Cholesteryl Ester Transfer Protein Inhibitors and Cardiovascular Outcomes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Keywords

Cholesteryl ester transfer protein inhibitors · High-density lipoproteins · Low-density lipoproteins · Cardiovascular events · Systematic review · Meta-analysis

Abstract

Background: Cholesteryl ester transfer protein (CETP) inhibitors increase serum high-density lipoprotein cholesterol (HDL-c) concentration; however, their impact on cardiovascular outcomes is not clear. This systematic review examines the effect of CETP inhibitors on serum lipid profiles, cardiovascular events, and all-cause mortality. **Methods:** We searched MEDLINE, Embase, and the Cochrane Library of Clinical Trials for placebo-controlled randomized controlled trials (RCTs) that examined the effect of a CETP inhibitor (dalcetapib, anacetrapib, evacetrapib, or TA-8995) on all-cause mortality, major adverse cardiovascular events (MACE), or the components of MACE at ≥6 months. Data were pooled using random-effects models. **Results:** A total of 11 RCTs ($n = 62,431$) were included in our systematic review; 4 examined dalcetapib ($n = 16,612$), 6 anacetrapib ($n = 33,682$), and 1 evacetrapib ($n = 12,092$). Compared to dalcetapib, ana-

cetrapib and evacetrapib were more efficacious at raising HDL-c levels (~100–130 vs. ~30%). Anacetrapib and evacetrapib also decreased low-density lipoprotein cholesterol (LDL-c) by approximately 30% while dalcetapib did not affect the LDL-c level. Overall, CETP inhibitors were not associated with the incidence of MACE (pooled relative risk [RR]: 0.97; 95% confidence interval [CI]: 0.91–1.04). CETP inhibitors may decrease the risks of nonfatal myocardial infarction (MI) (RR: 0.93; 95% CI: 0.87–1.00) and cardiovascular death (RR: 0.92; 95% CI: 0.83–1.01), though these trends did not reach statistical significance. **Conclusions:** CETP inhibitors are not associated with an increased risk of MACE or all-cause mortality. There is a trend towards small reductions in nonfatal MI and cardiovascular death, though the clinical importance of such reductions is likely modest.

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Introduction

Cholesteryl ester transfer protein (CETP) inhibitors, including dalcetapib, evacetrapib, and anacetrapib, are novel agents that have been developed to increase serum

high-density lipoprotein cholesterol (HDL-c) concentration. These agents increase HDL-c levels by inhibiting an enzyme that catalyzes the exchange of cholesteryl esters and triglycerides between HDL and low-density lipoproteins (LDL). Despite being efficacious at increasing HDL levels, the CETP inhibitors' impact on cardiovascular outcomes remains unclear, particularly as observed benefits could also be related to lowering LDL cholesterol (LDL-c) [1]. Previous trials of other HDL-c-raising medications such as fibrates and niacin have failed to demonstrate that the use of these medications impacts clinical outcomes among patients already taking statins [2]. Optimal HDL-c targets for clinical benefit are unclear, as extremely elevated HDL-c has been associated with increased all-cause mortality [1]. Anacetrapib, notably, is also known to accumulate in adipose tissues in the long-term [1]. With the publication of two large clinical trials of CETP inhibitors, REVEAL and ACCELERATE, there is a need to synthesize the available evidence concerning the efficacy of CETP inhibitors [3, 4]. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the effect of CETP inhibitors on cardiovascular outcomes and lipid levels.

Methods

Our systematic review with meta-analysis, which followed a prespecified protocol, was designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5].

Search Strategy

We systematically searched MEDLINE, Embase, and the Cochrane Library of Clinical Trials databases from inception to July 11, 2017, to identify RCTs that assessed the efficacy and safety of CETP inhibitors. Our search strategies (Appendices 1–3) were constructed using the drug names of interest: obicetrapib or TA-8995, evacetrapib or LY2484595, dalcetrapib or JTT-705, and anacetrapib or MK-0859. Torcetrapib was excluded from our search since it was no longer under investigation at the time our protocol was written, due to the increased mortality associated with its use [6]. MEDLINE and Embase searches were restricted to RCTs using a modified version of the McMaster RCT hedge [7]. Reference lists of included trials and relevant reviews were scanned to identify additional RCTs not included in the results of our electronic search. Lastly, ClinicalTrials.gov was also searched for RCTs that were registered and completed but not yet published.

