pressure over 10 days in 22 healthy individuals, similar profiles for systolic and diastolic blood pressure were observed for anacetrapib and placebo. These Phase I studies were short, involved a small number of patients, and were not powered to detect a difference in blood pressure of <6 mmHg. More recently, the efficacy and safety of anacetrapib were evaluated as monotherapy and in co-administration with atorvastatin (20 mg/day) in patients (n = 589) displaying either hypercholesterolaemia or mixed dyslipidaemia over an 8-week period; some 54% exhibited low HDL-C at baseline. For anacetrapib monotherapy, a dose-titration design revealed incremental reduction in LDL-C levels to −39% at the maximal 300 mg dose, with progressive elevation in HDL-C to +133% at this same dose. Co-administration of the CETP inhibitor with background statin therapy produced major incremental reductions in LDL-C attaining a maximal value at −70%; moreover, HDL-C elevations mediated by anacetrapib alone were maintained on co-administration of the two agents. Triglyceride levels at baseline exerted little effect on the dose-dependent reductions seen in LDL-C either in monotherapy or co-administration modes. The CETP inhibitor was well tolerated, no changes in blood pressure were noted, and the incidence of adverse effects was similar in placebo and active treatment groups. Further studies are now required to evaluate the long-term efficacy and safety of anacetrapib, both in monotherapy and in association with a statin. Indeed, the DEFINE study is ongoing and was designed to evaluate the lipid-lowering efficacy, tolerability, and safety of anacetrapib (100 mg/day) in normotriglyceridaemic subjects (n = 1623) with LDL-C < 100 mg/dL and HDL-C < 60 mg/dL on statin treatment over an 18-month period; here, the combination of background placebo or CETP inhibitor treatment is being compared with statin monotherapy.

Residual cardiovascular risk: validity of cholesteryl ester transfer protein as a therapeutic target

Despite recent genome-wide association scans identifying genetic variants influencing plasma lipid concentrations, and in the case of HDL-C those concerning the CETP gene, the use of gene therapy to improve the management of dyslipidaemia and reduce cardiovascular risk remains elusive. In the meantime, residual cardiovascular risk remains high even in patients treated with aggressive statin therapy, highlighting the need for add-on treatment to reduce the considerable cardiovascular event rate (Figure 3). Among risk factors other than LDL-C that are associated with atherogenic dyslipidaemia, a low level of HDL-C is now most recognized, especially as it is a key feature of common metabolic diseases. Moreover, the destructive anti-atherogenic function of HDL particles in metabolic disease is now established and has become recognized as a therapeutic target of similar significance to that of HDL-C level. Such defective HDL function is intimately linked to the abnormal metabolism of TG-rich lipoproteins and is consistent with concomitant therapeutic correction of both these anomalies in order to reduce residual risk.

The critical appraisal presented herein of the mechanisms of action implicated in the HDL-raising action of statins, fibrates, and niacin not only highlights but equally validates the central role of CETP in the modulation of perturbed lipid and cholesterol metabolism in dyslipidaemic subjects by these agents, particularly as it relates to HDL. Indeed, this evidence base substantiates the argument that CETP constitutes a preferential pharmacological target for HDL-raising therapies. The direct and/or indirect actions of statins, fibrates, and niacin on the CETP system impact, to a significant degree, both the quantitative and the qualitative features not only of the atherogenic lipoproteins, but equally of their anti-atherogenic counterparts, the high-density particles. As discussed, these agents favour normalization of HDL and apoA-I levels to varying degrees as a function of baseline lipid phenotype, but may exert distinct structural, metabolic, and functional effects on the heterogeneous population of HDL particles. In addition to raising HDL levels, they equally may potentiate at least partial normalization of defective HDL function, but this question remains only partially resolved.

Who may benefit clinically from treatment with cholesteryl ester transfer protein inhibitors?

