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Graphical Abstract

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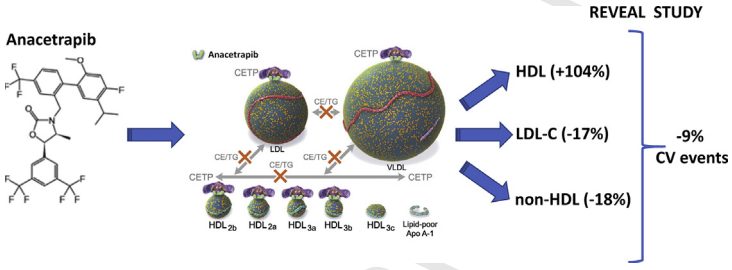
Present therapeutic role of cholesteryl ester transfer protein inhibitors

Nicola Ferri, Alberto Corsini*, Cesare R. Sirtori, Massimiliano Ruscica



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Present therapeutic role of cholesteryl ester transfer protein inhibitors

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ABSTRACT

Therapeutic interventions aimed at increasing high-density lipoprotein (HDL) levels in order to reduce the residual cardiovascular (CV) risk of optimally drug treated patients have not provided convincing results, so far. Transfer of cholesterol from extrahepatic tissues to the liver appears to be the major atheroprotective function of HDL, and an elevation of HDL levels could represent an effective strategy. Inhibition of the cholesteryl ester transfer protein (CETP), raising HDL-cholesterol (HDL-C) and apolipoprotein A-I (apoA-I) levels, reduces low-density lipoprotein-cholesterol (LDL-C) and apoB levels, thus offering a promising approach. Despite the beneficial influence on cholesterol metabolism, off-target effects and lack of reduction in CV events and mortality (with torcetrapib, dalcetrapib and evacetrapib) highlighted the complex mechanism of CETP inhibition. After the failure of the above mentioned inhibitors in phase III clinical development, possibly due to the short duration of the trials masking benefit, the secondary prevention REVEAL trial has recently shown that the inhibitor anacetrapib significantly raised HDL-C (+104%), reduced LDL-C (−18%), with a protective effect on major coronary events (RR, 0.91; 95%CI, 0.85–0.97; p = 0.004). Whether LDL-C lowering fully accounts for the CV benefit or if HDL-C-rise is a crucial factor still needs to be determined, although the reduction of non-HDL (−18%) and Lp(a) (−25%), should be also taken into account. In spite of the positive results of the REVEAL Study, Merck decided not to proceed in asking regulatory approval for anacetrapib. Dalcetrapib (Dal-GenE study) and CKD-519 remain the two molecules within this area still in clinical development.

Contents

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1. Introduction: the CETP inhibitors, aim of therapeutics and individual agents

Elevated low-density lipoprotein cholesterol (LDL-C) is the major risk factor for the development of cardiovascular disease (CVD) and treatment with statins has achieved considerable success in patients with dyslipidaemia and CVD [1]. However, a significant number of patients remains at increased risk, not because of LDL-C elevation, but due to other lipid abnormalities, such as low high- density lipoprotein (HDL) cholesterol [2]. Epidemiological and clinical studies link low levels of HDL with an increased risk of atherosclerotic CVD [3], although a direct causal role for HDL in CVD remains controversial [4,5]. Indeed, therapeutic interventions aimed at increasing HDL levels in order to reduce the residual CV risk of optimally drug treated patients have not provided convincing results, so far [6–9]. Among these therapeutic strategies, the inhibition of cholesteryl ester transfer protein (CETP) has provided the best results, with dose-dependent HDL-C elevations 100% or more [10].

The earliest evidence on the possible role of CETP in regulating HDL-C levels came from genetic studies in Japan, on communities where many individuals showed dramatic elevations of HDL-C. Remarkably, however, the very high HDL-C levels, initially believed to be associated with a reduced incidence of coronary heart disease (CHD), were instead linked to a paradoxically enhanced CV risk [11]. The crucial role of CETP mutations, with a loss of activity, became clear after the identification of this transfer protein. CETP is, indeed, a hydrophobic glycoprotein with a molecular weight of 74 kDa [12] responsible for a net transfer of cholesteryl esters (CE) from HDL to VLDL, IDL and LDL in exchange for triglycerides (TG); it also mediates the reciprocal transfer of TGs from LDL, VLDL to HDL. When VLDL levels are normal, then the transfer from HDL to LDL prevails. Conversely, when VLDL levels are raised, *eg* in type 2 diabetes, CE transfer is primarily from HDL to large VLDL particles which become CE enriched and potentially more atherogenic [13]. The end result of the process is a TG-enriched HDL leading to the catabolism of TGs in the newly formed HDL. The resulting "small, CE-poor HDL" appears to have an enhanced cholesterol efflux capacity [14] and, according to many authors, may be responsible for the arterial protection [15]. This process is mediated by the ATP binding cassette (ABC) transporters: ABCA1 exports cholesterol mainly to poorly-lipidated apo A-I (small pre-β1-HDL) or to lipid-free A-I; conversely, the ABCG1 transporter mediates cholesterol efflux to mature HDL [16].

The pharmacological inhibition of CETP has been pursued for the last 20 years or so and showed beneficial influence on cholesterol metabolism (*ie*, raised HDL-C and lowered LDL-C and apolipoprotein B (apo B) levels). Nevertheless, when the first three CETP inhibitors (torcetrapib, dalcetrapib and evacetrapib) were added to the background statin therapy, they either paradoxically increased the risk of CV disease and death (in the case of torcetrapib) or had neutral outcomes (dalcetrapib and evacetrapib) [17]. Further, off-target adverse effects were seen, in particular raised aldosterone and blood pressure (BP). Conversely, a new CETP inhibitor, anacetrapib, reduced CV events with modest off-target events [18].

2. Mechanism of action of CETP inhibitors

CETP is a hydrophobic glycoprotein, mainly secreted by the liver. Often bound to HDL in the circulation, it facilitates either homoexchange, *ie* the bidirectional transfer of the same neutral lipid, or heteroexchange, *ie* the net mass transfer of CE and TGs between lipoproteins [13,19]. CETP is a banana-shaped asymmetric protein forming a bridge between HDL, LDL and/or VLDL, with the N-terminal β-barrel domain penetrating the HDL surface and the C-terminal β-barrel domain penetrating the lipoprotein surface [20, 21]. The C-terminal domain of CETP may thus interact with HDL and LDL or VLDL, thus building a ternary complex leading to a conformational change, resulting in a hydrophobic tunnel whereby CE is transferred from HDL to lower density lipoproteins [22]. More recent findings, however, indicate that the ternary tunnel complex, *ie* HDL-CETP-LDL, is not a prerequisite for the transfer, since antibodies against different CETP epitopes do not interfere with the transfer of CE [23].

CETP inhibitors were thus designed with the aim of blocking or of interfering with the activity of CETP. Depending on their chemical structure, CETP inhibitors that have reached late stage clinical development are categorized into CETP inhibitors (torcetrapib, anacetrapib and evacetrapib) and modulators (dalcetrapib). As shown in Fig. 1, torcetrapib is representative of the tetrahydroquinoline series of inhibitors; it is a 3,5-bis-trifluoromethyl-benzene derivate. Anacetrapib contains the triad of trifluoromethyl groups found in torcetrapib with a distinct biaryl moiety. Evacetrapib contains a homologated core of torcetrapib and the 3,5-bis-trifluoromethyl-benzyl group with a methyl tetrazole and cyclohexane carboxylic acid side chain. Conversely, dalcetrapib belongs to the chemical class of benzenethiols containing an *ortho*-thio-anilide core [24].

Biochemical characterization of CETP inhibitors indicates that anacetrapib, torcetrapib and evacetrapib potently block CETP mediated CE-TG transfer activity, whereas dalcetrapib is a weaker inhibitor, displaying a time-dependent inhibition of CETP neutral lipid transfer activity [25]. Anacetrapib and torcetrapib bind CETP in a reversible manner, whereas, dalcetrapib does it covalently; this compound inhibits neutral lipid transfer by a disulfide bond formation with the cysteine 13 of CETP, thus leading to a conformational change in CETP [26]. These features characterizing homotransfer *vs* heterotransfer can have a direct impact on pre-β HDL formation. Indeed, CETP facilitates the remodeling of plasma HDL particles by favoring the interconversion of apoA-I-containing alpha-HDL to small, lipid-poor, pre-β-HDL [27] and by facilitating CE transfer among HDL subfractions [28].

Overall, the *in vitro* studies have confirmed that torcetrapib and anacetrapib can be classified as CETP inhibitors, whereas dalcetrapib, a CETP modulator, inhibits only the heterotypic (HDL to LDL/VLDL) transfer of CE/TG preserving pre-β-HDL formation. Relative to evacetrapib, eterotypic and homotypic CE transfer has not been fully elucidated [29, 30].

These particles are responsible for the ATP binding cassette subfamily A member 1 (ABCA1)-mediated cholesterol efflux and initiation of RCT [28]. Conversely, CETP inhibitors, by reducing both the heterotypic and HDL-to-HDL homotypic (HDL_3 to HDL_2) lipid transfers impede the pre-β-HDL formation [25,31] (Fig. 2). These differences in the mode of action can possibly explain the unchanged neutral fecal sterol formation in the case of the torcetrapib and anacetrapib, whereas dalcetrapib apparently increases the neutral sterol loss [31]. The only exception, evacetrapib, increased not only total cholesterol efflux capacity but also ABCA1-specific cholesterol efflux capacity and pre-β-HDL formation [32].

Somewhat at odds, the *in vivo* studies have shown that anacetrapib promotes pre-β-HDL functionality with no effects on cholesterol absorption [33]. An increased efflux from the basolateral side of the intestinal wall through ABCA1 to pre-β-HDL in fact occurs, potentially leading to a facilitated fecal cholesterol excretion. Anacetrapib treatment does not, however, impair the CE flux into the larger HDL_2 particles [34]. Of note, depending on the species considered (rabbits *vs* monkeys), anacetrapib and dalcetrapib have a different impact on HDL structure and function [35].

Finally, controversies in the remodeling of HDL particles upon CETP inhibition should be also considered. Carriers of CETP muta-

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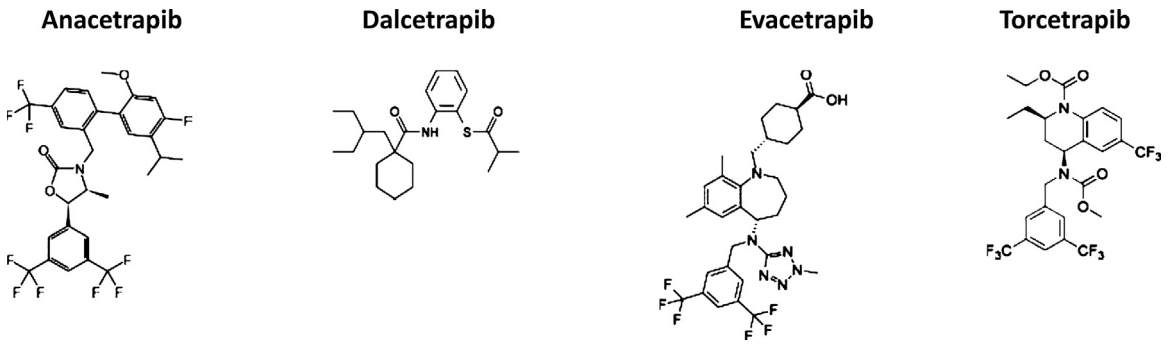

Fig. 1. Chemical structure of torcetrapib, anacetrapib, evacetrapib and dalcetrapib.

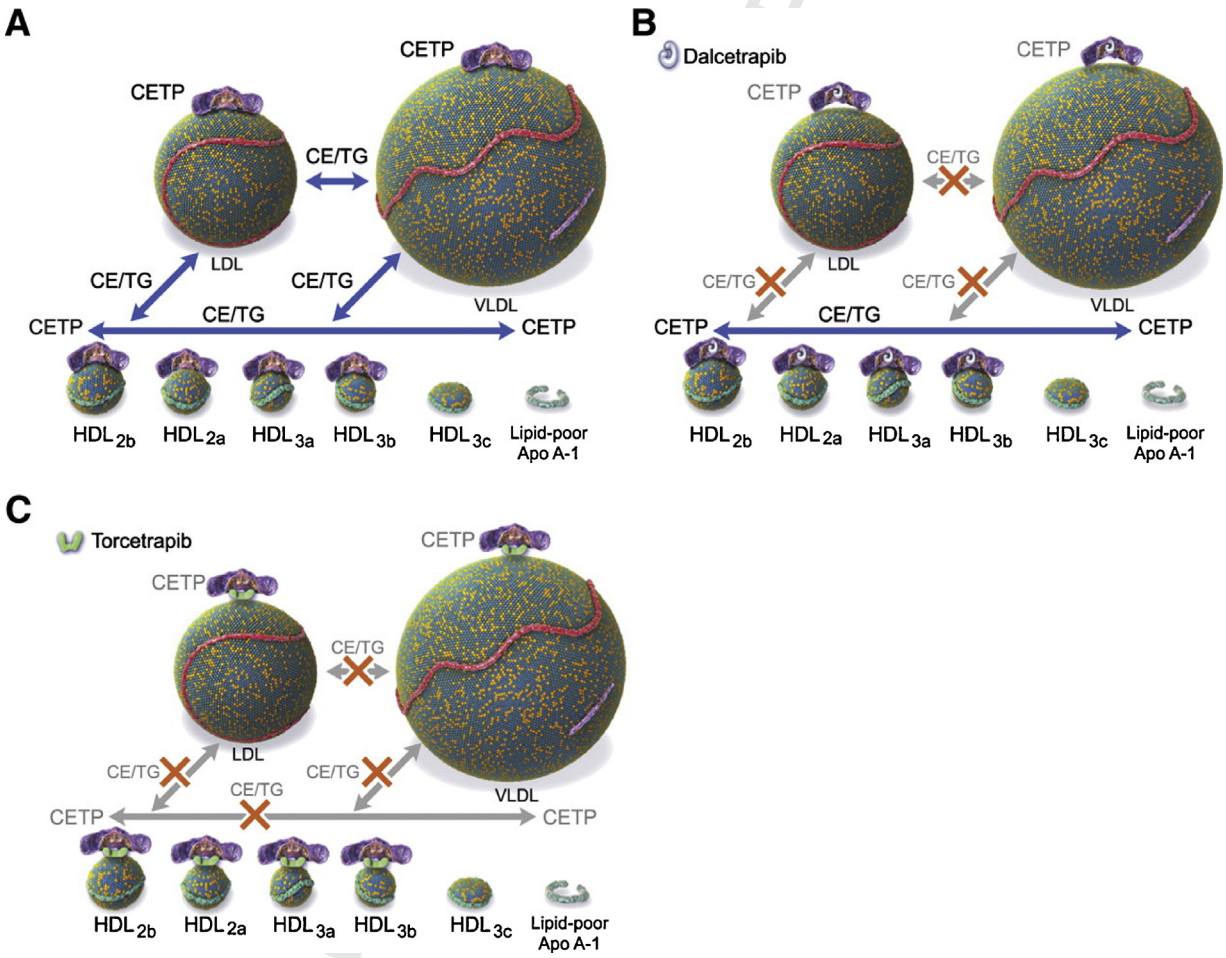

Fig. 2. Proposed effects of dalcetrapib and torcetrapib on neutral lipid transfers among high-density lipoprotein (HDL) subparticles. Panel A). Cholesteryl ester transfer protein (CETP) transfers neutral lipids (cholesteryl ester (CE) and triglycerides (TGs)) among HDL and HDL subparticles and changes conformation to accommodate low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). Panel B). Dalcetrapib prevents the change in conformation required for transfer activity, leaving unaffected CETP-mediated exchange among HDL subparticles. Panel C). Torcetrapib increases binding affinity of CETP for lipoproteins, decreasing CE and TG exchange between lipoproteins, including the one among HDL subparticles. Reproduced with permission [31].