Inclusion Criteria

The title and abstract of all publications identified in our electronic search were screened independently by two reviewers, with the full text of any potentially eligible publication retrieved

for subsequent review by two independent reviewers. Disagreements during full-text review were resolved by consensus or, when necessary, by a third reviewer. Based on our prespecified inclusion criteria, publications were included if they (1) reported data from RCTs comparing a CETP inhibitor (other than torcetrapib) to placebo; (2) included participants older than 18 years of age; (3) were not reviews, editorials, or letters to the editor; (4) included at least 100 participants; (5) had a follow-up duration of at least 6 months; and (6) reported at least one of our primary or secondary outcomes such as major adverse cardiovascular events (MACE) or its components, or lipid levels (see outcomes below). If multiple publications from the same trial were available, the publication with the largest and most complete reporting was included in our review. Conference abstracts were excluded if we were able to find a corresponding published manuscript to include in our study.

Data Extraction

Two independent reviewers extracted data from RCTs that met the inclusion criteria into a standardized, pilot-tested database. Discrepancies were resolved by consensus or by a third reviewer. Extracted study characteristics were year of publication, location of enrollment sites, overall number of participants, number of participants in each arm, study duration, and drug regimen. Baseline patient characteristics included age, sex, body mass index, statin use, and the prevalence of cardiovascular risk factors such as diabetes and hypertension. Finally, baseline levels of HDL-c and LDL-c were also recorded.

Our primary outcome of interest was MACE, including nonfatal myocardial infarction (MI), stroke, hospitalization for unstable angina, revascularization events, and cardiovascular death. Our secondary outcomes were the individual components of MACE, all-cause mortality, and lipid levels (LDL-c and HDL-c) at the reported longest follow-up and/or their percent changes from baseline to the longest follow-up.

Quality Assessment

We assessed the quality of included studies using the Cochrane Collaboration's tool for assessing risk of bias [8]. The tool incorporates the following criteria: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other potential sources of bias. Each domain was given a score of "high," "low," or "unclear" by two independent reviewers, and disagreements were resolved by consensus or by a third reviewer when necessary.

Statistical Analysis

We used DerSimonian and Laird random-effects models with inverse variance weighting to pool count data across included RCTs and estimate relative risks (RR) and the corresponding 95% confidence intervals (CI). Our primary analysis pooled data across all CETP inhibitors, and secondary analyses were stratified by CETP inhibitor molecule. We used the treatment arm continuity correction in RCTs with zero events in both arms. I^2 values were calculated to estimate the amount of between-study heterogeneity that was present. All analyses were conducted using R version 3.4.1.

Fig. 1. PRISMA flowchart describing the systematic literature search and the inclusion and exclusion of trials comparing cholesteryl ester transfer protein (CETP) inhibitors to placebo.

Results

Search Results

Our electronic search identified 729 potentially relevant publications (Fig. 1). One additional trial was identified via ClinicalTrials.gov [3]. We removed 306 duplicate records and screened the titles and abstracts of the remaining 423 records. A total of 18 underwent full-text review, of which 11 RCTs met our inclusion criteria and were included in our study [3, 4, 9–19].

Study and Patient Characteristics

Overall, the 11 included RCTs randomized a total of 62,431 patients (Table 1). The sample sizes ranged from 130 to 30,449 participants, and the follow-up durations ranged between 24 weeks and 4.1 years. Dalcetrapib was studied in 4 RCTs ($n = 16,612$), anacetrapib in 6 ($n = 33,682$), and evacetrapib in 1 ($n = 12,092$). Each CETP inhibitor had a large RCT with at least 12,000 participants. No studies on TA-8995 met our inclusion criteria; this finding was not unexpected since TA-8995 is in ear-

Table 1. Characteristics of randomized controlled trials comparing the use of a CETPi to placebo