The pharmacological signature of CETP inhibitors and their impact on dysmetabolism characteristic of mixed dyslipidaemia,
hypertriglyceridaemia, and hypercholesterolaemia suggests potential utility in treating common forms of dyslipidaemia associated with premature atherosclerosis.115,126,127,131,132,143,144 In particular, metabolic syndrome and type 2 diabetes may be ideal targets for intervention with CETP inhibitors, given the quantitative and qualitative anomalies of HDL particles in these insulin-resistant disease states (Figure 3).31,32,145

From a quantitative viewpoint, it is established that the relation of cardiovascular risk to HDL-C levels is especially steep in the range of 20–40 mg/dL, clearly indicating that therapeutic approaches targeted to HDL-C elevation may be critically important in many low HDL-C patients.146–148 Thus, the potent HDL-raising action of the CETP inhibitors would allow the clinician to efficaciously attain a potential HDL-C target of 40 mg/dL or higher in such patients, potentially affording major clinical benefit.

Qualitatively, and as a consequence of hypertriglyceridaemia and elevated CETP activity, functionally deficient HDL particles enriched in core TG and depleted in CE and apoA-I are formed intravascularly in both type 2 diabetic and metabolic syndrome patients.24,131,149,150 Thus, therapeutic normalization of both the quantity and the quality of HDL particles by CETP inhibitors constitutes a key target to efficaciously attenuate atherosclerosis in dyslipidaemic individuals with metabolic disease.

Statins, fibrates, and niacin attenuate plasma CETP activity principally by indirect mechanisms, and such effects are associated with favourable impact on both cholesterol homeostasis and the atherogenic process. In contrast, we do not fully understand the potential impact of partial, direct CETP inhibition on cholesterol homeostasis and atherosclerosis. Indeed, the therapeutic impact of such agents may vary as a function of individual metabolic phenotypes associated—or not—with insulin resistance. Long-term, large-scale morbi-mortality outcome trials are therefore essential to provide critical information on their efficacy, clinical benefit, and safety. Such clinical investigations are eagerly awaited, as the CETP inhibitors remain by far the most efficacious agents to raise HDL-C levels above the risk threshold range of ~40–50 mg/dL across a wide range of lipid phenotypes.146

Funding
Drs T. Haigh and C.V. Felton (Prime Healthcare) conducted the literature search and provided excellent editorial assistance supported by an educational grant from F. Hoffmann-La-Roche Ltd, Basel, Switzerland. Funding to pay the Open Access charge was provided by an educational grant from F. Hoffmann-La-Roche Ltd. M.J.C. and A.K. gratefully acknowledge the award of a Contrat d’Interface of the Assistance Publique-Hôpitaux de Paris/INSERM. The studies of the authors were supported by INSERM.

Conflict of interest: M.J.C. has received grant support from Pfizer, AstraZeneca, and MSD, and has been a consultant and member of the Speakers bureau of Pfizer, Abbott, AstraZeneca, MSD, and Merck-Schering Plough. A.K. was a recipient of an International HDL Award from Pfizer and grant funding from AstraZeneca. M.G. has received research grant funding from Pfizer and Sanofi-Aventis. W.L.G. has received grant support from MSD.