tions show remarkable changes in the concentration, composition, turnover and function of both HDL and LDL. The very large HDL in these patients are TG-poor, but enriched with CE, apo A-I, apo A-II, apo C-III and apo E [36]; apo E enrichment may lead to a higher affinity for the LDL-receptor. The increased HDL-C is mainly consequent to an increment of HDL_2-C, whereas HDL_3-C levels are normal or low [37]. HDL from CETP deficient patients appear to promote cholesterol-efflux from foam cells in an ABCG1-dependent manner, possibly due to an increment in LCAT and apo E content [37]. Addition of CETP to serum from deficient patients transforms large HDL to smaller very-high density lipoproteins with a potent cholesterol effluxing capacity [38].

In the context of the ongoing debate on the protective role of HDL, it should be noted that the HDL particle number rather than HDL-C concentrations *per se*, may be of greater importance in the prediction of CV risk: torcetrapib raised HDL particle number by only 1% despite a 53% increase in HDL-C [39,40] and dalcetrapib raised HDL particles by 9.3% despite a 29.1% increase in HDL-C [41]. Further, besides CETP, major enzymes and transporters are also involved in changes in HDL particle size, lipid and protein

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Table 1
Pharmacokinetic characteristics of CETP inhibitors.

	Torcetrapib	Dalcetrapib	Evacetrapib	Anacetrapib
Bioavailability	33–45%	NA	45%	4% (fasted) 26% (low fat) 49% (high fat)
Effect of food	Exposure is higher in fed than fasted state	2-fold increase (low-fat) or more with high-fat	44% higher with high-fat	2-, 3-fold increased (low-fat) or 6–8 fold (high-fat)
logP	7.35	7.92	7.03	7.95
Vd	1.1–2.5 l/kg (77–175 l)	NA	548–827 l	253 l
Tmax	6.3 h	3.5–6 h	3h	4–5 h
Half-life ($t_{1/2}$)	Estimated 25 h long (211 h) terminal half-life	18.4–20.4 h	40-44 h	Estimated 20 h long (2530 h) terminal half-life (accumulated in adipose tissue)
Metabolism (CYP450)	3A	No interaction with 3A4 inhibitors. Hydrolysis, glucuronidation, oxidation and methylations	3A4	3A4
Renal clearance	63%	NA	NA	<0.1%
Hepatic clearance	12.7%	NA	NA	87%
References	[48]	[52,58,141,142]	[43,44,54,55]	[46,51,53,59]

NA: not available.

composition, particularly in hypetriglyceridemic conditions: the lecithin-cholesterol acyltransferase (esterifying cholesterol), hepatic or lipoprotein lipases (hydrolyzing TGs) and the phospholipid transfer protein [42].

3. Pharmacokinetics and pharmacodynamics

The main pharmacokinetic parameters of CETP inhibitors are summarized in Table 1. The oral absorption of all CETP inhibitors is rapid with Tmax values of 3 h for evacetrapib [43,44], 4–5 h for anacetrapib [45, 46], 3.5–6 h for dalcetrapib [47] and 6.3 h for torcetrapib [48].

It is important to note that dalcetrapib is a thioester prodrug that is hydrolysed to generate a pharmacologically active thiol. Hydrolysis is rapid in lipase-containing gastrointestinal fluids [49,50], so that the thioester is not systemically available and the thiol appears to be the principal species absorbed from the gastrointestinal tract.

The bioavailability of anacetrapib is significantly influenced by the feeding status, with only 4% absorption under fasting condition, 26% after low fat meal and 49% with high fat meal [45,51]. Similar findings, although at lower extent, have been observed with torcetrapib [48], dalcetrapib [52], and evacetrapib [44]. Anacetrapib is characterized by poor water solubility (LogP ≈7) and modest permeability, hence, it is likely that the reason for poor bioavailability is largely a function of poor absorption rather than other factors, including first-pass metabolism. The lipophilic characteristics of CETP inhibitors, all characterized by high logP value, induce their accumulation in peripheral tissues, *ie* the adipose tissue, thus showing high volume of distribution (Table 1) [51]. For instance, it has been calculated that anacetrapib has a volume of peripheral compartment of 253 l [53], while evacetrapib shows a volume of distribution during the terminal phase following oral dose of 548–827L [54,55]. All agents have a prolonged half-life, maximal for anacetrapib that shows a 2530 h terminal half-life, due to accumulation in adipose tissue [51] (Table 1).

Interestingly, in a subset of patients from the DEFINE study, it was found that modest elevations in HDL-C and low anacetrapib concentrations were still detectable 2–4 years after the last dosing [56]. Preclinical and clinical experiments with extended recovery phases were then specifically designed to assess whether there was a deep tissue reservoir that may be contributing to persistent plasma exposure to anacetrapib after cessation of treatment [51]. In particular, it appears that the brown adipose tissue may be a temporary reservoir for the drug in the short term whereas white adipose is likely to be a major long-term reservoir [51,57].

All agents seem to have a mean route of elimination by hepatic metabolism mainly by CYP3A4/5 and, in case of dalcetrapib, by hydrolysis, glucuronidation, oxidation and methylations (Table 1). Both hepatic and renal impairment altered dalcetrapib pharmacokinetics and increased its exposure [58]. Differently, pharmacokinetic studies conducted with anacetrapib have shown that the majority of the radioactive dose is recovered as unchanged parent drug in the feces [59]. Anacetrapib is negligibly excreted in the urine with <0.1% of the radioactive dose recovered as unchanged parent. For this reason, also severe renal insufficiency does not significantly affect anacetrapib pharmacokinetic profile [60].

Since anacetrapib is primarily metabolized by cytochrome CYP3A, its pharmacokinetic profile is influenced by strong inhibitors and inducers of CYP3A [61–63]. Anacetrapib exposure is not impacted by age, weight, sex, and moderate hepatic impairment [60,63]. Finally, no meaningful differences have been observed between Japanese and white subjects with respect to pharmacokinetic parameters after single oral doses of anacetrapib [46].

Considering the pharmacodynamic profile of the different CETP inhibitors, torcetrapib inhibits CETP by forming a complex between CETP and HDL, thus, leading to a high significant HDL rise in humans (+60%) with a concomitant LDL-C reduction of approximately 20%. Torcetrapib inhibits CE transfer with high potency ($IC_{50} = 13 \pm 2.7$ nM) but the ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events) trial was prematurely ended due to an increased morbidity and mortality in the active treatment group compared with the placebo group [64]. After the termination of this and other negative trials (RADIANCE 1 and ILLUSTRATE), it was found that treatment with torcetrapib raises systolic blood pressure (SBP), although rather inconstantly in the different studies [65]. Aldosterone, sodium and bicarbonate levels were also raised while potassium decreased [66].

The specific off-target effects of torcetrapib do not clarify the increased incidence of cardiovascular (CV) events. Indeed, in the four studies with torcetrapib (ILLUMINATE, ILLUSTRATE, RADIANCE 1 and RADIANCE 2) the calculated event rate, before and after torcetrapib, was estimated as 28.4% (10-y risk) by using the classical Framingham risk score. Conversely, treatment with torcetrapib plus atorvastatin, leading to a total cholesterol of 200 and HDL-C of 50 mg/dl should reduce the risk estimate to 14.3%. The lack of this benefit is not explained by a rise of blood pressure to 140 mmHg, extreme for a patient treated with this combination: this should

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raise the risk score to just 16.3%, *ie* certainly far from the assumption that it could fully cancel the risk benefit of torcetrapib [67].

The following CETP inhibitors, developed with the objective of obtaining drugs with no off-target effects, led to the identification of dalcetrapib, evacetrapib and anacetrapib. Whereas dalcetrapib has a 90 fold weaker potency ($IC_{50} = 1.170 \pm 443$ nM) *vs* torcetrapib ($IC_{50} = 13 \pm 2.7$ nM), anacetrapib has a similar potency ($IC_{50} = 17 \pm 4.8$ nM) [68,69]. The *in vitro* activity of evacetrapib shows a more potent activity based on IC_{50} values, (*ie,* 5.5 nM), thus making evacetrapib the most potent among available CETP inhibitors (Table 1) [68].

The effect of anacetrapib on atherosclerosis has been extensively investigated in animal models, including the APOE*3Leiden.CETP mice [70], rabbits [35], and monkeys [35]. The atheroprotective [70] effect and positive lipid profile modifications [35] were in line with the evidence that, in mouse atherosclerosis models, CETP expression aggravates atherosclerosis development [71,72].

Discordant results have, however, been observed with different CETP inhibitors (dalcetrapib, evacetrapib and anacetrapib) on experimental atherosclerosis [35,73]. While in rabbits both dalcetrapib and anacetrapib increased HDL-C, in monkeys dalcetrapib had the opposite effects, with an increase of LDL-C and a reduction of HDL-C [35], indicating that the impact on HDL metabolism can vary according to the metabolic environment [35]. Torcetrapib also failed to enhance the antiatherogenic effects of atorvastatin and induced a pro-inflammatory, vulnerable plaque phenotype in APOE*3Leiden.CETP mice [74]. Finally, different effects on endothelial function were displayed by evacetrapib and anacetrapib in the APOE*3Leiden.CETP mice [73]. Thus, most but not all studies in rabbits and mice have shown a favorable effect of CETP inhibition on atherosclerosis development [73–75].

The off-target effects of these molecules, in particular of torcetrapib, may be possibly responsible for their failures in phase III clinical development [64]. Interestingly, off-target effects have been also observed in experimental settings for both anacetrapib and dalcetrapib [76]. The two inhibitors reduced the mature form of sterol-regulatory element binding protein 2 (SREBP2), leading to a lower transcription of the liver LDL receptor (LDLR) and of proprotein convertase subtilisin kexin type 9 (PCSK9) [76]. The negative regulation of the SREBP pathway by anacetrapib manifested also in mice, with absent CETP activity, with a consequent rise of cholesterolemia [76. Similar results were observed in the APOE*3Leiden mice, also n]ot expressing CETP, where anacetrapib decreased both plasma levels of PCSK9 and cholesterolemia [77]. A protective effect of anacetrapib on vascular restenosis has been observed in the New Zealand White rabbits [78], leading to the intriguing hypothesis that anacetrapib could inhibit smooth muscle cell proliferation and migration by reducing PCSK9 expression [79].

In conclusion, CETP inhibitors that have undergone clinical development show strikingly different pharmacokinetic and pharmacodynamic profiles as well as peculiar pharmacological activities that go beyond the inhibition of CETP. In particular, whereas the effect on CETP is completely inhibited by torcetrapib, anacetrapib and evacetrapib, dalcetrapib exerts a modulatory activity. In terms of the HDL-C rise, evacetrapib and anacetrapib are the most potent, followed by dalcetrapib, whereas LDL-C reduction is in a similar range for torcetrapib, evacetrapib and anacetrapib, with minimal effects of dalcetrapib (Table 2).

4. Clinical studies on CETP inhibitors

Ten randomized controlled trials on CETP inhibitors, *ie* torcetrapib, dalcetrapib, evacetrapib and anacetrapib have been completed (Table 2), enrolling a total of 78,602 patients, the largest being the last, *ie* the REVEAL Study, enrolling 30,449 individuals in Europe, North America and China. All randomizations were between the addition of all CETP inhibitors and placebo with all patients receiving statin treatment. Duration of follow up ranged from 8 to 48 months.

4.1. Anacetrapib

The dose-dependent effects of anacetrapib on the lipoprotein profile have been first evaluated in a multi-center phase II randomized controlled trial, after the administration of 10, 40, 150 and 300 mg daily for 8 weeks, in the presence or absence of 20 mg atorvastatin [80]. Similar to evacetrapib, anacetrapib exerted a maximal reduction of LDL-C, *ie* of about 40%, and of 70% in combination with atorvastatin, compared to placebo. Anacetrapib raised HDL-C levels by about 130%; the effect was similar when combined to atorvastatin.