Study, year	Enrollment sites	Inclusion criteria	Total, n	Arm, n		F/U duration	Daily dose, mg
				CETPi	placebo		
<i>Dalcetrapib</i> dal-OUTCOMES [15], 2012	27 countries in North America, Europe, Asia, and Australia	Patients 45 years of age or older who had recently been hospitalized for an ACS	15,871	7,938	7,933	36 months (median 31 months)	600
dal-VESSEL [14], 2012	7 countries in Europe	18- to 75-year-old patients with CAD or at high risk for CAD with HDL-c <50 mg/dL	476	238	238	36 weeks	600
dal-PLAQUE [12], 2011	USA, Canada	18- to 75-year-old patients with CAD or at high risk for CAD	130	64	66	24 months	600
Stein et al. [16], 2010	USA, Germany	18- to 75-year-old patients with CAD or at high risk for CAD	135	89	46	24 weeks core, 24 weeks extension	900
<i>Anacetrapib</i> REVEAL [3], 2017	Europe, North America, China	Patients older than 50 years with high cardiovascular risk	30,449	15,225	15,224	4.1 years	100
DEFINE [11], 2010	20 countries in North America, Europe, Asia, and Australia	18–80 years old with CHD or at high risk for CHD	1,623	811	812	24 weeks lipids, 52 weeks extension	100
Ballantyne et al. [10], 2017	Brazil, Russia, China, Korea, Taiwan, Turkey, Mexico	18–80 years old with hypercholesterolemia who were not at their LDL-c goal per NCEP ATP III coronary heart disease risk	583	290	293	24 weeks	100
Ballantyne et al. [9], 2017	NR	18–80 years old with hypercholesterolemia who were not at their LDL-c goal per NCEP ATP III coronary heart disease risk	459†	153	154	36 weeks	100
Teramoto et al. [17], 2017	Japan	18–80 years old with dyslipidemia who were not at their LDL-c goal	307	204	103	52 weeks	100
REALIZE [13], 2015	9 countries in Europe	18–80 years old with genotype-confirmed or clinical diagnosis of heterozygous familial hypercholesterolemia	306	204	102	52 weeks	100
<i>Evacetrapib</i> ACCELERATE [4], 2017	36 countries in North America, South America, Europe, Asia, and Australia	18 years and older who had high-risk vascular disease, treated with statin for 30 days before screening	12,092	6,038	6,054	26 months (median)	130

ACS, acute coronary syndrome; CAD, coronary artery disease; CHD, coronary heart disease; CETPi, cholesteryl ester transfer protein inhibitor; F/U, follow-up; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NR, not reported.

† The study had 3 experimental arms. Placebo and the arm with 100 mg daily dosage were included in the review.

lier stages of development compared to the other drugs [18].

Included participants (Table 2) were predominantly male (between 55 and 90%) with a mean age ranging from 55.0 to 64.8 years. Most trials recruited patients with al-

ready established cardiovascular disease (e.g., history of acute coronary syndrome) or at high risk for cardiovascular disease (e.g., had risk factors such as diabetes or hypercholesterolemia). One trial included patients with genetically confirmed familial hypercholesterolemia [13].

Table 2. Baseline characteristics of patients in randomized controlled trials comparing the use of a CETPi to placebo

Study, year	Age (SD), years		Mean BMI		Statin use ^a , %		Men, %		Diabetes, %		HT, %		Mean LDL-c, mg/dL		Mean HDL-c, mg/dL	
	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo
<i>Dalcetrapib</i>																
dai-OUTCOMES [15], 2012	60.3 (9.1)	60.1 (9.1)	28.6	28.6	97	98	80	81	24	25	67	68	76.4	75.8	42.5	42.2
dai-VESSEL [14], 2012	62.3 (7.1)	61.9 (7.9)	29.6	28.7	94	97	91	90	47	44	74	75	81.4	79.2	39.1	38.4
dai-PLAQUE [12], 2011	62.6 (8.2)	64.6 (7.8)	29.6	29.8	81	92	80	83	30	30	73	73	73	73	42	46
Stein et al. [16], 2010	61.2 (7.8)	60.2 (7.5)	30.5	30.1	NR	NR	76	83	54	54	73	65	77	77	41	41
<i>Anacetrapib</i>																
REVEAL [3], 2017	67 (8)	67 (8)	28.6	28.6	97.2	96.9	84	84	37.1	37.2	NR	NR	61	61	40	40
DEFINE [11], 2010	62.5 (8.7)	62.9 (9.0)	30.4	30.1	99	99	78	76	53	53	69	67	81.4	82.2	40.5	40.4
Ballantyne et al. [10], 2017	60.3 (9.1)	60.9 (8.9)	27.7	27.8	100	100	76	69	9	6	64	72	87.2	88.7	43.5	43.6
Ballantyne et al. [9], 2017	58.7 (9.6)	60.3 (8.9)	31.1	31	100	100	66	70	48	51	72	74	95.7	93	46.2	47.7
Teramoto et al. [17], 2017	60.9 (9.6)	60.5 (9.9)	25.2	25.4	100	100	70	64	34	44	NR	NR	125.7	128.2	53.9	56
REALIZE [13], 2015	55.0 (11.8)	55.7 (11.9)	28.2	27.9	100	100	59	49	5	6	30	39	130	130	54	54
<i>Evacetrapib</i>																
ACCELERATE [4], 2017	64.8 (9.4)	65.0 (9.5)	NR	NR	96.4	96.6	77	77	68.4	67.9	87.3	87.6	81.6	81.1	45.3	45.3

BMI, body mass index; CETPi, cholesteryl ester transfer protein inhibitor; HT, hypertension; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NR, not reported.