References
1. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. J Am Coll Cardiol 2005;46:1225–1228.
2. Bagnell C, Keech A, Kearney PM, Blackwell L, Buck G, Pollinico C, Kirby A, Saurinjia T, Peto R, Collins R, Simes R, Cholesterol Treatment Trials’ (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,565 participants in 14 randomised trials of statins. Lancet 2005;366:1267–1278.
3. Chapman MJ. Therapeutic elevation of HDL-cholesterol to prevent athero- sclerosis and coronary heart disease. Progr Cardiovasc Dis 2006;49:93–108.
4. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotta AM Jr, Kastelein JJ, Koening W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2009;359:2195–2207.
5. Lijnen HR, CP, Braunwald E, Tardif JC, CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, Pravastatin or Atorvastatin Evaluation for琦Stability of InMyocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–1504.
6. Laffossa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotta AM, Greten H, Kastelein JJ, Shepherd J, Wengen NKR. Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–1435.
7. Singh IM, Shishibohin MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. JAMA 2007;298:786–798.
8. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E, PROVE IT-TIMI 22 Investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2008;51:724–730.
9. Wolfram RM, Brewer HB, Xue Z, Satler LF, Richards AD, Kent KM, Waksman R. Impact of low high-density lipoproteins on in-hospital events and one-year clinical outcomes in patients with non-ST-elevation myocardial infarction acute coronary syndrome treated with drug-eluting stent implantation. Am J Cardiol 2006;98:711–717.
10. Gordon T, Castelli WP, Hjortorff LC, Kannel WB, Dawber TR. High-density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med 1977;62:707–714.
11. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Knoke JD, M.J. Chapman. Value of HDL cholesterol, apolipoprotein A-I, lipoprotein A-I, and lipoprotein A-II is inversely associated with risk of future coronary artery disease. Circulation 1999;99:799–815.
12. Azman G, Schulte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. Atherosclerosis 1994;124(Suppl):S11–S20.
13. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, Sharman E, Pachter KP, Castelli WP, D’Agostino RB, Vasan RS, Wolf PA, Robins SJ, Kannel WB. Risk factors for incident coronary events in the Urban–Rural community Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2001;104:1108–1113.
14. Luc G, Bard JM, Fernéries J, Evans A, Amouyal P, Arveiler D, Fruchart JC, Ducimetière P. Value of HDL cholesterol, apolipoprotein A-I, lipoprotein A-I, and lipoprotein A-II/III in prediction of coronary heart disease: the PRIME Study. Prospective Epidemiological Study of Myocardial Infarction. Arterioscler Thromb Vasc Biol 2002;22:1155–1161.
15. Brixhonouru RS, Dallinga-Thie GM, Kuivenhoven JA, Stroes ESG, Otis JD, Wareham NJ, Luben R, Kastelein JJP, Khaw KT, Boekholt SM. Apolipoprotein A-II is inversely associated with risk of future coronary artery disease. Circulation 2007;116:2029–2035.
16. van der Steeg WA, Holme I, Boekholt SM, Larsen ML, Lindahl C, Stroes ES, Tikkanen MJ, Wareham NJ, Faergeman O, Olofsson AG, Pedersen TR, Khaw KT, Kastelein JJ. High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies. J Am Coll Cardiol 2008;51:634–642.
17. Briel M, Ferreira-Gonzalez I, You JY, Karonarcsas PJ, Aul EA, Wu P, Blechaes B, Basdaler DL, Wei X, Sharman A, Whitt I, Alves da Silva S, Khalid Z, Nordmann AJ, Zhou Q, Walter SD, Vale N, Bhatnager N, O’Regan C, Mills EJ, Cuyruch HC, Mtoni VM, Guatay GH. Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. BMJ 2009;338:b329; doi: 10.1136/bmj.b329.
18. Goldenberg I, Boyko V, Tenenbaum A, Tanne D, Behar S, Guetta V. Long-term benefit of high-density lipoprotein cholesterol-raising therapy with bezafibrate. Arch Intern Med 2009;169:508–514.
19. Nissen SE, Nicholls SJJ, Sipah I, Libby P, Racchiens JS, Ballantyne CM, Davignon J, Erbelt R, Fruchart JC, Tardif JF, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM. ASTEROID Investigators. Effect of very high-intensity
CETP in the action of current lipid-modulating agents

23. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Kontush A, Chapman MJ. Functionally defective high-density lipoprotein: a new therapeutic target in atherogenic dyslipidemia. *J Clin Invest* 2007; 117: 746–756.

29. Vaisar T, Pennathur S, Green PS, Gharib SA, Hoofnagle AN, Cheung MC, Byun J, McGovern M. Niaspan

33. Chapman MJ, Assmann G, Fruchart JC, Shepherd J, Sirtori C, The European Consensus Panel on HDL-C. Differential contributions of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *Am J Cardiol* 2008; 101: 1084–1091.