The DEFINE phase III study was then performed by recruiting 1623 patients with or at high risk of coronary disease treated with statins [81]. Anacetrapib 100 mg lowered LDL-C by about 40% and raised HDL-C by about 140%, *ie* similar to the phase II trial. Interestingly, in this study, Lp(a) was reduced of about 40%. The lipoprotein profile was maintained in patients who continued treatment for two years. Regarding safety, evaluated after 76 weeks of treatment, anacetrapib did not lead to significant differences in BP, electrolytes, CPK elevations, or muscle symptoms. However, significantly, more patients in the placebo group experienced ALT/AST elevations (0.1% *vs* 1.0%; $p = 0.02$). In terms of coronary revascularization, anacetrapib showed a positive effect after 76 weeks: 8 patients (1%) on anacetrapib *vs* 28 patients (3.5%) on placebo. This effect was lost at the 2-year follow-up: 13 patients (3.5%) anacetrapib *vs* 13 patients (3%) placebo were revascularized.

Anacetrapib was then tested in patients with heterozygous familial hypercholesterolaemia (FH). The REALIZE trial, a 52-week, randomized, placebo-controlled study was conducted in patients under optimal lipid-lowering therapy for at least 6 weeks at baseline, and then randomized to either placebo or anacetrapib 100 mg [82]. The baseline LDL-cholesterol concentration was 2.59 mmol/L or higher, 1.81 mmol/L or higher in patients with CV disease. Change of LDL-C was the primary efficacy endpoint. Anacetrapib lowered the mean LDL-C by 39.7%, compared to placebo. Furthermore, HDL-C increased by 102.1%, and Lp(a) decreased by 31.8% in anacetrapib-treated patients.

CV outcomes as a primary efficacy endpoint have been finally examined in the REVEAL study, in which 30,449 patients with established CV disease were enrolled [83]. Patients were on intensive atorvastatin regimen (*ie*, LDL-C ≤ 77 mg/dL) and started from a very well controlled lipid profile (mean LDL-C 61 mg/dL; mean non-HDL-C 92 mg/dL and mean HDL-C 40 mg/dL) [18]. Patients had a mean age of 67 years; 88% had a history of CHD, 22% of cerebrovascular disease, and 8% of peripheral-artery disease. During the 4.1-year follow-up, 2277 (7.5%) patients died. Anacetrapib treatment raised HDL-C by 43 mg/dL (+104%) and non-HDL-C was reduced by 17 mg/dL (−18%). Mean LDL-C was lowered by 17%.

The prespecified primary outcome was the first major coronary event, *ie* a composite of coronary death, MI or coronary revascularizations. It was reduced by 9% in the anacetrapib group (1640 of 15,225 patients [10.8%] *vs.* 1803 of 15,224 patients [11.8%]; RR, 0.91; 95%CI, 0.85–0.97; p = 0.004) [18]. Specific analysis of the different components showed a positive effect of anacetrapib on MI (−13%; RR: 0.87; 95%CI, 0.78–0.96; p = 0.007), on the composite of MI or coronary death (−11%; RR: 0.89; 95%CI, 0.81–0.97; p = 0.008), as well as on coronary revascularization procedures (-10%; RR: 0.90; 95%CI, 0.83–0.97; p = 0.01).

Regarding secondary outcomes, the major atherosclerotic events, *ie* a composite of coronary death, MI or presumed ischemic stroke, were reduced by a non-significant −7% (RR: 0.93; 95%CI,

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Table 2
(a) Features of CETP inhibitor, (b) lipid percentage changes and (c) blood pressure variations upon Torcetrapib, Dalcetrapib, Evacetrapib and Anacetrapib administration.

	Torcetrapib	Dalcetrapib	Evacetrapib	Anacetrapib
a) In vitro				
Mechanism of action	CETP inh.	CETP modulator	CETP inh.	CETP inh.
Inhibition of CETP (IC_{50})	13 ± 2.7 nM	1170 ± 443 nM	5.5 nM	17 ± 4.8 nM
b) Clinical trials	ILLUMINATE	Dal-OUTCOMES	ACCELERATE	REVEAL
daily dose	*60* mg	*600* mg	*130* mg	*100* mg
N. of patients	15,067	15,871	12,092	30,449
LDL-C (mg/dL)	−24.9%	minimal effect	−31.1%	−41%* or −17%**
apoB (mg/dL)	NA	minimal effect	−15.5%	−18%
HDL-C (mg/dL)	+72.1%	Range: +31–40%	+133.2%	+104%
non-HLD-C (mg/dL)	NA	NA	NA	−18%
c) Blood pressure	ILLUMINATE	Dal-OUTCOMES	ACCELERATE	REVEAL
Systolic (mmHg)	$ +5.4	$ +0.6	$ +1.2	$ +0.74
Diastolic (mmHg)	$ +2.0	no significant between-group differences	$ +0.4	$ +0.28
References	[64]	[100]	[93]	[18]

For torcetrapib, dalcetrapib and evacetrapib data are expressed as changes from baseline in the treatment group. For anacetrapib, data are expressed as absolute differences (value in the anacetrapib group minus the value in placebo group).
N., number; inh., inhibitor.
*direct method; ** beta quantification; $significant between-group differences; NA, not-applicable.

0.86–1.00; p = 0.052). Although the effect of anacetrapib on presumed ischemic stroke was not formally tested, the results showed no significant effects (RR: 0.99; 95% CI, 0.87–1.12). A statistical reduction in the secondary outcome of major vascular events, *ie*, a composite of major coronary event or presumed ischemic stroke was instead found (-7%; RR: 0.93; 95% CI, 0.87–0.99, p = 0.02).

Interestingly, anacetrapib appeared to reduce the incidence of new-onset diabetes mellitus (5.3% *vs.* 6.0%) and it lowered mean glycated hemoglobin levels (-0.03%). This effect was not found in patients with diabetes at baseline. Anacetrapib modestly raised BP (systolic +0.7 mm Hg; diastolic +0.3 mm Hg) and, by the end of the trial, an estimated glomerular filtration rate (GFR) of less than 60 ml/min per 1.73 m^2 body surface area (11.5% *vs* 10.6%, p = 0.04) was noted in the anacetrapib group. However, no difference was observed in albuminuria. Finally, anacetrapib led to moderate rates of creatine kinase elevations (10–40 times the upper limit of normal, ULN), but it reduced rates or more severe elevations (>40 times ULN). Thus, the REVEAL study in patients with atherosclerotic vascular disease, under intensive statin therapy for approximately 4 years, showed that CETP inhibition reduced the incidence of major CV events by 9% *vs* placebo.

Relative to the effects of anacetrapib on CV risk reduction, some further considerations relative to LDL-C, Lp(a) and non-HDL-C lowering deserve attention. While a reduction in the concentration of cholesterol in LDL can be explained in terms of a block in the transfer of CEs from HDL to LDL, this cannot explain the reduction in LDL particle concentrations, as reflected by a decrease in plasma apo B levels [84]. This open question may be in part overcome by the notion that, at least in experimental models, anacetrapib reduces plasma levels of PCSK9 [77], so far, one of the main regulators of LDL receptors [85–87].

In the case of Lp(a), in mildly hypercholesterolemic subjects, with Lp(a) levels >20 nmol/L, anacetrapib lowers Lp(a) by 34.1%, consequent to a 41% reduction in apo(a) production rate, with no effects on the fractional catabolic rate [88]. This effect is of a special interest since (i) elevated Lp(a) are robustly associated with an increased risk for major CVD events [89] and (ii) Lp(a) may promote expression of adhesion molecules and inflammatory cells [90].

Non-HDL has been significantly associated with an increased risk of mortality in coronary patients and baseline levels may be a predictor of long-term fatality in these patients [91]. In experimental models, anacetrapib alone or in combination with atorvastatin reduced the atherosclerotic lesion area and severity and increased the plaque stability index [70].

4.2. Evacetrapib

The recently completed ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High-Risk for Vascular Outcomes; NCT01687998) study was aimed at evaluating whether the addition of evacetrapib to standard medical therapy reduced the risk of CV morbidity and mortality in patients with high-risk vascular disease [92]. 12,092 patients (mean age, 64.9), only in secondary prevention, were randomized to either evacetrapib (130 mg; n = 6038) or matching placebo (n = 6054), administered daily for up to 4 years, in addition to standard medications (*eg*, any statin, high-intensity statin, medication to treat high-blood pressure and aspirin). The diagnosis of high risk vascular disease comprised at least one of the following diagnostic criteria: i) history of acute coronary syndrome within the previous 30–365 days before randomization, ii) cerebrovascular atherosclerotic disease, iii) peripheral arterial disease and iv) diabetes mellitus (type 1 or type 2) with CAD. The primary endpoint was time to first occurrence of the composite endpoint of CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina. Evaluation of changes from baseline to 3 months in LDL-C and HDL-C levels were listed among the secondary end-points.

After 26 months, the primary composite end-point occurred in 12.9% of patients in the evacetrapib and in 12.8% of those in the placebo arms (HR: 1.01, 95% CI: 0.91–1.11, p = 0.91). Due to the insufficient efficacy, the Data Safety Monitoring Board recommended early termination. Despite the failure of the primary end-point, compared to placebo, evacetrapib showed highly significant effects on reducing LDL-C (−37%) and on raising HDL-C (+132%). A lowering effect on TG (-6%), apoB (−12%) and Lp(a) (−22%) were also found, as well as an increment in apoA-I (+49%). Relative to safety, evacetrapib administration was associated to minor increments of BP (11.4% *vs* 10.1 placebo, p = 0.02) and of hs-CRP (8.6%, p < 0.001) [93].

Notably, the ground for this large phase 3 clinical trial laid on the results of the NCT01105975 phase 2 study reporting that, compared to placebo, evacetrapib as monotherapy (30, 100 and 500 mg/die) or in combination to statins, increased HDL-C by up to 129% and reduced LDL-C by up 36%. Moreover, as monotherapy, evacetrapib

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reduced in a dose-dependent fashion non-HDL-C, apoB and TG. hs-CRP levels were raised by up to 1.2 mg/dl [94].

A meta-analysis of 14 randomized treatment arms over a mean of 2 months treatment, reported that evacetrapib raised HDL-C (+86%, 95% CI: +67.6, +104.4, $p < 0.001$) and reduced LDL-C (−21%, 95% CI: −24.9, −17.3, $p < 0.001$). No significant effects of evacetrapib were found on plasma TG (−3.0%, 95% CI: −8.6, +2.7, $p = 0.303$) [95].

The evacetrapib program cessation led to the premature ending of other phase 3 studies, namely, (i) NCT02260635, evaluating the efficacy and safety of evacetrapib in Japanese participants with primary hypercholesterolemia, (ii) NCT02260648, evaluating efficacy and safety of evacetrapib when administered in combination with atorvastatin for 12 weeks in Japanese participants with primary hypercholesterolemia and (iii) ACCENTUATE (The Addition of Evacetrapib to Atorvastatin Compared to Placebo, High Intensity Atorvastatin, and Atorvastatin With Ezetimibe to Evaluate LDL-C Lowering in Patients With Primary Hyperlipidemia; NCT02227784), a study aimed at evaluating whether evacetrapib can be effective in treating participants with high cholesterol and ASCVD and/or diabetes. Data on this latter trial gave possible insights on the lack of clinical benefit observed in the above described ACCELERATE trial.

4.3. Dalcetrapib

Dalcetrapib has been the second CETP inhibitor tested in clinical trials. Efficacy was evaluated in the dal-HEART program composed of five major studies, namely, dal-PLAQUE [96], dal-VESSEL [97], dal-PLAQUE2 [98], dal-ACUTE [99] and dal-OUTCOMES [100]. This last was terminated prematurely after 31 months due to futility, thus leading Hoffmann-La Roche to discontinue the entire dalcetrapib development. However, as discussed later, the *era* of genome-wide association study has led to the launch of the DalGenE study, an RCT with a design similar to the Dal-OUTCOMES, except for the eligibility of patients.

Enrolling 15,871 patients and designed to evaluate the efficacy of dalcetrapib *vs* placebo on CV mortality and morbidity in clinically stable patients with recent acute coronary syndromes, the dal-OUTCOMES trial (NCT00658515) did not show significant effects on any primary end-point (HR: 1.04, 95% CI: 0.93–1.16, $p = 0.52$). Over a follow-up of 31 months, the administration of dalcetrapib (600 mg) led to an increment of HDL-C by up to 40% with no impact on LDL-C. hs-CRP levels were 0.2 mg/L higher than in placebo group (+18% after three months of randomization), as was SBP (+0.6 mmHg; $p < 0.001$). Of note, diarrhea and insomnia were more frequent with dalcetrapib. There were no significant differences in diastolic blood pressure, pulse rate, levels of plasma aldosterone, potassium, or bicarbonate [100].

By using magnetic resonance imaging (MRI) and ^{18}Fluorodeoxyglucose (^{18}FDG) PET/CET, the dal-PLAQUE study (NCT00655473), involving 130 patients with or at high risk of CHD, evaluated structural and inflammatory changes of atherosclerotic plaques after dalcetrapib (600 mg) *vs* placebo. Major findings were the reduction of total vessel area in the dalcetrapib arm (−4.01 mm^2 (90% CI: −7.23 to 0.80; $p = 0.04$) and a 7% reduction in the most-diseased-carotid segments [96]. A *post-hoc* analysis of the dal-PLAQUE showed that dalcetrapib therapy did not affect vascular calcification [101], a marker of the extent of atherosclerosis and predictive of CV events and mortality [102].

Of note, dalcetrapib showed neutral effects also on carotid wall imaging in the dal-PLAQUE-2 study (NCT01059682) designed to test the hypothesis that dalcetrapib slowed atherosclerosis progression in patients with evidence of CHD and carotid intima-media thickness (IMT) ≥0.65 mm in the far wall of the common carotids [98,103]. No differences were finally observed in the dal-VESSEL trial, where dalcetrapib did not affect NO-dependent endothelial function, BP, or markers of inflammation and oxidative stress [97].