Table 3. Reported clinical outcomes at longest follow-up in randomized controlled trials comparing the use of a CETPi to placebo

Study, year	Arm count, n		MACE, n (%)		Nonfatal MI, n (%)		Stroke, n (%)		Hospitalization for UA/ACS, n (%)		Revascularization, n (%)		CV death, n (%)		All-cause mortality, n (%)	
	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo
<i>Dalcetrapib</i>																
dai-OUTCOMES [15], 2012	7,938	7,933	656 ^a (8.3)	414 (5.2)	407 (5.1)	91 (1.1)	73 (0.9)	84 (1.1)	92 (1.2)	674 (8.5)	672 (8.5)	118 (1.5)	125 (1.6)	226 (2.8)	229 (2.9)	NR
dai-VESSEL [14], 2012	236	236	11 (4.6)	2 (0.8)	3 (1.3)	0 (0)	0 (0)	0 (0)	1 (0.4)	9 (3.8)	7 (3.0)	0 (0)	1 (0.4)	NR	NR	NR
dai-PLAQUE [12], 2011	63	65	2 (3.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1	2	2
Stein et al. [16], 2010	89	46	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<i>Anacetrapib</i>																
REVEAL [3], 2017	15,225	15,224	2,068 (13.5)	669 (4.4)	769 (5.1)	547 (3.6)	559 (3.7)	NR	NR	1,081 (7.1)	1,201 (7.9)	520 (3.4)	564 (3.7)	1,122 (7.4)	1,155 (7.6)	NR
DEFINE [11], 2010	808	804	16 ^a (2.0)	6 (0.7)	9 (1.1)	5 (0.6)	5 (0.6)	1 (0.1)	6 (0.7)	8 (1.0)	28 (3.5)	4 (0.1)	1 (0.5)	11 (1.4)	8 (1.0)	NR
Ballantyne et al. [10], 2017	290	292	0 (0)	0 (0)	1 (0.3)	0 (0)	2 (0.8)	0 (0)	4 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	2 (0.7)	NR
Ballantyne et al. [9], 2017	153	154	1 (0.6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1 (0.6)	0 (0)	NR
Teramoto et al. [17], 2017	204	103	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
REALIZE [13], 2015	203	102	3 (1.5)	1 (0.5)	0 (0)	0 (0)	0 (0)	3 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<i>Evacetrapib</i>																
ACCELERATE [4], 2017	6,038	6,054	779 (12.9)	258 (4.3)	259 (4.3)	94 (1.6)	98 (1.6)	155 (2.6)	146 (2.4)	487 (8.1)	485 (8.0)	143 (2.4)	166 (2.7)	231 (3.8)	276 (3.8)	NR

ACS, acute coronary syndrome; CV, cardiovascular; CETPi, cholesteryl ester transfer protein inhibitor; MACE, major adverse cardiovascular events; MI, myocardial infarction; NR, not reported; UA, unstable angina.

^a Coronary revascularization was not included in the MACE count.

Fig. 2. Forest plot comparing the relative risk of MACE at longest follow-up in patients randomized to a cholesteryl ester transfer protein (CETP) inhibitor compared with patients randomized to placebo. MACE, major adverse cardiovascular event; CI, confidence interval; RR, relative risk. The asterisk indicates Ballantyne et al. [10] in contrast to Ballantyne et al. [9], both references from 2017.

On average, more than 90% of enrolled patients were already taking statins or were given statins prior to randomization. Mean LDL-c levels at baseline were below 100 mg/dL for all trials except for 2: one that included patients with heterozygous familial hypercholesterolemia and another that included patients with dyslipidemia refractory to statins [13, 17]. In all trials, patients' mean serum HDL-c levels were lower than 60 mg/dL.

Quality Assessment

All included trials had a low risk of bias according to the Cochrane Collaboration's Tool for Assessing Risk of Bias (Appendix 4). They were double-blinded and included placebo as a comparator. Sequence generation and allocation concealment criteria were not clearly described in 4 out of 11 studies [9, 10, 16, 17].

MACE and Its Components

Most included trials reported MACE (Table 3) as a composite incidence of cardiovascular death, nonfatal MI, hospitalization due to unstable angina or acute coronary

syndrome, stroke, and coronary revascularization. In the REVEAL trial, hospitalization for unstable angina was not included as part of their composite end point. Two studies did not include revascularization as a component of MACE [11, 15]. Certain trials, such as dal-PLAQUE, did not report many of the secondary outcomes of interest [12].