40. Chapman MJ. Fibrates in 2003: therapeutic action in atherogenic dyslipidaemia. *Pharmaco Ther* 2004; 101:17–38.

45. Le Goff W, Guérin M, Chapman MJ. Pharmacological modulation of cholesterol ester transfer protein, a new therapeutic target in atherogenic dyslipidaemia. *Pharmacol Ther* 2004; 104:1–17.

Barter PJ, Kastelein JJ. Targeting cholesterol ester transfer protein for the prevention and management of cardiovascular disease. *J Am Coll Cardiol* 2006; 47: 492–499.

Schaler EJ, Assalitos BF. Increasing high-density lipoprotein cholesterol, inhibition of cholesterol esterification, and heart disease risk reduction. *Am J Cardiol* 2007; 100(Suppl): 25N–31N.

Barter PJ, Brewer HB Jr, Chapman MJ, Henningsen CH, Rader DJ, Tall AR. Cholesterol ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler Thromb Vasc Biol* 2003; 23: 160–167.

Lewis GF, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circ Res* 2005; 96:1221–1232.

Voutilainen CC, Varis-Lüönniemi S, Kastelein JJ, Saksamaa T, Bihlmaier K, Chapman MJ. Cholesterol ester ester transfer, transfer, and output in vivo in humans. *J Lipid Res* 2004; 45: 1594–1607.

Brewer HB Jr. High-density lipoproteins: a new potential therapeutic target for the prevention of cardiovascular disease. *Arterioscler Thromb Vasc Biol* 2004; 24: 387–391.

Tall AR. Plasma cholesterol ester transfer protein. *J Lipid Res* 1993; 34: 1255–1274.

Williams KJ. Tabas I. The response-to-rejection hypothesis of early atherogenesis. *Arterioscler Thromb Vasc Biol* 1995; 15:551–561.

Lattis AS, Guérin M, Auboiron S, Chapman MJ, Guy-Grand B. Preferential cholesterol ester acceptors among triglyceride-rich lipoproteins during dietary lipemia in normolipidemic subjects. *Arterioscler Thromb Vasc Biol* 1998; 18:65–74.

Lamarche B, Uffelman KD, Carpenter A, Cohn JI, Steiner G, Barrett PH, Lewis GF. Triglyceride enrichment of HDL enhances in vivo metabolic clearance of HDL apo A-I in healthy men. *J Clin Invest* 1999; 103:1191–1199.

Lund-Jaekel S, Laplaud PM, Philips MC, Chapman MJ. Apolipoprotein B-100 concentration and particle surface charge in human LDL subclasses: implication for LDL receptor interaction. *Biochemistry* 1998; 37: 12867–12874.

Simpson HS, Williamson CM, Olivercrona T, Pringle S, Maclean J, Lorimer AR, Ronnoeus F, Bogavieysk Y, Packard CJ, Shepherd J. Postprandial lipemia, fenofibrate and coronary artery disease. *Atherosclerosis* 1990; 85:193–202.

Guérin M, Egger P, Soudant C, Le Goff W, van Tol A, Dupuis R, Chapman MJ. Cholesterol ester ester transfer protein to VLDL is preferentially enhanced in type IIb hyperlipidemia in the postprandial state. *J Lipid Res* 2002; 43:1652–1660.

Nordestgaard BG, Benn M, Schnoor P, Tybjerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA* 2007; 298:299–308.

Bansal S, Buring JE, Ralai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA* 2007; 298:309–316.

Williams KJ. Molecular processes that handle—and mediate—dietary lipids. *J Clin Invest* 2008; 118:3247–3259.

Castro GR, Fielding CJ. Effects of postprandial lipemia on plasma cholesterol metabolism. *J Clin Invest* 1985; 75:874–882.