The re-evaluation of all of these apparently negative results by using a pharmacogenomic approach has very recently unearthed unexpected findings, *ie*, clear interindividual differences in dalcetrapib responses. Among the 5,543,264 common genetic variants analyzed, a single region with genome-wide significance in the dalcetrapib arm of dal-OUTCOMES study, was associated with CV events and identified in the *ADCY9* (adenylate cyclase type 9) gene on chromosome 16, the single genotyped SNP (rs1967309) as the most significant. Among the 5749 drug treated patients of the dal-OUTCOMES study, dalcetrapib reduced by 39% the risk of CV events (HR: 0.61; 95% CI, 0.41–0.92) as well as by 1.0% hs-CRP ($p = 0.89$) in patients bearing the genotype AA at SNP rs1967309 [98, 104]. Significant genotype-dependent effects of dalcetrapib were also found in the re-evaluation of dal-PLAQUE-2 study in which regression of cIMT (-0.021 ± 0.083 mm, at 12 months) was associated with the AA genotype [98, 105]. The dal-GenE study has thus been planned in order to evaluate the effects of dalcetrapib *vs* placebo on CV risk in a genetically defined population with a recent CV event and the AA genotype at rs1967309 in the *ADCY9*. The study is expected to be concluded by August 2020, *ie* with a time frame of 30 months. Primary end-point will be the time of the first event, *ie* CV death, resuscitated cardiac arrest, non-fatal MI, or non-fatal ischemic stroke (NCT02525939).

4.4. Torcetrapib

Torcetrapib was the first agent in the group of CETP inhibitors and its efficacy on atherosclerosis was evaluated in three clinical studies, ILLUSTRATE (NCT00134173), RADIANCE 1 (NCT00136981) and RADIANCE 2 (NCT00134238), whereas the effect on CV outcomes was evaluated in the ILLUMINATE trial (NCT00134264). For this latter, 15,067 patients were recruited. Despite a 72.1% increase of HDL-C and −24.9% reduction of LDL-C in the torcetrapib arm, there was a significant rise in the incidence of primary composite cardiovascular endpoints (HR: 1.25; 95% CI, 1.09–1.44; $p = 0.001$) as well as in all-cause mortality (HR: 1.58; 95% CI, 1.14–2.19; $p = 0.006$) [64]. Due to these untoward findings, the study was prematurely ended. Although this increased mortality was attributed to a slight rise in BP (+5.4 mm Hg systolic and +2.0 mmHg diastolic) [64], prolongation of the QT interval (by +3.3 msec) should be also considered. Indeed, in uncomplicated hypertensive patients, a prolonged ventricular repolarization is a risk factor for IHD and CV mortality [106].

Interestingly, a *post hoc* exploratory analysis of the ILLUMINATE trial, showed that among the 34 excess deaths in the torcetrapib group, 91% occurred in the 10 mg atorvastatin dose subgroup (HR: 2.68; 95% CI, 1.58–4.54; $p < 0.001$); the strongest baseline predictor of death was age >70 years (Fig. 3) [107].

In the attempt to explain the failure of ILLUMINATE trial, another *post-hoc* analysis showed that torcetrapib significantly raised the apoC-III content of HDL-C, a phenomenon elsewhere described as potentially associated to an increased ASCVD risk, *ie* by stimulating the adhesion of monocytes to endothelial cells and the production of inflammatory mediators [108]. Notably, in patients with type 2 diabetes, torcetrapib improved glycemic control, as evaluated by a decrement in glucose, insulin levels, HOMA-IR and Hb1Ac. All these effects remained apparent up to 12 months [109].

Relative to the vascular imaging studies ILLUSTRATE, RADIANCE 1 and 2 on a total of 2000 recruited patients with coronary disease [110], familial hypercholesterolemia [111] or mixed dyslipidemia [112], torcetrapib failed to demonstrate any favorable effect on atheroma volume or atherosclerosis progression, as evaluated by carotid intima media thickness (cIMT) and coronary intravascular

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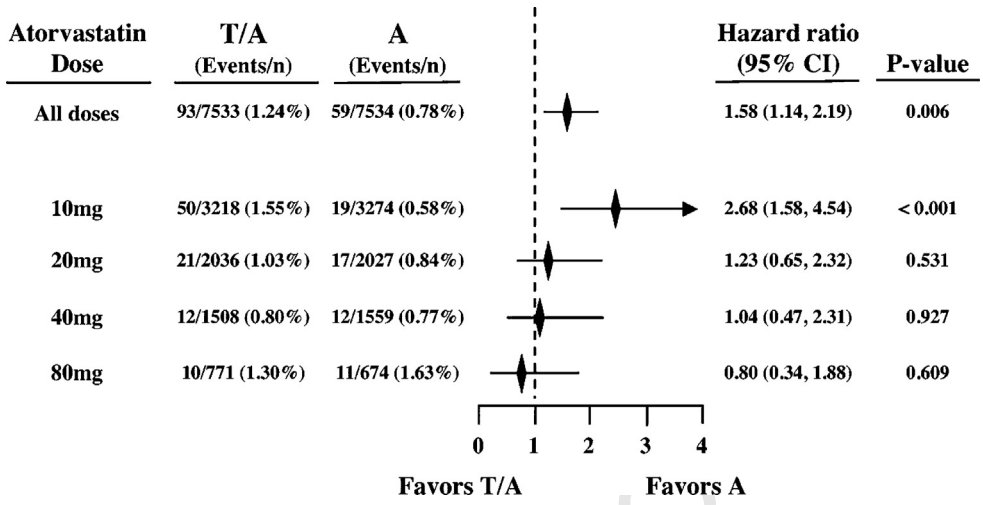

Fig. 3. Estimated Hazard Ratio for all-cause mortality (ACM) by atorvastatin dose (10, 20, 40 and 80 mg). T/A, torcetrapib treatment on background atorvastatin; A indicates atorvastatin background treatment alone. Reproduced with permission of [107].

ultrasound (IVUS). The issue of off target effects has been earlier discussed.

Controversies on torcetrapib effects were also raised by the results of animal studies. In New Zealand White rabbits fed a 0.2% cholesterol + 10% coconut oil diet leading to a cholesterolemia of 702 mg/dl after 16 weeks [75], torcetrapib treatment raised HDL-C >3-fold and prevented the development of atherosclerotic lesions, potentially by activating the reverse cholesterol pathway. Sera from the torcetrapib-treated rabbits stimulated cholesterol efflux to a significantly greater extent than *vs* control animals [75]. This report indicating a potential stimulation of CE efflux by CETP inhibitory treatment, did not find support in a clinical trial where, contrary to expectations, drug treatment failed to raise fecal sterol elimination [113].

5. Different clinical efficacy between evacetrapib and anacetrapib: potential explanations

The different effects of evacetrapib *vs* those of anacetrapib in the ACCELERATE and REVEAL studies, respectively, may be potentially explained just by the different durations of follow-up [114]. Indeed, whereas the ACCELERATE trial was prematurely halted after 2 years of follow-up, the REVEAL study was completed after 4.1 years. Moreover, ACCELERATE involved less than half the number of patients *vs* REVEAL (12,092 *vs* 30,449, respectively).

From the time analysis of the first major coronary events per year of follow-up in the REVEAL trial, it emerges that the anacetrapib protective effect starts after the second year of treatment [18]. Interestingly, a similar kinetics of the protective effect has been reported after statin treatment, *ie* a mean 9% reduction in risk of major events at 1 year and 22% at 2 years of follow-up [115]. Thus, if the protective activity on major CV events is to be attributed to an effect on the lipid profile, similar results should be expected with evacetrapib at a similar follow-up; both molecules exert very similar lipoprotein changes. The authors of the REVEAL Study, by analyzing non-HDL-C data from the statin trials, concluded that the lower levels of non-HDL-C (−17 mg/dL) found after 4.1 years of anacetrapib, should result in a 10% relative decrease in the risk of coronary death or MI, a finding entirely consistent with the 11% reduction found in their trial [18].

The unmet primary endpoints of ACCELERATE trial with evacetrapib may possibly be attributed to both on- and off-target effects. In the ACCENTUATE study, *ie* on a combination of evacetrapib with atorvastatin, the robust LDL-C reduction (−33.4%) was less pronounced compared to that of apoB levels (-23%) [116]. Moreover, evacetrapib increased: (i) apoC-III levels, that *per se* may exert a direct pro-inflammatory effect at the arterial wall level by activating vascular cell adhesion molecule-1 and nuclear factor kB, (ii) the HDL apoC-III content, thus impairing HDL functional activity [117] and (iii) both apoE (+28%) [116] and C-reactive protein levels [18], a marker of CV risk [118]. In subjects treated with anacetrapib monotherapy, instead, there were no significant changes in the apoE pool size, whereas apoC-III pool size also rose by 76% [119], consequent to a nonsignificant increase in the apoC-III production rate and a 35% reduction in the fractional catabolic rate [119]. Further, In the DEFINE study with anacetrapib, there were no significant changes in C-reactive protein levels [120]. The potential significance of a focal anti-inflammatory activity of anacetrapib is supported by the very recently described reduction of in-stent restenosis in rabbits treated with the analog des-fluoro anacetrapib [121], also confirming prior data showing reduced intimal hyperplasia and functional endothelial regeneration with this agent [121].

Studies on the relative ability of evacetrapib and anacetrapib to promote cholesterol efflux from cholesterol loaded macrophages showed that HDL from evacetrapib treated subjects had increased cholesterol efflux capacity compared to those on anacetrapib [122,123], a difference ascribable to the evacetrapib capacity to enhance ABCA1-specific cholesterol efflux and pre-β-HDL formation [32]. Anacetrapib treatment did not change pre-β-HDL formation, while increasing the ABCA1-dependent CE efflux into larger HDL_2 particles [33, 34,124].

Evacetrapib and anacetrapib further show a different activity on endothelial function. CETP-transgenic mice display a marked increment in HDL-C following evacetrapib treatment, but not an improved endothelial function; this was modestly worsened by anacetrapib [73]. Overall, these last findings do not support a direct vascular protection by CETP inhibition and are unlikely to explain the different results of the large clinical trials with the two drugs.

Relative to the safety profile, evacetrapib raised SBP by 1.2 mmHg (ACCELERATE trial) *vs* +0.6 mmHg after anacetrapib (REVEAL trial). These off-target effects were similar in magnitude to those reported for dalcetrapib, but much smaller than the 5 mm Hg mean rise seen with torcetrapib [64,93,100]. Finally, a major drawback for the clinical use of anacetrapib is the unique pharmacokinetic profile. Data from a small cohort (n = 30) of the DEFINE trial have shown detectable concentrations of anacetrapib in plasma 2.5–4 years after the last drug dose, associated with mod-

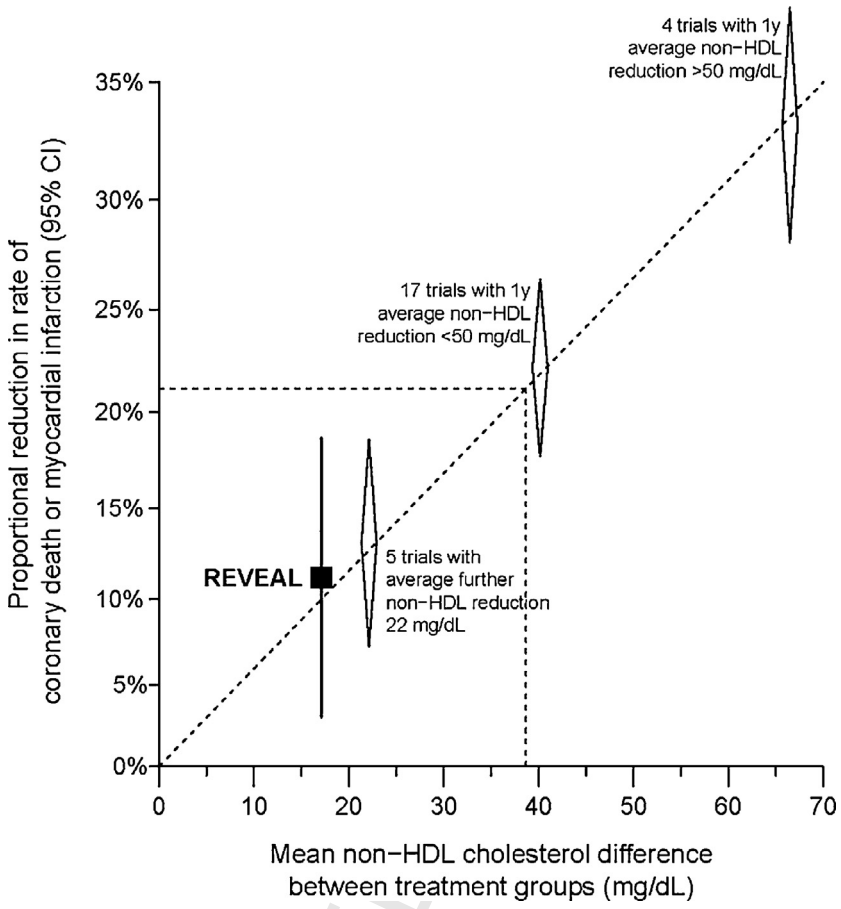

Fig. 4. Effect of anacetrapib on coronary death or myocardial infarction. Comparison of the effects of anacetrapib in the REVEAL trial and statins in the Cholesterol Treatment Trialists meta-analysis on coronary death or myocardial infarction, plotted according to the size of the absolute reduction in non-HDL cholesterol. Reproduced with permission [18].

est HDL-C elevations [56]. This finding is likely consequent to a long-term accumulation of drug in the adipose tissue after one-year of treatment [51], as also reported in mice [57]. This was possibly a factor in the final decision not to continue drug development.

6. Evidence from Mendelian randomization analyses

In the effort to study the complexities of lipid biology and thus also of CETP inhibition, the genetic procedure of Mendelian randomization represents an analog of randomized clinical trials. Individuals are randomly assigned either to an exposure group (carriers of an allele promoting the biological exposure of interest) or to a control group (carriers of a different allele). Overall, the basis of Mendelian randomization is that if the exposure is causal for a given outcome (*eg*, LDL-C is causally associated with the risk of CHD), genetic variants associated with exposure should also be associated with the outcome [125].