Overall, pooled data suggest that CETP inhibitors do not decrease MACE compared to placebo (RR: 0.97; 95% CI: 0.91–1.04) (Fig. 2). Similarly, pooled data across all CETP inhibitors found no difference in risks of stroke (RR: 1.00; 95% CI: 0.90–1.11) (Appendix 5), hospitalization due to acute coronary syndrome (RR: 0.99; 95% CI: 0.83–1.18) (Appendix 6), revascularization (RR: 0.95; 95% CI: 0.85–1.05) (Appendix 7) or all-cause mortality (RR: 0.95; 95% CI: 0.89–1.02) (Appendix 8). However, our pooled data suggest that CETP inhibitors may modestly decrease the risks of nonfatal MI (RR: 0.93; 95% CI: 0.87–1.00) (Fig. 3) and cardiovascular death (RR: 0.92; 95% CI: 0.83–1.01) (Appendix 9), though these trends did not reach statistical significance. Analyses stratified by CETP inhibitor found no difference in MACE or its components, with one exception:

Fig. 3. Forest plot comparing the relative risk of nonfatal myocardial infarction at longest follow-up in patients randomized to a cholesteryl ester transfer protein (CETP) inhibitor compared with patients randomized to placebo. CI, confidence interval; RR, relative risk. The asterisk indicates Ballantyne et al. [10], 2017.

patients randomized to anacetrapib had a reduced risk of nonfatal MI compared to those randomized to placebo (RR: 0.87; 95% CI: 0.78–0.96) (Fig. 3). This finding was mainly driven by the results from the REVEAL trial [3].

Changes in Plasma Lipid Levels

CETP inhibitors increased HDL-c with varying efficacy (Table 4). In the REVEAL trial, anacetrapib increased mean HDL-c levels from 38 to 85 mg/dL, a relative increase of 104%. Similarly, in the ACCELERATE trial, treatment with evacetrapib increased mean HDL-c levels from 54.7 to 104.1 mg/dL (133.2% increase). Dalcetrapib, in contrast, had a milder impact on HDL-c. In the dal-PLAQUE study, dalcetrapib increased HDL-c by 30.9% from baseline. The observed changes were consistent with those of smaller trials included in our review.

In addition to increasing HDL-c levels, anacetrapib and evacetrapib decreased LDL-c levels in all included trials. In the ACCELERATE trial, treatment with evacetrapib decreased LDL-c levels by 31.1%. Interestingly, in both anacetrapib trials with statin-treated patients with mean baseline LDL-c levels of more than 100 mg/dL, treatment with anacetrapib significantly lowered serum LDL-c lev-

els: in the REALIZE trial, patients with familial hypercholesterolemia had lower mean LDL-c levels (79.0 mg/dL in the treated group compared to 126.7 mg/dL in the placebo group) [13]. Likewise, in the trial by Teramoto et al. [19], a similar change was observed, with a mean 31.3% reduction in LDL-c. In contrast to anacetrapib and evacetrapib, dalcetrapib had a minimal impact on mean LDL-c.

Discussion

Our systematic review with meta-analysis was designed to assess the impact of CETP inhibitors (anacetrapib, dalcetrapib, and evacetrapib) on clinical outcomes and serum lipid profiles. Although we found no benefit for MACE or all-cause mortality, there was a trend towards reduced risks of nonfatal MI and cardiovascular death. However, the clinical significance of these potential benefits is likely modest. When analyses were stratified by drug, there was no difference in any outcome except for anacetrapib, which reduced the incidence of nonfatal MI. All CETP inhibitors increased HDL-c, to varying degrees, with anacetrapib and evacetrapib appearing to increase HDL-c substantively

Table 4. Reported lipid outcomes at longest follow-up in randomized controlled trials comparing the use of a CETPi to placebo