Tall A, Sammet E, Granot E. Mechanisms of enhanced cholesteryl ester transfer from high density lipoproteins to apolipoprotein B-containing lipoproteins during dietary lipemia. *J Clin Invest* 1986; 77:1163–1172.

Contacos C, Barter PJ, Varga L, Sullivan DR. Cholesterol ester transfer in hypercholesterolaemia: fasting and postprandial states with and without pravastatin. *Atherosclerosis* 1998; 141:87–98.

Rashid S, Barrett PH, Uffelman KD, Watanabe T, Adei K, Lewis GF. Lipolytically modified triglyceride-enriched HDLs are rapidly cleared from the circulation. *Arterioscler Thromb Vasc Biol* 2002; 22:483–487.

Brewer HB Jr. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol* 2003; 92:23K–29K.

Guérin M, Dolphin PJ, Talusost C, Gardette J, Berthézée F, Chapman MJ. Pravastatin modulates cholesterol ester transfer from HDL to apoB-containing lipoproteins.
lipoproteins and lipoprotein subspecies profile in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 1995;15:1339–1368.

69. Streja L, Packard CJ, Shepherd J, Cobbe S, Ford I, WOSCOPS Group. Factors affecting HDL cholesterol. Arterioscler Thromb Vasc Biol 1999;19:673–672.

70. Streja L, Le Goff W, Fridell E, Schneider S, Milasavljevic D, Bruckert E, Chapman MJ. Action of ciprofibrate in type IIb hyperlipoproteinemia: modulation of the apolipoprotein phenotype and stimulation of high-density lipoprotein-mediated cellular cholesterol efflux. J Clin Endocrinol Metab 2003;88:3738–3746.

71. Streja L, Le Goff W, Lassle TS, Van Tol A, Steiner G, Chapman MJ. Atherogenic role of elevated CE transfer from HDL to VLDL and normalization of the atherogenic, dense LDL profile in combined hyperlipidemia. Arterioscler Thromb Vasc Biol 1996;16:282–288.

72. Schaefer Jr, Schweer H, Ikewaki K, Stracke H, Seyerth B, Haffar K, Maisch B, Steinmetz A. Metabolic basis of high density lipoproteins and apolipoprotein A-I increase by HMG-CoA reductase inhibition in healthy subjects and a patient with coronary artery disease. Atherosclerosis 1999;144:177–184.

73. Oliveira HC, Chouinard RA, Agellon LB, Bruce C, Ma L, Walsh A, Breslow JL, Tall AR. Low-density cholesterol transfer protein gene proximal promoter contains a regulatory element that differentially responds to peroxisome proliferator-activated receptor alpha modulation. Atherosclerosis 2001;162:31831–31838.

74. Gue´rin M, Bruckert E, Dolphin PJ, Turpin G, Chapman MJ. Fenofibrate reduces plasma cholesterol in type IIa hyperlipoproteins: decreases in plasma cholesterol and apolipoproteins B, A-I and plasma triglycerides. Atherosclerosis 2002;161:361–369.

75. Martin G, Duez H, Blancart C, Berezovsky V, Poullain P, Fruchart JC, Najib-Fruchart J, Gilner C. Tadolini’s. Arterioscler Thromb Vasc Biol 2001;21:1407–1413.

76. Asztalos BF, Horvath KV, McNamara JR, Roheims PS, Rubinstein J, Schaefer EJ. Comparing the effects of five different statins on the HDL subpopulation profiles of coronary heart disease patients. Atherosclerosis 2002;161:361–369.

77. Asztalos BF, Le Maffl F, Dalgal GE, Stein E, Jones PH, Horvath KV, McTaggart F, Schaefer EJ. Comparison of the effects of high doses of rosuvastatin versus atorvastatin on the subpopulations of high density lipoproteins. Am J Cardiol 2007;99:681–685.

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

79. Asztalos BF, Le Maffl F, Dalgal GE, Stein E, Jones PH, Horvath KV, McTaggart F, Schaefer EJ. Comparing the effects of high doses of rosuvastatin versus atorvastatin on the subpopulations of high density lipoproteins. Am J Cardiol 2007;99:681–685.