By using a Mendelian randomization analysis, Ference et al. gave insights on why CETP inhibitors were less effective than expected in clinical trials. The Authors concluded that changes in apoB levels are better predictors of clinical response to CETP inhibitors plus statin *vs* either LDL-C or HDL-C levels. Thus, the clinical benefit of lowering LDL-C depends on how LDL-C lowering is achieved, rather than on the reduction in cholesterol carried by those particles [126].

The analysis, comprehensive of 358,205 participants from 77 studies, aimed at evaluating the causal effects of LDL-C lowering of CV events due to genetic variants that mimic the effects of CETP inhibitors. A specific genetic score was assigned in order to simulate statin-CETP treatment (CETP score ≥ median and HMGCR score ≥ median) or CETP monotherapy according to a specific score (CETP score ≥ median and HMGCR score ≤ median). The latter genotype results in a rise of HDL-C (mean: +4.64 mg/dL) and reduction of LDL-C (mean: −2.16 mg/dL) and apoB (−1.93 mg/dL); it also associates with a significant lowering of the CHD risk (OR: 0.946; 95%CI, 0.921–0.972; p = 0.036). Exposure to gene variants that recapitulate statin-CETP treatment led to an attenuation of both apoB reduction (mean: −0.59 mg/dL) and CHD risk (OR: 0.985; 95%CI, 0.959-1.012; no longer statistically significant). These conclusions were validated in a genome-wide association study in which 21 genetic variants, with naturally occurring discordance between changes in LDL-C and apoB levels, were associated to the risk of CV events; reduction in events was more closely related to the lowering of apoB (OR per 10 mg/dL lower apoB: 0.772, 95%CI, 0.701–0.844) *vs* that of LDL-C (OR per 10 mg/dL lower LDL-C: 0.916, 95%CI, 0.890–0.943) [127].

Overall, this Mendelian randomization study clearly indicates that apoB is a superior marker of risk of CV events *vs* LDL, and these findings are in line with epidemiological evidence highlighting that apoB may improve risk assessment of future coronary heart disease events over and beyond LDL-C or non-HDL-C [128–130].

Previous Mendelian randomization studies did not evaluate the combined effect of *CETP* and *HMGGCR* variants and did not always report concordant findings. Niu et al. showed that long-term genetically reduced circulating levels of CETP, due to the *CETP* rs708272 polymorphism, might be causally associated with a low risk of CHD. Specifically, comparing carriers of rs708272-B1B1 genotype or B1 allele with carriers of B2B2 genotype, a 0.2 μg/mL reduction in circulating CETP resulted in a 25% (OR: 0.75; 95%CI, 0.10–0.91) and

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in a 17% (OR: 0.83; 95%CI, 0.41–0.96) CHD risk reduction, respectively [131]. Of note, rs708272-B1B1 and B1 allele genotype are associated to marginally lower circulating CETP levels compared to those observed in B2B2 genotype carriers. These results are in contrast with others failing to demonstrate a causal relevance between increased circulating HDL-C levels and reduced CHD risk in carriers of the *CETP* rs708272 [132]. Thompson et al. demonstrated that genotypes, associated with moderate inhibition of CETP activity, have a weak inverse association with coronary risk [133].

7. Conclusions

The results of the REVEAL study have elicited more questions than answers relative to the efficacy and suitability of inhibiting the CETP enzyme as a new preventive strategy for CV diseases. First, it is still unclear whether the CV benefit is related to LDL-C lowering or to HDL-C-raising, not leaving out the ancillary properties on Lp(a) and non-HDL. The REVEAL data shows a correlation between non-HDL-C and CVD risk, in line with the data from the CTT meta-analysis (Fig. 4). This observation certainly does not exclude the contribution of HDL-C raising to the CV benefit, especially because anacetrapib preferentially increases the proportion of pro-atherogenic small, lipid-poor LDL particles (LDL subfractions 4a,4b baseline 9.6% of total LDL *vs* anacetrapib 26% of total LDL) [134,135]. Furthermore, the optimal HDL baseline levels for achieving a clinical benefit with anacetrapib still need to be defined, also considering the recent results from two prospective population-based studies, showing that in the rare cases of extremely elevated HDL cholesterol a high all-cause mortality may be detected [136]. Remarkably, HDL particles found in the high HDL-C induced by anacetrapib appear to exhibit physical and functional properties of those from healthy normolipidemic subjects [134,137].

The adverse events observed with anacetrapib seem to be, to a certain degree, similar to those reported after the CETP inhibitors tested in large phase III clinical RCTs, *eg* a small rise in BP (Table 2). Whether adverse events are a result of an off-target effect or directly consequent to CETP inhibition is still a matter of debate. Interestingly, an analysis of the 1307 Framingham Study participants free of CVD showed that a lower plasma CETP activity was associated with a greater increase in pulse pressure, possibly because of raised vascular stiffness [138], this latter a sensitive marker of arterial disease [139]. CETP inhibition, leading to enlarged HDL particles, may result in a faulty interaction between HDL and the Scavenger Receptor class B type I (SR-BI), a mandatory mechanism for the activation of endothelial nitric oxide synthase [140].

In conclusion, the possible therapeutic window for anacetrapib in dyslipidemic patients with CHD could be envisioned in a more personalized therapy for selected patients with low HDL-C at high CV risk or low HDL-C patients intolerant to statins in whom LDL-C would typically be >100 mg/dL. The combination with other lipid lowering therapies, *ie* ezetimibe, could also be considered. Unfortunately, Merck already announced that it will not seek regulatory approval for anacetrapib, since its clinical profile does not support regulatory filings. With this waiver, dalcetrapib (Dal-GenE study) and CKD-519 (NCT02977065) remain the two molecules within this area still in clinical development.

Acknowledgments

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References

[1] C. Baigent, A. Keech, P.M. Kearney, L. Blackwell, G. Buck, C. Pollicino, A. Kirby, T. Sourjina, R. Peto, R. Collins, R. Simes, C. Cholesterol Treatment Trialists, Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, Lancet 366 (2005) 1267–1278.
[2] C.P. Cannon, E. Braunwald, C.H. McCabe, D.J. Rader, J.L. Rouleau, R. Belder, S.V. Joyal, K.A. Hill, M.A. Pfeffer, A.M. Skene, E. and I. Pravastatin or Atorvastatin, Infection therapy-thrombolysis in myocardial Infarction. Intensive versus moderate lipid lowering with statins after acute coronary syndromes, N. Engl. J. Med. 350 (2004) 1495–1504.
[3] G.E. Ronseinand, J.W. Heinecke, Time to ditch HDL-C as a measure of HDL function? Curr. Opin. Lipidol. 28 (2017) 414–418.
[4] L. Calabresi, M. Gomaraschi, G. Franceschini, High-density lipoprotein quantity or quality for cardiovascular prevention? Curr. Pharm. Des. 16 (2010) 1494–1503.
[5] R.S. Rosenson, H.B. Brewer Jr., P.J. Barter, J.L.M. Bjorkegren, M.J. Chapman, D. Gaudet, D.S. Kim, E. Niesor, K.A. Rye, F.M. Sacks, J.C. Tardif, R.A. Hegele, HDL and atherosclerotic cardiovascular disease: genetic insights into complex biology, Nat. Rev. Cardiol. (2017).
[6] J.T. Kuvin, A.A. Alsheikh-Ali, R.H. Karas, High-density lipoprotein cholesterol-raising strategies, J. Cardiovasc. Pharmacol. 47 (2006) 196–204.
[7] E. Bruckert, J. Labreuche, P. Amarenco, Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis, Atherosclerosis 210 (2010) 353–361.
[8] C.L. Bisgaier, R. Ackermann, T. Réa, W.V. Rodrigueza, D. Hartman, ApoA-IMilano phospholipid complex (ETC-216) infusion in human volunteers. Insights into the phenotypic characteristics of ApoA-IMilano carriers, Pharmacol. Res. 111 (2016) 86–99.
[9] R.S. Rosenson, CETP inhibition improves the lipid profile but has no effect on clinical cardiovascular outcomes in high-risk patients, Evid. Based Med. 22 (2017) 184–185.
[10] A. Kontush, M. Guerin, M.J. Chapman, Spotlight on HDL-raising therapies: insights from the torcetrapib trials, Nat. Clin. Pract. Cardiovasc. Med. 5 (2008) 329–336.
[11] S. Zhong, D.S. Sharp, J.S. Grove, C. Bruce, K. Yano, J.D. Curb, A.R. Tall, Increased coronary heart disease in Japanese-American men with mutation in the cholesteryl ester transfer protein gene despite increased HDL levels, J. Clin. Invest. 97 (1996) 2917–2923.
[12] A.R. Tall, Plasma cholesteryl ester transfer protein, J. Lipid Res. 34 (1993) 1255–1274.
[13] P.J. Barter, H.B. Brewer Jr., M.J. Chapman, C.H. Hennekens, D.J. Rader, A.R. Tall, Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 23 (2003) 160–167.
[14] S. Yamashitaand, Y. Matsuzawa, Re-evaluation of cholesteryl ester transfer protein function in atherosclerosis based upon genetics and pharmacological manipulation, Curr. Opin. Lipidol. 27 (2016) 459–472.
[15] M. Cucheland, D.J. Rader, Macrophage reverse cholesterol transport: key to the regression of atherosclerosis? Circulation 113 (2006) 2548–2555.
[16] G.E. Ronseinand, T. Vaisar, Inflammation, remodeling, and other factors affecting HDL cholesterol efflux, Curr. Opin. Lipidol. 28 (2017) 52–59.
[17] R.A. Hegele, CETP inhibitors – a new inning? N. Engl. J. Med. 377 (2017) 1284–1285.
[18] H.T.R.C. Group, L. Bowman, J.C. Hopewell, F. Chen, K. Wallendszus, W. Stevens, R. Collins, S.D. Wiviott, C.P. Cannon, E. Braunwald, E. Sammons, M.J. Landray, Effects of anacetrapib in patients with atherosclerotic vascular disease, N. Engl. J. Med. 377 (2017) 1217–1227.
[19] A.P. Serdyukand, R.E. Morton, Lipid transfer inhibitor protein defines the participation of lipoproteins in lipid transfer reactions: CETP has no preference for cholesteryl esters in HDL versus LDL, Arterioscler. Thromb. Vasc. Biol. 19 (1999) 718–726.
[20] X. Qiu, A. Mistry, M.J. Ammirati, B.A. Chrunyk, R.W. Clark, Y. Cong, J.S. Culp, D.E. Danley, T.B. Freeman, K.F. Geoghegan, M.C. Griffor, S.J. Hawrylik, C.M. Hayward, P. Hensley, L.R. Hoth, G.A. Karam, M.E. Lira, D.B. Lloyd, K.M. McGrath, K.J. Stutzman-Engwall, A.K. Subashi, T.A. Subashi, J.F. Thompson, I.K. Wang, H. Zhao, A.P. Seddon, Crystal structure of cholesteryl ester transfer protein reveals a long tunnel and four bound lipid molecules, Nat. Struct. Mol. Biol. 14 (2007) 106–113.
[21] L. Zhang, F. Yan, S. Zhang, D. Lei, M.A. Charles, G. Cavigiolio, M. Oda, R.M. Krauss, K.H. Weisgraber, K.A. Rye, H.J. Pownall, X. Qiu, G. Ren, Structural basis of transfer between lipoproteins by cholesteryl ester transfer protein, Nat. Chem. Biol. 8 (2012) 342–349.
[22] M. Zhang, R. Charles, H. Tong, L. Zhang, M. Patel, F. Wang, M.J. Rames, A. Ren, K.A. Rye, X. Qiu, D.G. Johns, M.A. Charles, G. Ren, HDL surface lipids mediate CETP binding as revealed by electron microscopy and molecular dynamics simulation, Sci. Rep. 5 (2015) 8741.
[23] M.E. Lauer, A. Graff-Meyer, A.C. Rufer, C. Maugeais, E. von der Mark, H. Matile, B. D'Arcy, C. Magg, P. Ringler, S.A. Muller, S. Scherer, G. Dernick, R. Thoma, M. Hennig, E.J. Niesor, H. Stahlberg, Cholesteryl ester transfer between lipoproteins does not require a ternary tunnel complex with CETP, J. Struct. Biol. 194 (2016) 191–198.
[24] S. Liu, A. Mistry, J.M. Reynolds, D.B. Lloyd, M.C. Griffor, D.A. Perry, R.B. Ruggeri, R.W. Clark, X. Qiu, Crystal structures of cholesteryl ester transfer