Study, year	Mean LDL-c (SD), mg/dL		LDL-c percent change from baseline (SD or IQR)		Mean HDL-c (SD), mg/dL		HDL-c percent change from baseline (SD or IQR)	
	CETPi	placebo	CETPi	placebo	CETPi	placebo	CETPi	placebo
<i>Dalcetrapib</i>								
dal-OUTCOMES [15], 2012	NR	NR	NR	NR	NR	NR	NR	NR
dal-VESSEL [14], 2012	NR	NR	4.4 (2.2)	8.7 (21.8)	NR	NR	30.7 (1.4)	−0.1 (1.4)
dal-PLAQUE [12], 2011	69.6 (3.9)	77.3 (3.9)	0.1 (NR)	7.3 (NR)	54.1 (3.9)	50.3 (3.9)	30.9 (NR)	4.0 (NR)
Stein et al. [16], 2010	NR	NR	4.8 (NR)	3.0 (NR)	NR	NR	33.8 (NR)	3.7 (NR)
<i>Anacetrapib</i>								
REVEAL [3], 2017	38 (NR)	64 (NR)	NR	NR	85 (NR)	42 (NR)	NR	NR
DEFINE [11], 2010	45 (NR)	77 (NR)	NR	NR	101 (NR)	46 (NR)	NR	NR
Ballantyne et al. [10], 2017	60.3 (31.4)	90.8 (32.2)	−27.6 (−31.8, −23.4)	9.1 (4.8, 13.5)	94.6 (27.3)	45.2 (13.7)	123.7 (118.2, 129.2)	5.5 (−0.1, 11.2)
Ballantyne et al. [9], 2017	68.6 (36.8)	96.6 (33.2)	−28 (−33.7, −22.3)	0.9 (−4.9, 6.7)	91.7 (32.2)	48.5 (14.0)	98.6 (91.7, 105.4)	3.9 (−2.9, 10.7)
Teramoto et al. [17], 2017	79.0 (30.6)	126.7 (32.2)	−31.3 (−41.7, −36.6)	−1.1 (−4.7, 2.5)	135.8 (25.9)	59.8 (13.8)	157.6 (152.9, 162.3)	8.7 (2.2, 15.2)
REALIZE [13], 2015	81.2 (30.9)	135.3 (61.9)	−36.0 (−39.5, −32.5)	3.7 (−1.2, 8.6)	108.3 (27.1)	54.1 (15.5)	105.8 (101.1, 110.6)	3.7 (−2.8, 10.3)
<i>Evacetrapib</i>								
ACCELERATE [4], 2017	54.7 (26.4)	83.7 (30.8)	−31.1 (27.6)	6.0 (29.0)	104.1 (31.4)	45.6 (12.3)	133.2 (57.2)	1.6 (17.5)

CETPi, cholesteryl ester transfer protein inhibitor; HDL-c, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; SD, standard deviation.

more than dalcetrapib. Dalcetrapib also had a minimal effect on LDL-c, whereas anacetrapib and evacetrapib significantly decreased LDL-c compared to placebo.

The effect of HDL-raising medications on cardiovascular outcomes and lipid levels has previously been studied [2, 20, 21]; however, our meta-analysis includes 2 more recent large clinical trials (REVEAL and ACCELERATE), which provided 42,541 additional patients. Previous meta-analyses also included torcetrapib, which was no longer under investigation at the time of our search due to unexpected increases in mortality (RR: 1.25; 95% CI: 1.09–1.44) compared to placebo [6]. This increase was attributed to off-target effects of torcetrapib on aldosterone levels that caused an increase in blood pressure (mean increase in systolic blood pressure of 5.4 mm Hg) [22]. Subsequently developed CETP inhibitors have limited adverse effects on blood pressure. A small increase in systolic blood pressure was observed with dalcetrapib (mean increase of 0.6 mm Hg) [15]

and anacetrapib (mean increase of 0.7 mm Hg) [3], and no effect on blood pressure was seen with evacetrapib [23].

Our findings are consistent with previous studies that suggest uncertain clinical benefit from raising HDL-c, despite a biological rationale for improved cardiovascular outcomes with increased HDL-c. A meta-analysis of HDL-raising drugs, including niacin, fibrates, and CETP inhibitors, found no association with cardiovascular mortality, stroke, or all-cause mortality [24]. HDL-c modifiers did reduce the risk of MI; however, this benefit was attenuated when the analysis was restricted to trials in which participants also used statins [24]. This finding is consistent with previous research which indicates that while drugs such as niacin and fibrates mildly increase HDL-c levels by 20–30% [25], when tested in trials with patients taking statins, these drugs fail to improve clinical outcomes [2]. CETP inhibitors are the most recent addition to the family of HDL-c-raising agents.

HDL-c-raising agents are lipophilic molecules that inhibit the cholesteryl ester transfer protein. This enzyme facilitates the exchange of cholesteryl esters and triglycerides between HDL-c particles and apolipoprotein B (Apo-B)-associated lipoproteins such as LDL and very-low-density lipoprotein. As HDL-c particles are progressively depleted of their cholesteryl esters and are enriched with triglycerides, they are cleared from the plasma more rapidly. Based on epidemiological studies, higher serum HDL-c levels are associated with more favorable clinical outcomes [26]. One proposed mechanism for such clinical benefit is the “reverse cholesterol pathway,” which is primarily supported by animal studies [27]. This hypothesis suggests that HDL-c reduces plaque burden by transporting cholesteryl esters from atherosclerotic lesions to the liver and other steroidogenic tissues [28].