80. Berk-Planken II, Hoogerbrugge N, Stolk RP, Bootsma AH, Jansen H, DALI Study Group. Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: The Diabetes Atherosclerosis Intervention Study (DAIS). Circulation 2003;107:1733–1737.

81. Ashen MD, Blumenthal RS. Low HDL cholesterol levels. JAMA 1996;276:31831–31838.

82. Schonfeld G. The effects of fibrates on lipoprotein and hemostatic coronary risk factors. Atherosclerosis 1994;111:161–174.

83. De 2001;357:905–910. Erratum in: Lancet 2001;357:905–911. Erratum in: Lancet 2002;366:1415, 1420.

84. Correlation between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: The Diabetes Atherosclerosis Intervention Study (DAIS). Circulation 2003;107:1733–1737.

85. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan receptors to drug discovery. J Med Chem 2000;43:527–550.

86. Vakkila J, Steiner G, Ansorcu JS, Akinb F, Rattier S, Foucher C, Hamsten A, Taskinen MR, DAIS Group. Relationships between low-density lipoprotein genotype, plasma lipoproteins, and progression of coronary artery disease: The Diabetes Atherosclerosis Intervention Study (DAIS). Circulation 2003;107:1733–1737.

87. Rhein A, Sjöqvist J, Berntson A, Orja A. The role of fibrates in the prevention of cardiovascular disease—a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am Heart J 2007;154:943–953.

88. Fazio S, Linton MF. The role of fibrates in managing hyperlipidemia: mechanisms of action and clinical efficacy. Curr Atheroscler Rep 2006;4:148–157.

89. Atherosclerosis 2005;366:1849–1861. Erratum in: Lancet 2006;366:1415, 1420.

90. Saha SA, Kishakeppunun LG, Bahaker A, Arora RR. The role of fibrates in the prevention of cardiovascular disease—a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am Heart J 2007;154:943–953.

91. Field. J Am Coll Cardiol 2002;39:493–498.

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

93. Lamon-Fava S, Diffenderfer MR, Barrett PH, Buchsbaum A, Nyaku M, Horvath KV, Asztalos BF, Otakiwasa S, Ai M, Matthson NA, Lichtenstein AH, Dolinkowski GG, Schaefer EJ. Extended-release niacin alters the metabolism of plasma apolipoprotein (Apo) A-I and ApoB-containing lipoproteins. Arterioscler Thromb Vasc Biol 2009;28:1672–1678.

94. Wang W, Basinger A, Neece RA, Shane B, Myong S, Christiansen M, Hellerstein MK. Effect of nicotinic acid administration on hepatic very low density lipoprotein-triglyceride production. Am J Physiol Endocrinol Metab 2001;280:E540–E547.

95. van der Hoorn JW, de Haan W, Berbeé JF, Havekes LM, Jukema JW, Rensen PC, van der Meulen WH, Thunting M, Ethnom HL, Laakso M, FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 7975 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–1861. Erratum in: Lancet 2006;366:1415, 1420.

96. Diabetes Atherosclerosis Intervention Study (DAIS) Group. Effect of fenofibrate on progression of coronary artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study (DAIS), a randomised trial. Lancet 2001;357:905–1051. Erratum in: Lancet 2001;357:910.

97. Kamanna VS, Kashyap ML. Mechanism of action of niacin. Diabetes 2005;54:S27–S50.

98. Zeldovitch S, Lotan-Sadan H, Liner M, Grossman A, Neeman M, Pardo C, Rabinovitz R, Abu-Saad H, Taskinen MR, DAIS Group. Relationships between low-density lipoprotein genotype, plasma lipoproteins, and progression of coronary artery disease: The Diabetes Atherosclerosis Intervention Study (DAIS). Circulation 2003;107:1733–1737.