Please cite this article in press as: N. Ferri, et al., Present therapeutic role of cholesteryl ester transfer protein inhibitors, Pharmacol Res (2017), https://doi.org/10.1016/j.phrs.2017.12.028

protein in complex with inhibitors, J. Biol. Chem. 287 (2012) 37321–37329.
[25] E.J. Niesor, Different effects of compounds decreasing cholesteryl ester transfer protein activity on lipoprotein metabolism, Curr. Opin. Lipidol. 22 (2011) 288–295.
[26] C. Maugeais, A. Perez, E. von der Mark, C. Magg, P. Pflieger, E.J. Niesor, Evidence for a role of CETP in HDL remodeling and cholesterol efflux: role of cysteine 13 of CETP, Biochim. Biophys. Acta 1831 (2013) 1644–1650.
[27] K.A. Ryeand, P.J. Barter, Formation and metabolism of prebeta-migrating, lipid-poor apolipoprotein A-I, Arterioscler. Thromb. Vasc. Biol. 24 (2004) 421–428.
[28] V.M. Paromovand, R.E. Morton, Lipid transfer inhibitor protein defines the participation of high density lipoprotein subfractions in lipid transfer reactions mediated by cholesterol ester transfer protein (CETP), J. Biol. Chem. 278 (2003) 40859–40866.
[29] A.H. Mohammadpourand, F. Akhlaghi, Future of cholesteryl ester transfer protein (CETP) inhibitors: a pharmacological perspective, Clin. Pharmacokinet. 52 (2013) 615–626.
[30] H. Shinkai, Cholesteryl ester transfer-protein modulator and inhibitors and their potential for the treatment of cardiovascular diseases, Vasc. Health Risk Manag. 8 (2012) 323–331.
[31] E.J. Niesor, C. Magg, N. Ogawa, H. Okamoto, E. von der Mark, H. Matile, G. Schmid, R.G. Clerc, E. Chaput, D. Blum-Kaelin, W. Huber, R. Thoma, P. Pflieger, M. Kakutani, D. Takahashi, G. Dernick, C. Maugeais, Modulating cholesteryl ester transfer protein activity maintains efficient pre-beta-HDL formation and increases reverse cholesterol transport, J. Lipid Res. 51 (2010) 3443–3454.
[32] S.J. Nicholls, G. Ruotolo, H.B. Brewer, J.P. Kane, M.D. Wang, K.A. Krueger, S.J. Adelman, S.E. Nissen, D.J. Rader, Cholesterol efflux capacity and pre-beta-1 HDL concentrations are increased in dyslipidemic patients treated with evacetrapib, J. Am. Coll. Cardiol. 66 (2015) 2201–2210.
[33] S.P. Wang, E. Daniels, Y. Chen, J. Castro-Perez, H. Zhou, K.O. Akinsanya, S.F. Previs, T.P. Roddy, D.G. Johns, In vivo effects of anacetrapib on prebeta HDL: improvement in HDL remodeling without effects on cholesterol absorption, J. Lipid Res. 54 (2013) 2858–2865.
[34] D.G. Johns, Y. Chen, S.P. Wang, J. Castro-Perez, S.F. Previs, T.P. Roddy, Inhibition of cholesteryl ester transfer protein increases cholesteryl ester content of large HDL independently of HDL-to-HDL homotypic transfer: in vitro vs in vivo comparison using anacetrapib and dalcetrapib, Eur. J. Pharmacol. 762 (2015) 256–262.
[35] M.R. Brodeur, D. Rhainds, D. Charpentier, T. Mihalache-Avram, M. Mecteau, G. Brand, E. Chaput, A. Perez, E.J. Niesor, E. Rheaume, C. Maugeais, J.C. Tardif, Dalcetrapib and anacetrapib differently impact HDL structure and function in rabbits and monkeys, J. Lipid Res. 58 (2017) 1282–1291.
[36] B.F. Asztalos, K.V. Horvath, K. Kajinami, C. Nartsupha, C.E. Cox, M. Batista, E.J. Schaefer, A. Inazu, H. Mabuchi, Apolipoprotein composition of HDL in cholesteryl ester transfer protein deficiency, J. Lipid Res. 45 (2004) 448–455.
[37] S. Yamashita, D.L. Sprecher, N. Sakai, Y. Matsuzawa, S. Tarui, D.Y. Hui, Accumulation of apolipoprotein E-rich high density lipoproteins in hyperalphalipoproteinemic human subjects with plasma cholesteryl ester transfer protein deficiency, J. Clin. Invest. 86 (1990) 688–695.
[38] S. Yamashita, M. Ishigami, T. Arai, N. Sakai, K. Hirano, K. Kameda-Takemura, K. Tokunaga, Y. Matsuzawa, Very high density lipoproteins induced by plasma cholesteryl ester transfer protein (CETP) have a potent antiatherogenic function, Ann. N. Y. Acad. Sci. 748 (1995) 606–608.
[39] C.E. Kosmas, E. DeJesus, D. Rosario, T.J. Vittorio, CETP inhibition: past failures and future hopes, Clin. Med. Insights Cardiol. 10 (2016) 37–42.
[40] N. Rashedi, D. Brennan, J.J. Kastelein, S.E. Nissen, S. Nicholls, Impact of cholesteryl ester transfer protein inhibition on nuclear magnetic resonance derived lipoprotein particle parameters (abstr), Atheroscler. Suppl. 12 (2011) 48.
[41] C.M. Ballantyne, M. Miller, E.J. Niesor, T. Burgess, D. Kallend, E.A. Stein, Effect of dalcetrapib plus pravastatin on lipoprotein metabolism and high-density lipoprotein composition and function in dyslipidemic patients: results of a phase IIb dose-ranging study, Am. Heart J. 521 (521) (2012) e511–e513.
[42] T. Murakami, S. Michelagnoli, R. Longhi, G. Gianfranceschi, F. Pazzucconi, L. Calabresi, C.R. Sirtori, G. Franceschini, Triglycerides are major determinants of cholesterol esterification/transfer and HDL remodeling in human plasma, Arterioscler. Thromb. Vasc. Biol. 15 (1995) 1819–1828.
[43] D.S. Small, J. Royalty, E.A. Cannady, C. Hale, M.D. Wang, D. Downs, J.G. Suico, Impact of increased gastric pH on the pharmacokinetics of evacetrapib in healthy subjects, Pharmacotherapy 36 (2016) 749–756.
[44] D.S. Small, W. Zhang, J. Royalty, E.A. Cannady, D. Downs, S. Friedrich, J.G. Suico, A multidose study to examine the effect of food on evacetrapib exposure at steady state, J. Cardiovasc. Pharmacol. Ther. 20 (2015) 483–489.
[45] R. Krishna, A. Garg, D. Panebianco, J. Cote, A.J. Bergman, P. Van Hoydonck, T. Laethem, K. Van Dyck, J. Chen, C. Chavez-Eng, L. Archer, R. Lutz, D. Hilliard, K. Snyder, B. Jin, L. Van Bortel, K.C. Lasseter, N. Al-Huniti, K. Dykstra, K. Gottesdiener, J.A. Wagner, Single-dose pharmacokinetics and pharmacodynamics of anacetrapib, a potent cholesteryl ester transfer protein (CETP) inhibitor, in healthy subjects, Br. J. Clin. Pharmacol. 68 (2009) 535–545.
[46] R. Krishna, F. Gheyas, Y. Liu, J. Cote, O. Laterza, J.L. Ruckle, J.A. Wagner, A.E. Denker, Pharmacokinetics and pharmacodynamics of anacetrapib following single doses in healthy, young Japanese and white male subjects, J. Clin. Pharmacol. (2017).
[47] M. Derks, J. Anzures-Cabrera, L. Turnbull, M. Phelan, Safety, tolerability and pharmacokinetics of dalcetrapib following single and multiple ascending doses in healthy subjects: a randomized, double-blind, placebo-controlled, phase I study, Clin. Drug Investig. 31 (2011) 325–335.
[48] D. Dalvie, W. Chen, C. Zhang, A.D. Vaz, T.A. Smolarek, L.M. Cox, J. Lin, R.S. Obach, Pharmacokinetics, metabolism, and excretion of torcetrapib, a cholesteryl ester transfer protein inhibitor, in humans, Drug Metab. Dispos. 36 (2008) 2185–2198.
[49] D. Bentley, A.M. Young, L. Rowell, G. Gross, J. Tardio, D. Carlile, Evidence of a drug–drug interaction linked to inhibition of ester hydrolysis by orlistat, J. Cardiovasc. Pharmacol. 60 (2012) 390–396.
[50] G. Gross, J. Tardio, O. Kuhlmann, Solubility and stability of dalcetrapib in vehicles and biological media, Int. J. Pharm. 437 (2012) 103–109.
[51] R. Krishna, F. Gheyas, Y. Liu, D.R. Hagen, B. Walker, A. Chawla, J. Cote, R.O. Blaustein, D.E. Gutstein, Chronic administration of anacetrapib is associated with accumulation in adipose and slow elimination, Clin. Pharmacol. Ther. (2017).
[52] M. Derks, H. Kawamura, M. Abt, G. Meneses-Lorente, M. Phelan, T. Ishikawa, Effects of food intake on the pharmacokinetic properties of dalcetrapib: findings from three phase I, single-dose crossover studies in healthy volunteers, Clin. Ther. 33 (2011) 754–765.
[53] R. Krishna, A.J. Bergman, B. Jin, M. Fallon, J. Cote, P. Van Hoydonck, T. Laethem, I.N. Gendrano 3rd, K. Van Dyck, D. Hilliard, O. Laterza, K. Snyder, C. Chavez-Eng, R. Lutz, J. Chen, D.M. Bloomfield, M. De Smet, L.M. Van Bortel, M. Gutierrez, N. Al-Huniti, K. Dykstra, K.M. Gottesdiener, J.A. Wagner, Multiple-dose pharmacodynamics and pharmacokinetics of anacetrapib, a potent cholesteryl ester transfer protein (CETP) inhibitor, in healthy subjects, Clin. Pharmacol. Ther. 84 (2008) 679–683.
[54] S. Friedrich, J.J. Kastelein, D. James, T. Waterhouse, S.E. Nissen, S.J. Nicholls, K.A. Krueger, The pharmacokinetics and pharmacokinetic/pharmacodynamic relationships of evacetrapib administered as monotherapy or in combination with statins, CPT: Pharmacom. Syst. Pharmacol. 3 (2014) e94.
[55] E.A. Cannady, A. Aburub, C. Ward, C. Hinds, B. Czeskis, K. Ruterbories, J.G. Suico, J. Royalty, D. Ortega, B.W. Pack, S.L. Begum, W.F. Annes, Q. Lin, D.S. Small, Absolute bioavailability of evacetrapib in healthy subjects determined by simultaneous administration of oral evacetrapib and intravenous [(13) C8]-evacetrapib as a tracer, J. Labell. Comp. Radiopharm. 59 (2016) 238–244.
[56] A.M. Gotto Jr., C.P. Cannon, X.S. Li, S. Vaidya, U. Kher, E.A. Brinton, M. Davidson, J.E. Moon, S. Shah, H.M. Dansky, Y. Mitchel, P. Barter, D. Investigators, Evaluation of lipids, drug concentration, and safety parameters following cessation of treatment with the cholesteryl ester transfer protein inhibitor anacetrapib in patients with or at high risk for coronary heart disease, Am. J. Cardiol. 113 (2014) 76–83.
[57] G. Hartmann, S. Kumar, D. Johns, F. Gheyas, D. Gutstein, X. Shen, A. Burton, H. Lederman, R. Lutz, T. Jackson, C. Chavez-Eng, K. Mitra, Disposition into adipose tissue determines accumulation and elimination kinetics of the cholesteryl ester transfer protein inhibitor anacetrapib in mice, Drug Metab. Dispos. 44 (2016) 428–434.
[58] M. Phelan, J. Anzures-Cabrera, D.J. Carlile, L. Rowell, O. Kuhlmann, G. Arold, R. Robson, D. Bentley, Effect of hepatic and renal impairment on the pharmacokinetics of dalcetrapib: altered distribution of the active thiol? Clin. Pharmacokinet. 52 (2013) 255–265.
[59] S. Kumar, E.Y. Tan, G. Hartmann, Z. Biddle, A.J. Bergman, J. Dru, J.Z. Ho, A.N. Jones, S.J. Staskiewicz, M.P. Braun, B. Karanam, D.C. Dean, I.N. Gendrano, M.W. Graves, J.A. Wagner, R. Krishna, Metabolism and excretion of anacetrapib, a novel inhibitor of the cholesteryl ester transfer protein, in humans, Drug Metab. Dispos. 38 (2010) 474–483.
[60] B. Lauring, X.S. Li, Y. Liu, C. Corr, N. Lazarus, J. Cote, P. Larson, A.O. Levonas, K.C. Lasseter, R.A. Preston, W.B. Smith, E. Lai, J.A. Wagner, Influence of renal and hepatic impairment on the pharmacokinetics of anacetrapib, J. Clin. Pharmacol. 54 (2014) 1247–1255.
[61] M.S. Anderson, J. Cote, Y. Liu, D. Stypinski, P. Auger, A. Hohnstein, S. Rasmussen, A.O. Johnson-Levonas, D.E. Gutstein, Effects of Rifampin, a potent inducer of drug-metabolizing enzymes and an inhibitor of OATP1B1/3 transport, on the single dose pharmacokinetics of anacetrapib, J. Clin. Pharmacol. 53 (2013) 746–752.
[62] A. Garg, A. Maes, C. Corr, B. Jin, T. Wadhwa, N. Handa, K. Van Dyck, I. De Lepeleire, J. Shah, J.A. Wagner, R. Krishna, Effect of diltiazem, a moderate CYP3A inhibitor, on the pharmacokinetics of anacetrapib, a potent cholesteryl ester transfer protein inhibitor, in healthy subjects, J. Clin. Pharmacol. 51 (2011) 436–439.
[63] R. Krishna, A.J. Bergman, B. Jin, A. Garg, B. Roadcap, R. Chiou, J. Dru, J. Cote, T. Laethem, R.W. Wang, V. Didolkar, E. Vets, K. Gottesdiener, J.A. Wagner, Assessment of the CYP3A-mediated drug interaction potential of anacetrapib, a potent cholesteryl ester transfer protein (CETP) inhibitor, in healthy volunteers, J. Clin. Pharmacol. 49 (2009) 80–87.
[64] P.J. Barter, M. Caulfield, M. Eriksson, S.M. Grundy, J.J. Kastelein, M. Komajda, J. Lopez-Sendon, L. Mosca, J.C. Tardif, D.D. Waters, C.L. Shear, J.H. Revkin, K.A. Buhr, M.R. Fisher, A.R. Tall, B. Brewer, I. Investigators, Effects of torcetrapib in patients at high risk for coronary events, N. Engl. J. Med. 357 (2007) 2109–2122.
[65] C.R. Sirtoriand, G. Mombelli, Cholesteryl ester transfer protein antagonism by drugs—a poor choice, Clin. Chem. 56 (2010) 1550–1553.
[66] M.J. Forrest, D. Bloomfield, R.J. Briscoe, P.N. Brown, A.M. Cumiskey, J. Ehrhart, J.C. Hershey, W.J. Keller, X. Ma, H.E. McPherson, E. Messina, L.B.

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Peterson, W. Sharif-Rodriguez, P.K. Siegl, P.J. Sinclair, C.P. Sparrow, A.S. Stevenson, S.Y. Sun, C. Tsai, H. Vargas, M. Walker 3rd, S.H. West, V. White, R.F. Woltmann, Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone, Br. J. Pharmacol. 154 (2008) 1465–1473.