Most CETP inhibitors simultaneously increase HDL-c and decrease LDL-c levels. However, dalcetrapib increases HDL-c without having a significant impact on LDL-c. This difference has been attributed to its smaller chemical structure lacking a trifluoride moiety [29]. In the dal-OUTCOMES trial ($n = 15,871$), dalcetrapib failed to improve clinical outcomes in patients with a recent episode of acute coronary syndrome [15]. Its use was associated with a mild (0.6 mm Hg) increase in systolic blood pressure as well as an increase in high-sensitivity C-reactive protein levels by 18%. Increases in high-sensitivity C-reactive protein have also been observed with torcetrapib (3% increase) and evacetrapib (9% increase) [30]. DNA analysis on samples from the dal-OUTCOMES and dal-PLAQUE trials found a differing therapeutic response to dalcetrapib depending on the patients’ genotype. An AA allele was associated with improved cholesterol efflux and no significant increase in C-reactive protein levels. A trial is currently under way to evaluate the impact of this drug on cardiovascular outcomes in participants with the AA phenotype, with results expected in 2020 (NCT02525939).

Anacetrapib and evacetrapib have similar impacts on serum lipid profiles. They are potent HDL-c-raising agents that simultaneously reduce LDL-c levels in patients already treated with statins. Despite the similarities, the REVEAL trial (anacetrapib) found a reduction in coronary events (coronary death, MI, and revascularization) at 3 years, while ACCELERATE (evacetrapib) was terminated for futility after 26 months [4]. In REVEAL, it was not until the third year of treatment that improvements in clinical outcomes were observed. Nonetheless, there was a trend towards better outcomes by the end of the second year of REVEAL. Anacetrapib has an extended half-life compared to the other CETP inhibitors, with re-

sidual effects on lipid levels lasting more than 12 weeks after treatment discontinuation, and detectable levels of the drug 4 years after discontinuation [31]. It has now been shown that anacetrapib accumulates in adipose tissues [32]. Unlike anacetrapib, there was no sign of improvement in outcomes in ACCELERATE after 2 years.

Overall, it would be reasonable to expect the reductions in LDL-c with anacetrapib and evacetrapib to be associated with improved cardiovascular outcomes, regardless of improvements in HDL-c. However, a Mendelian randomization study offers a plausible explanation for why this is not the case. This study suggests that the combined reduction of LDL-c using statins and CETP inhibition causes an attenuated reduction in Apo-B relative to LDL-c levels [33]. Therefore, when both 3-hydroxy-3-methylglutaryl coenzyme A and CETP are inhibited using statins and CETP inhibitors, one might not observe the improved clinical outcomes associated with the reduction of LDL-c levels. A clinical trial in which a CETP inhibitor is used without concomitant statin use could test this hypothesis. Further research is needed to explain why anacetrapib is associated with some improvements in cardiovascular outcomes, while evacetrapib is not.

Overall, it appears unlikely that CETP inhibitors will provide sufficient cardiovascular benefits to justify routine use. Torcetrapib was withdrawn due to increased mortality [6], and large dalcetrapib and evacetrapib trials were stopped early for futility [4, 15]. While anacetrapib has a similar efficacy and safety profile as some routinely used nonstatins (e.g., ezetimibe), regulatory approval is not being sought [30]. Our study had several potential limitations. First, our primary objective was to assess the association between CETP inhibitors and cardiovascular outcomes. Consequently, we restricted inclusion to studies which included at least 100 participants and had follow-up duration of at least 6 months. This restriction limited our review of lipid changes, which have been assessed in small, short-term trials. Nonetheless, our findings remained consistent with those of previous studies. Second, there was some variation in study design (e.g., population, follow-up duration). For this reason, we used random-effects models to account for both within- and between-study variability. Third, we were not able to include TA-8995 in our analysis, as it is still in earlier stages of development and no studies were available that met our inclusion criteria. Lastly, given the differential effects of anacetrapib, dalcetrapib, and evacetrapib on HDL-c and LDL-c, and varying elimination half-lives, it is possible that the cardiovascular benefits may vary by CETP inhibitor. However, the limited absolute number of adverse

events at this time makes it reasonable to examine this group of drugs as a class, as a preliminary assessment of the impact of CETP inhibitors on cardiovascular events.

Conclusion

Overall, despite being efficient at increasing HDL-c, CETP inhibitors were not associated with improvements in cardiovascular outcomes overall or all-cause mortality. While pooled data suggest that there is a trend towards small reductions in nonfatal MI and cardiovascular death with the use of CETP inhibitors, the clinical significance of such reductions is likely modest, with anacetrapib driving the potential reduction in nonfatal MI. Further research is needed to clarify the relationship between raising HDL-c and cardiovascular events.