99. Ashen MD, Blumenthal RS. Low HDL cholesterol levels. JAMA 1996;276:31831–31838.
109. Green PS, Vaisar T, Bennett DR, Kasten JR, Cruickshank AM, Vlassara H, \( n \), Trivedi M, Kloner RA, Auerbach AD, Perlmutter AS, Hulbert-Shearon J, Jacobson TA, McCullough PA. \( n \), Nilsson PO, Madsen JH, O'Leary DH, Offermanns S, Rader DJ, Ingwall JS, Seedorf U, Irons J, Amoren A, Melander O, Ganten D, Ballermann BJ, Givertz MM, Goldstein JL, Brown MS, Kostenuik PJ, Harkness EB. \( n \), Sekiya Y, Niwa H, Fujita T, Yamauchi T, Nakamura Y, Noda K, Matsuoka S, Goto A, Tomiyama R, Kuwano Y, Setoguchi H, Ueki K, Nakanishi K, Tanaka K, Nishida J-I, Kitada N, Okazaki H, Aoyama T, Kanazawa H, Tanaka S, Nishizawa K, Kojima T, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanishi T, Hori M, Takahashi T, Kamada T, Fujita T, Nakamura M, Itoh M, Kojima S, Shida T, Ohashi N, Fujita H, Inoue H, Takeda H, Iwakiri K, Takahashi H, Nakanish
Left aortic sinus to right atrial tunnel

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A 21-year-old asymptomatic lady detected to have heart disease at 12 years of age during a routine medical examination referred to us for further evaluation. The clinical examination was normal except for a grade 3/6 continuous murmur over the right sternal border. Echocardiogram showed minimal dilatation of the right-sided chambers and a fistulous tract originating from the left aortic sinus and draining into right atrium (Panel A). To define the anatomy precisely, a computed tomographic angiogram was done which showed a dilated and elongated left aortic sinus with a fistulous communication to the right atrium near the superior vena cava–right atrial junction (Panels B and C). The left main coronary artery originated just below the aortic origin of the fistula. Catheterization revealed a 12% step-up of blood oxygen saturation in the right atrium with a pulmonary to systemic flow ratio of 1.67:1. The pulmonary artery pressure was normal. An aortic root angiogram was done which demonstrated the fistulous communication to the right atrium. Patient underwent successful percutaneous closure of the fistula using an 8/6 mm Amplatzer Duct Occluder (AGA medical corporation, USA) in the same sitting (Panel D).

Aorta–right atrial tunnel is an abnormal tubular extra cardiac communication between the ascending aorta and the right atrium. Congenital deficiency of the elastic lamina in the aortic media is proposed as the probable cause for this anomaly. This abnormal communication can arise from any of the three sinuses of Valsalva and the left sinus origin is more common. The preference for rupture into the right atrium is unclear. Depending on the origin and course in relation to the ascending aorta, it is divided into anterior and posterior types. Tunnels from the right sinus usually run anteriorly and tunnels from the left sinus follow a posterior course. This differs from ruptured sinus of Valsalva by having an extra cardiac tunnel.

Aorta–right atrial communication behaves like a left to right shunt at the atrial level. Most of the patients are asymptomatic and continuous murmur at the right parasternal border is the common finding. Diagnosis can be established non-invasively by echocardiography and more definitively by computed tomographic angiogram and cardiac magnetic resonance imaging or invasively by aortogram. Surgical or percutaneous closure is indicated once the diagnosis is established as communication can result in volume overload of both ventricles, bacterial endocarditis, aneurysm formation, or spontaneous rupture.

Panel A Echocardiogram in parasternal short-axis view at the aortic valve level demonstrating the left aortic sinus to right atrial fistula.

Panels B and C Computed tomographic images revealing the fistulous tract originating from the left coronary sinus following a posterior course behind aorta and draining into right atrium at its junction with superior vena cava.

Panel D Follow-up image showing device in situ. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; AO, aorta; PA, pulmonary artery; SVC, superior vena cava; LAS, left aortic sinus; TUN, tunnel.

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