[67] C.R. Sirtori, Investigational CETP antagonists for hyperlipidemia and atherosclerosis prevention, Expert Opin. Investig. Drugs 20 (2011) 1543–1554.

[68] G. Cao, T.P. Beyer, Y. Zhang, R.J. Schmidt, Y.Q. Chen, S.L. Cockerham, K.M. Zimmerman, S.K. Karathanasis, E.A. Cannady, T. Fields, N.B. Mantlo, Evacetrapib is a novel, potent, and selective inhibitor of cholesteryl ester transfer protein that elevates HDL cholesterol without inducing aldosterone or increasing blood pressure, J. Lipid Res. 52 (2011) 2169–2176.

[69] M. Ranalletta, K.K. Bierilo, Y. Chen, D. Milot, Q. Chen, E. Tung, C. Houde, N.H. Elowe, M. Garcia-Calvo, G. Porter, S. Eveland, B. Frantz-Wattley, M. Kavana, G. Addona, P. Sinclair, C. Sparrow, E.A. O'Neill, K.S. Koblan, A. Sitlani, B. Hubbard, T.S. Fisher, Biochemical characterization of cholesteryl ester transfer protein inhibitors, J. Lipid Res. 51 (2010) 2739–2752.

[70] S. Kuhnast, S.J. van der Tuin, J.W. van der Hoorn, J.B. van Klinken, B. Simic, E. Pieterman, L.M. Havekes, U. Landmesser, T.F. Luscher, K. Willems van Dijk, P.C. Rensen, J.W. Jukema, H.M. Princen, Anacetrapib reduces progression of atherosclerosis, mainly by reducing non-HDL-cholesterol, improves lesion stability and adds to the beneficial effects of atorvastatin, Eur. Heart J. 36 (2015) 39–48.

[71] A.S. Plump, L. Masucci-Magoulas, C. Bruce, C.L. Bisgaier, J.L. Breslow, A.R. Tall, Increased atherosclerosis in ApoE and LDL receptor gene knock-out mice as a result of human cholesteryl ester transfer protein transgene expression, Arterioscler. Thromb. Vasc. Biol. 19 (1999) 1105–1110.

[72] M. Westerterp, C.C. van der Hoogt, W. de Haan, E.H. Offerman, G.M. Dallinga-Thie, J.W. Jukema, L.M. Havekes, P.C. Rensen, Cholesteryl ester transfer protein decreases high-density lipoprotein and severely aggravates atherosclerosis in APOE*3-Leiden mice, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 2552–2559.

[73] B. Simic, P. Mocharla, M. Crucet, E. Osto, A. Kratzer, S. Stivala, S. Kuhnast, T. Speer, P. Doycheva, H.M. Princen, J.W. van der Hoorn, J.W. Jukema, H. Giral, A. Tailleux, U. Landmesser, B. Staels, T.F. Luscher, Anacetrapib, but not evacetrapib, impairs endothelial function in CETP-transgenic mice in spite of marked HDL-C increase, Atherosclerosis 257 (2017) 186–194.

[74] W. de Haan, J. de Vries-van der Weij, J.W. van der Hoorn, T. Gautier, C.C. van der Hoogt, M. Westerterp, J.A. Romijn, J.W. Jukema, L.M. Havekes, H.M. Princen, P.C. Rensen, Torcetrapib does not reduce atherosclerosis beyond atorvastatin and induces more proinflammatory lesions than atorvastatin, Circulation 117 (2008) 2515–2522.

[75] L.A. Morehouse, E.D. Sugarman, P.A. Bourassa, T.M. Sand, F. Zimetti, F. Gao, G.H. Rothblat, A.J. Milici, Inhibition of CETP activity by torcetrapib reduces susceptibility to diet-induced atherosclerosis in New Zealand White rabbits, J. Lipid Res. 48 (2007) 1263–1272.

[76] B. Dong, A.B. Singh, C. Fung, K. Kan, J. Liu, CETP inhibitors downregulate hepatic LDL receptor and PCSK9 expression in vitro and in vivo through a SREBP2 dependent mechanism, Atherosclerosis 235 (2014) 449–462.

[77] S.J. van der Tuin, S. Kuhnast, J.F. Berbee, L. Verschuren, E.J. Pieterman, L.M. Havekes, J.W. van der Hoorn, P.C. Rensen, J.W. Jukema, H.M. Princen, K. Willems van Dijk, Y. Wang, Anacetrapib reduces (V)LDL cholesterol by inhibition of CETP activity and reduction of plasma PCSK9, J. Lipid Res. 56 (2015) 2085–2093.

[78] B.J. Wu, Y. Li, K.L. Ong, Y. Sun, S. Shrestha, L. Hou, D. Johns, P.J. Barter, K.A. Rye, Reduction of in-stent restenosis by cholesteryl ester transfer protein inhibition, Arterioscler. Thromb. Vasc. Biol. 37 (2017).

[79] N. Ferri, S. Marchiano, G. Tibolla, R. Baetta, A. Dhyani, M. Ruscica, P. Uboldi, A.L. Catapano, A. Corsini, PCSK9 knock-out mice are protected from neointimal formation in response to perivascular carotid collar placement, Atherosclerosis 253 (2016) 214–224.

[80] D. Bloomfield, G.L. Carlson, A. Sapre, D. Tribble, J.M. McKenney, T.W. Littlejohn 3rd, C.M. Sisk, Y. Mitchel, R.C. Pasternak, Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients, Am. Heart J. 360 (2009) e352.

[81] A.M. Gotto, Jr., U. Kher, M.S. Chatterjee, Y. Liu, X.S. Li, S. Vaidya, C.P. Cannon, E.A. Brinton, J.E. Moon, S. Shah, H.M. Dansky, Y. Mitchel, P. Barter, D. Investigators, Lipids, safety parameters, and drug concentrations after an additional 2 years of treatment with anacetrapib in the DEFINE study, J. Cardiovasc. Pharmacol. Ther. 19 (2014) 543–549.

[82] J.J. Kastelein, J. Besseling, S. Shah, J. Bergeron, G. Langslet, G.K. Hovingh, N. Al-Saady, M. Koeijvoets, J. Hunter, A.O. Johnson-Levonas, J. Fable, A. Sapre, Y. Mitchel, Anacetrapib as lipid-modifying therapy in patients with heterozygous familial hypercholesterolaemia (REALIZE): a randomised, double-blind, placebo-controlled, phase 3 study, Lancet 385 (2015) 2153–2161.

[83] M.J. Landray, G. Reveal Collaborative, F.C.E.S.J.C.H.K.W.W.S.E.V.-M.S.W.C.P.C.E.B.R.C.L. Bowman, Randomized evaluation of the effects of anacetrapib through lipid-modification (REVEAL)-A large-scale, randomized, placebo-controlled trial of the clinical effects of anacetrapib among people with established vascular disease: trial design, recruitment, and baseline characteristics, Am. Heart J. 187 (2017) 182–190.

[84] P.J. Barter, F. Tabet, K.A. Rye, Reduction in PCSK9 levels induced by anacetrapib: an off-target effect? J. Lipid Res. 56 (2015) 2045–2047.

[85] N. Ferri, A. Corsini, C. Macchi, P. Magni, M. Ruscica, Proprotein convertase subtilisin kexin type 9 and high-density lipoprotein metabolism: experimental animal models and clinical evidence, Transl. Res. J. Lab. Clin. Med. 173 (2016) 19–29.

[86] N. Ferriand, M. Ruscica, Proprotein convertase subtilisin/kexin type 9 (PCSK9) and metabolic syndrome: insights on insulin resistance, inflammation, and atherogenic dyslipidemia, Endocrine 54 (2016) 588–601.

[87] B.J. Arsenault, F. Petrides, F. Tabet, W. Bao, G.K. Hovingh, S.M. Boekholdt, S. Ramin-Mangata, O. Meilhac, D. DeMicco, K.A. Rye, D.D. Waters, J.J.P. Kastelein, P. Barter, G. Lambert, Effect of atorvastatin, cholesterol ester transfer protein inhibition, and diabetes mellitus on circulating proprotein subtilisin kexin type 9 and lipoprotein(a) levels in patients at high cardiovascular risk, J. Clin. Lipidol. (2017).

[88] T. Thomas, H. Zhou, W. Karmally, R. Ramakrishnan, S. Holleran, Y. Liu, P. Jumes, J.A. Wagner, B. Hubbard, S.F. Previs, T. Roddy, A.O. Johnson-Levonas, D.E. Gutstein, S.M. Marcovina, D.J. Rader, H.N. Ginsberg, J.S. Millar, G. Reyes-Soffer, CETP (Cholesteryl ester transfer protein) inhibition with anacetrapib decreases production of lipoprotein(a) in mildly hypercholesterolemic subjects, Arterioscler. Thromb. Vasc. Biol. 37 (2017) 1770–1775.

[89] C. Waldeyer, N. Makarova, T. Zeller, R.B. Schnabel, F.J. Brunner, T. Jorgensen, A. Linneberg, T. Niiranen, V. Salomaa, P. Jousilahti, J. Yarnell, M.M. Ferrario, G. Veronesi, P. Brambilla, S.G. Signorini, L. Iacoviello, S. Costanzo, S. Giampaoli, L. Palmieri, C. Meisinger, B. Thorand, F. Kee, W. Koenig, F. Ojeda, J. Kontto, U. Landmesser, K. Kuulasmaa, S. Blankenberg, Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium, Eur. Heart J. 38 (2017) 2490–2498.

[90] M. Pirro, V. Bianconi, F. Paciullo, M.R. Mannarino, F. Bagaglia, A. Sahebkar, Lipoprotein(a) and inflammation: a dangerous duet leading to endothelial loss of integrity, Pharmacol. Res. 119 (2017) 178–187.

[91] P. Liao, R. Zeng, X. Zhao, L. Guo, M. Zhang, Prognostic value of non-high-density lipoprotein cholesterol for mortality in patients with coronary heart disease: a systematic review and meta-analysis, Int. J. Cardiol. 227 (2017) 950–955.

[92] S.J. Nicholls, A.M. Lincoff, P.J. Barter, H.B. Brewer, K.A. Fox, C.M. Gibson, C. Grainger, V. Menon, G. Montalescot, D. Rader, A.R. Tall, E. McErlean, J. Riesmeyer, B. Vangerow, G. Ruotolo, G.J. Weerakkody, S.E. Nissen, Assessment of the clinical effects of cholesteryl ester transfer protein inhibition with evacetrapib in patients at high-risk for vascular outcomes: rationale and design of the ACCELERATE trial, Am. Heart J. 170 (2015) 1061–1069.

[93] A.M. Lincoff, S.J. Nicholls, J.S. Riesmeyer, P.J. Barter, H.B. Brewer, K.A.A. Fox, C.M. Gibson, C. Granger, V. Menon, G. Montalescot, D. Rader, A.R. Tall, E. McErlean, K. Wolski, G. Ruotolo, B. Vangerow, G. Weerakkody, S.G. Goodman, D. Conde, D.K. McGuire, J.C. Nicolau, J.L. Leiva-Pons, Y. Pesant, W. Li, D. Kandath, S. Kouz, N. Tahirkheli, D. Mason, S.E. Nissen, A. Investigators, Evacetrapib and cardiovascular outcomes in high-risk vascular disease, N. Engl. J. Med. 376 (2017) 1933–1942.

[94] S.J. Nicholls, H.B. Brewer, J.J. Kastelein, K.A. Krueger, M.D. Wang, M. Shao, B. Hu, E. McErlean, S.E. Nissen, Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial, JAMA 306 (2011) 2099–2109.

[95] A. Sahebkar, L.E. Simental-Mendia, F. Guerrero-Romero, J. Golledge, G.F. Watts, Efficacy and safety of evacetrapib for modifying plasma lipids: a systematic review and meta-analysis of randomized controlled trials, Curr. Pharm. Des. 22 (2016) 595–608.

[96] Z.A. Fayad, V. Mani, M. Woodward, D. Kallend, M. Abt, T. Burgess, V. Fuster, C.M. Ballantyne, E.A. Stein, J.C. Tardif, J.H. Rudd, M.E. Farkouh, A. Tawakol, P.I. dal, Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial, Lancet 378 (2011) 1547–1559.

[97] T.F. Luscher, S. Taddei, J.C. Kaski, J.W. Jukema, D. Kallend, T. Munzel, J.J. Kastelein, J.E. Deanfield, V.I. dal, Vascular effects and safety of dalcetrapib in patients with or at risk of coronary heart disease: the dal-VESSEL randomized clinical trial, Eur. Heart J. 33 (2012) 857–865.

[98] J.C. Tardif, E. Rheaume, L.P. Lemieux Perreault, J.C. Gregoire, Y. Feroz Zada, G. Asselin, S. Provost, A. Barhdadi, D. Rhainds, P.L. L'Allier, R. Ibrahim, R. Upmanyu, E.J. Niesor, R. Benghozi, G. Suchankova, F. Laghrissi-Thode, M.C. Guertin, A.G. Olsson, I. Mongrain, G.G. Schwartz, M.P. Dube, Pharmacogenomic determinants of the cardiovascular effects of dalcetrapib, Circul. Cardiovasc. Genet. 8 (2015) 372–382.

[99] K.K. Ray, M. Ditmarsch, D. Kallend, E.J. Niesor, G. Suchankova, R. Upmanyu, J. Anzures-Cabrera, V. Lehnert, M. Pauly-Evers, I. Holme, J. Stasek, M.W. van Hessen, P. Jones, A.I. dal, The effect of cholesteryl ester transfer protein inhibition on lipids, lipoproteins, and markers of HDL function after an acute coronary syndrome: the dal-ACUTE randomized trial, Eur. Heart J. 35 (2014) 1792–1800.