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Appendix 1

Description of MEDLINE search through Ovid for trials including evacetrapib, dalcetrapib, anacetrapib, or obicetrapib.

Search No.	Search term	Number of results
1	(obicetrapib or ta-8995).mp	11
2	(evacetrapib or ly2484595).mp	88
3	(dalcetrapib or jtt-705).mp	225
4	(anacetrapib or mk-0859).mp	200
5	cholesterol ester transfer protein inhibitor*.mp	208
6	1 or 2 or 3 or 4 or 5	510
7	([randomized controlled trial or controlled clinical trial].pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/not humans.sh.)	3,613,199
8	6 and 7	312

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Eisenberg and Dr. Filion conceived, designed, and oversaw the conduct of the study. Mr. Taheri executed the literature search and wrote the initial draft of this manuscript. Ms. Reynier analyzed the data. All authors critically revised the manuscript for important intellectual content. All authors are responsible for the content of the manuscript and have read and approved the final paper.

Appendix 2

Description of EMBASE search through Ovid for trials including evacetrapib, dalcetrapib, anacetrapib, or obicetrapib.

Search No.	Search term	Number of results
1	(obicetrapib or ta-8995).mp	28
2	(evacetrapib or ly2484595).mp	249
3	(dalcetrapib or jtt-705).mp	773
4	(anacetrapib or mk-0859).mp	626
5	cholesterol ester transfer protein inhibitor*.mp	247
6	1 or 2 or 3 or 4 or 5	1,188
7	crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or (random* or factorial* or crossover* or cross over* or placebo* or [doubl* adj blind*] or [singl* adj blind*] or assign* or allocat* or volunteer*).tw	1,889,036
8	6 and 7	245

Appendix 3

Description of Cochrane search for trials including evacetrapib, dalcetrapib, anacetrapib, or obicetrapib.

Search No.	Search term	Number of results
1	obicetrapib or ta-8995	4
2	evacetrapib or ly2484595	23
3	dalcetrapib or jtt-705	52
4	anacetrapib or mk-0859	47
5	cholesterol ester transfer protein inhibitor*	131
6	1 or 2 or 3 or 4 or 5	176

Appendix 4

Quality assessment table.

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel, and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
<i>Dalcetrapib</i>						
dal-OUTCOMES [15], 2012	low	low	low	low	low	low
dal-VESSEL [14], 2012	low	low	low	low	low	low
dal-PLAQUE [12], 2011	low	low	low	low	unclear	low
Stein et al. [16], 2010	unclear	unclear	low	low	low	unclear
<i>Anacetrapib</i>						
REVEAL [3], 2017	low	low	low	low	low	low
DEFINE [11], 2010	low	low	low	low	low	low
Ballantyne et al. [10], 2017	unclear	unclear	low	low	low	low
Ballantyne et al. [9], 2017	unclear	unclear	low	low	low	low
Teramoto et al. [17], 2017	unclear	unclear	low	low	low	low
REALIZE [13], 2015	low	low	low	low	low	low
<i>Evacetrapib</i>						
ACCELERATE [4], 2017	low	low	low	low	low	low

For each criterion, the risk of bias was classified as being “high,” “low,” or “unclear” according to the guidelines of the Cochrane Collaboration’s tool for assessing risk of bias.

Appendix 5

Forest plot comparing the relative risk of stroke at longest follow-up in patients randomized to a CETP inhibitor compared with patients randomized to placebo. CI, confidence interval; RR, relative risk. The asterisk indicates Ballantyne et al. [10], 2017.

Appendix 6

Forest plot comparing the relative risk of hospitalization due to acute coronary syndrome at longest follow-up in patients randomized to a CETP inhibitor compared with patients randomized to placebo. CI, confidence interval; RR, relative risk. The asterisk indicates Ballantyne et al. [10], 2017.

Appendix 7

Forest plot comparing the relative risk of revascularization at longest follow-up in patients randomized to a CETP inhibitor compared with patients randomized to placebo. CI, confidence interval; RR, relative risk. The asterisk indicates Ballantyne et al. [10], 2017.

Appendix 8

Forest plot comparing the relative risk of all-cause mortality at longest follow-up in patients randomized to a CETP inhibitor compared with patients randomized to placebo. CI, confidence interval; RR, relative risk. The asterisk indicates Ballantyne et al. [10] in contrast to Ballantyne et al. [9], both references from 2017.

Appendix 9

Forest plot comparing the relative risk of cardiovascular mortality at longest follow-up in patients randomized to a CETP inhibitor compared with patients randomized to placebo. CI, confidence interval; RR, relative risk. The asterisk indicates Ballantyne et al. [10], 2017.

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