[100] G.G. Schwartz, A.G. Olsson, M. Abt, C.M. Ballantyne, P.J. Barter, J. Brumm, B.R. Chaitman, I.M. Holme, D. Kallend, L.A. Leiter, E. Leitersdorf, J.J. McMurray, H. Mundl, S.J. Nicholls, P.K. Shah, J.C. Tardif, R.S. Wright, O.I. dal, Effects of dalcetrapib in patients with a recent acute coronary syndrome, N. Engl. J. Med. 367 (2012) 2089–2099.

[101] F.R. Joshi, N.K. Rajani, M. Abt, M. Woodward, J. Bucerius, V. Mani, A. Tawakol, D. Kallend, Z.A. Fayad, J.H. Rudd, Does vascular calcification accelerate

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inflammation? A substudy of the dal-PLAQUE trial, J. Am. Coll. Cardiol. 67 (2016) 69–78.
[102] M.A. Allison, S. Hsi, C.L. Wassel, C. Morgan, J.H. Ix, C.M. Wright, M.H. Criqui, Calcified atherosclerosis in different vascular beds and the risk of mortality, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 140–146.
[103] J.C. Tardif, F. Lesage, F. Harel, P. Romeo, J. Pressacco, Imaging biomarkers in atherosclerosis trials, Circ. Cardiovasc. Imaging 4 (2011) 319–333.
[104] J.C. Tardif, D. Rhainds, M. Brodeur, Y. Feroz Zada, R. Fouodjio, S. Provost, M. Boule, S. Alem, J.C. Gregoire, P.L. L'Allier, R. Ibrahim, M.C. Guertin, I. Mongrain, A.G. Olsson, G.G. Schwartz, E. Rheaume, M.P. Dube, Genotype-dependent effects of dalcetrapib on cholesterol efflux and inflammation: concordance with clinical outcomes, Circ. Cardiovasc. Genet. 9 (2016) 340–348.
[105] J.C. Tardif, D. Rhainds, E. Rheaume, M.P. Dube, CETP: pharmacogenomics-based response to the CETP inhibitor dalcetrapib, Arterioscler. Thromb. Vasc. Biol. 37 (2017) 396–400.
[106] G. Schillaci, M. Pirro, T. Ronti, F. Gemelli, G. Pucci, S. Innocente, C. Porcellati, E. Mannarino, Prognostic impact of prolonged ventricular repolarization in hypertension, Arch. Intern. Med. 166 (2006) 909–913.
[107] P.J. Barter, K.A. Rye, M.S. Beltangady, W.C. Ports, W.T. Duggan, S.M. Boekholdt, D.A. DeMicco, J.J. Kastelein, C.L. Shear, Relationship between atorvastatin dose and the harm caused by torcetrapib, J. Lipid Res. 53 (2012) 2436–2442.
[108] J. Bagdade, P. Barter, C. Quiroga, P. Alaupovic, Effects of torcetrapib and statin treatment on apoC-III and apoprotein-defined lipoprotein subclasses (from the ILLUMINATE trial), Am. J. Cardiol. 119 (2017) 1753–1756.
[109] P.J. Barter, K.A. Rye, J.C. Tardif, D.D. Waters, S.M. Boekholdt, A. Breazna, J.J. Kastelein, Effect of torcetrapib on glucose, insulin, and hemoglobin A1c in subjects in the investigation of lipid level management to understand its impact in atherosclerotic events (ILLUMINATE) trial, Circulation 124 (2011) 555–562.
[110] S.E. Nissen, J.C. Tardif, S.J. Nicholls, J.H. Revkin, C.L. Shear, W.T. Duggan, W. Ruzyllo, W.B. Bachinsky, G.P. Lasala, E.M. Tuzcu, I. Investigators, Effect of torcetrapib on the progression of coronary atherosclerosis, N. Engl. J. Med. 356 (2007) 1304–1316.
[111] J.J. Kastelein, S.I. van Leuven, L. Burgess, G.W. Evans, J.A. Kuivenhoven, P.J. Barter, J.H. Revkin, D.E. Grobbee, W.A. Riley, C.L. Shear, W.T. Duggan, M.L. Bots, R. Investigators, Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia, N. Engl. J. Med. 356 (2007) 1620–1630.
[112] M.L. Bots, F.L. Visseren, G.W. Evans, W.A. Riley, J.H. Revkin, C.H. Tegeler, C.L. Shear, W.T. Duggan, R.M. Vicari, D.E. Grobbee, J.J. Kastelein, R. Investigators, Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial, Lancet 370 (2007) 153–160.
[113] M.E. Brousseau, M.R. Diffenderfer, J.S. Millar, C. Nartsupha, B.F. Asztalos, F.K. Welty, M.L. Wolfe, M. Rudling, I. Bjorkhem, B. Angelin, J.P. Mancuso, A.G. Digenio, D.J. Rader, E.J. Schaefer, Effects of cholesteryl ester transfer protein inhibition on high-density lipoprotein subspecies, apolipoprotein A-I metabolism, and fecal sterol excretion, Arterioscler. Thromb. Vasc. Biol. 25 (2005) 1057–1064.
[114] A.R. Talland, D.J. Rader, The trials and tribulations of CETP inhibitors, Circ. Res. (2017).
[115] R. Collins, C. Reith, J. Emberson, J. Armitage, C. Baigent, L. Blackwell, R. Blumenthal, J. Danesh, G.D. Smith, D. DeMets, S. Evans, M. Law, S. MacMahon, S. Martin, B. Neal, N. Poulter, D. Preiss, P. Ridker, I. Roberts, A. Rodgers, P. Sandercock, K. Schulz, P. Sever, J. Simes, L. Smeeth, N. Wald, S. Yusuf, R. Peto, Interpretation of the evidence for the efficacy and safety of statin therapy, Lancet 388 (2016) 2532–2561.
[116] S.J. Nicholls, K.K. Ray, C.M. Ballantyne, L.A. Beacham, D.L. Miller, G. Ruotolo, S.E. Nissen, J.S. Riesmeyer, A. Investigators, Comparative effects of cholesteryl ester transfer protein inhibition, statin or ezetimibe on lipid factors: the ACCENTUATE trial, Atherosclerosis 261 (2017) 12–18.
[117] M. Luo, A. Liu, S. Wang, T. Wang, D. Hu, S. Wu, D. Peng, ApoCIII enrichment in HDL impairs HDL-mediated cholesterol efflux capacity, Sci. Rep. 7 (2017) 2312.
[118] M. Ruscica, N. Ferri, A. Corsini, C.R. Sirtori, PCSK9 antagonists and inflammation, Atherosclerosis (2017).
[119] J.S. Millar, M.E. Lassman, T. Thomas, R. Ramakrishnan, P. Jumes, R.L. Dunbar, E.M. deGoma, A.L. Baer, W. Karmally, D.S. Donovan, H. Rafeek, J.A. Wagner, S. Holleran, J. Obunike, Y. Liu, S. Aoujil, T. Standiford, D.E. Gutstein, H.N. Ginsberg, D.J. Rader, G. Reyes-Soffer, Effects of CETP inhibition with anacetrapib on metabolism of VLDL-TG and plasma apolipoproteins C-II, C-III, and E, J. Lipid Res. 58 (2017) 1214–1220.
[120] C.E. Lewis, Defining the safety of anacetrapib, a CETP inhibitor, in patients at high risk for coronary heart disease: the DEFINE study, Curr. Cardiovasc. Risk Rep. 5 (2011) 109–112.
[121] B.J. Wu, Y. Li, K.L. Ong, Y. Sun, S. Shrestha, L. Hou, D. Johns, P.J. Barter, K.A. Rye, Reduction of in-stent restenosis by cholesteryl ester transfer protein inhibition, Arterioscler. Thromb. Vasc. Biol. 37 (2017) 2333–2341.
[122] A.V. Khera, M. Cuchel, M. de la Llera-Moya, A. Rodrigues, M.F. Burke, K. Jafri, B.C. French, J.A. Phillips, M.L. Mucksavage, R.L. Wilensky, E.R. Mohler, G.H. Rothblat, D.J. Rader, Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis, N. Engl. J. Med. 364 (2011) 127–135.
[123] A. Rohatgi, A. Khera, J.D. Berry, E.G. Givens, C.R. Ayers, K.E. Wedin, I.J. Neeland, I.S. Yuhanna, D.R. Rader, J.A. de Lemos, P.W. Shaul, HDL cholesterol efflux capacity and incident cardiovascular events, N. Engl. J. Med. 371 (2014) 2383–2393.
[124] J. Castro-Perez, F. Briand, K. Gagen, S.P. Wang, Y. Chen, D.G. McLaren, V. Shah, R.J. Vreeken, T. Hankemeier, T. Sulpice, T.P. Roddy, B.K. Hubbard, D.G. Johns, Anacetrapib promotes reverse cholesterol transport and bulk cholesterol excretion in Syrian golden hamsters, J. Lipid Res. 52 (2011) 1965–1973.
[125] P.C. Robinson, H.K. Choi, R. Do, T.R. Merriman, Insight into rheumatological cause and effect through the use of Mendelian randomization, Nat. Rev. Rheumatol. 12 (2016) 486–496.
[126] A.D. Sniderman, E.D. Peterson, Genetic studies help clarify the complexities of lipid biology and treatment, JAMA 318 (2017) 915–917.
[127] B.A. Ference, J.J.P. Kastelein, H.N. Ginsberg, M.J. Chapman, S.J. Nicholls, K.K. Ray, C.J. Packard, U. Laufs, R.D. Brook, C. Oliver-Williams, A.S. Butterworth, J. Danesh, G.D. Smith, A.L. Catapano, M.S. Sabatine, Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk, JAMA 318 (2017) 947–956.
[128] M.J. Pencina, R.B. D'Agostino, T. Zdrojewski, K. Williams, G. Thanassoulis, C.D. Furberg, E.D. Peterson, R.S. Vasan, A.D. Sniderman, Apolipoprotein B improves risk assessment of future coronary heart disease in the Framingham heart study beyond LDL-C and non-HDL-C, Eur. J. Prevent. Cardiol. 22 (2015) 1321–1327.
[129] J.T. Wilkins, R.C. Li, A. Sniderman, C. Chan, D.M. Lloyd-Jones, Discordance between apolipoprotein B and LDL-cholesterol in young adults predicts coronary artery calcification: the CARDIA study, J. Am. Coll. Cardiol. 67 (2016) 193–201.
[130] P.R. Lawler, A.O. Akinkuolie, P.M. Ridker, A.D. Sniderman, J.E. Buring, R.J. Glynn, D.I. Chasman, S. Mora, Discordance between circulating atherogenic cholesterol mass and lipoprotein particle concentration in relation to future coronary events in women, Clin. Chem. 63 (2017) 870–879.
[131] W. Niuand, Y. Qi, Circulating cholesteryl ester transfer protein and coronary heart disease: mendelian randomization meta-analysis, Circ. Cardiovasc. Genet. 8 (2015) 114–121.
[132] Z. Wu, Y. Lou, X. Qiu, Y. Liu, L. Lu, Q. Chen, W. Jin, Association of cholesteryl ester transfer protein (CETP) gene polymorphism, high density lipoprotein cholesterol and risk of coronary artery disease: a meta-analysis using a Mendelian randomization approach, BMC Med. Genet. 15 (2014) 118.
[133] A. Thompson, E. Di Angelantonio, N. Sarwar, S. Erqou, D. Saleheen, R.P. Dullaart, B. Keavney, Z. Ye, J. Danesh, Association of cholesteryl ester transfer protein genotypes with CETP mass and activity, lipid levels, and coronary risk, JAMA 299 (2008) 2777–2788.
[134] R.M. Krauss, K. Wojnooski, J. Orr, J.C. Geaney, C.A. Pinto, Y. Liu, J.A. Wagner, J.M. Luk, A.O. Johnson-Levonas, M.S. Anderson, H.M. Dansky, Changes in lipoprotein subfraction concentration and composition in healthy individuals treated with the CETP inhibitor anacetrapib, J. Lipid Res. 53 (2012) 540–547.
[135] P.T. Williams, H.R. Superko, W.L. Haskell, E.L. Alderman, P.J. Blanche, L.G. Holl, R.M. Krauss, Smallest LDL particles are most strongly related to coronary disease progression in men, Arterioscler. Thromb. Vasc. Biol. 23 (2003) 314–321.
[136] C.M. Madsen, A. Varbo, B.G. Nordestgaard, Extreme high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies, Eur. Heart J. 38 (2017) 2478–2486.
[137] L. Yvan-Charvet, J. Kling, T. Pagler, H. Li, B. Hubbard, T. Fisher, C.P. Sparrow, A.K. Taggart, A.R. Tall, Cholesterol efflux potential and antiinflammatory properties of high-density lipoprotein after treatment with niacin or anacetrapib, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 1430–1438.
[138] J.P. Zachariah, M.J. Pencina, A. Lyass, G. Kaur, R.B. D'Agostino, J.M. Ordovas, R.S. Vasan, Circulating plasma cholesteryl ester transfer protein activity and blood pressure tracking in the community, J. Hypertens. 29 (2011) 863–868.
[139] G. Schillaci, G. Pucci, M. Pirro, L. Settimi, R. Hijazi, S.S. Franklin, E. Mannarino, Combined effects of office and 24-h blood pressure on aortic stiffness in human hypertension, J. Hypertens. 29 (2011) 869–875.
[140] I.S. Yuhanna, Y. Zhu, B.E. Cox, L.D. Hahner, S. Osborne-Lawrence, P. Lu, Y.L. Marcel, R.G. Anderson, M.E. Mendelsohn, H.H. Hobbs, P.W. Shaul, High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase, Nat. Med. 7 (2001) 853–857.
[141] A.J. Hooperand, J.R. Burnett, Dalcetrapib: a cholesteryl ester transfer protein modulator, Expert Opin. Investig. Drugs 21 (2012) 1427–1432.
[142] M. Derks, S. Fowler, O. Kuhlmann, A single-center, open-label, one-sequence study of dalcetrapib coadministered with ketoconazole, and an in vitro study of the S-methyl metabolite of dalcetrapib, Clin. Ther. 31 (2009) 586–599.

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