Cholesteryl Ester Transfer Protein Inhibition as a Safe and Effective Means for Treating Dyslipidemia and Potentially Reducing Cardiovascular Risk in Patients with CHD or Risk Equivalents

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Abstract

Background: Secondary prevention of coronary events in patients with known CHD and dyslipidemia has traditionally been focused on decreasing LDL-C through the use of statins. However, significant risk remains in individuals whose LDL-C has been optimized but HDL-C remains low. A new class of medications, cholesteryl ester transfer protein inhibitors, is effective at significantly increasing HDL-C and potentially reducing cardiovascular risk in such patients. There are currently three CETP inhibitors being developed, two of which have been studied for safety and efficacy in patients with CHD or risk equivalents: anacetrapib and dalcetrapib. Following the safety concerns of torcetrapib, both study medications have demonstrated that they do not have the same off-target effects as those seen in the ILLUMINATE trial.

Methods: A systematic search of the literature was performed utilizing three databases: MEDLINE, CINAHL, and Evidence-Based Medicine Reviews Multifile. Four double-blind, placebo-controlled clinical trials met the inclusion and exclusion criteria for review.

Results: Anacetrapib demonstrated an impressive 138.1% greater increase in HDL-C, and 39.8% greater reduction in LDL-C as compared to placebo without any differences in tolerability or AEs. Although not a pre-determined end-point, there was a significant reduction in revascularization rates with anacetrapib as compared to placebo as well (8 vs 21). Dalcetrapib was also shown to be safe and effective, although its lipid-modifying effects were significantly less than those seen with anacetrapib. The dal-PLAQUE trial also suggested a potential benefit in reducing atherosclerotic lesions in the carotid arteries. Neither medication was shown to increase blood pressure or cardiovascular morbidity or mortality.

Conclusion: Both anacetrapib and dalcetrapib have established themselves as safe and effective agents for increasing HDL-C, and to a lesser extent decreasing LDL-C. Although short-term data suggests a potential cardioprotective benefit with CETP inhibition, definitive conclusions

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Cholesteryl Ester Transfer Protein Inhibition as a Safe and Effective Means of Treating Dyslipidemia and Potentially Reducing Cardiovascular Risk in Patients with CHD or Risk Equivalents: A Systematic Review

Anthony Montes

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 10, 2012

Faculty Advisor: Robert P. Rosenow, Pharm.D., O.D.

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Biography

Born and raised in the Phoenix-metro area, Anthony feels blessed to have found a new home in the lush Pacific Northwest. Prior to scamming his way into the Pacific University Physician Assistant program, Anthony lived the good life as a wildland firefighter in the summer months and vagabond extraordinaire during the winter. Believing PA school would provide some stability to his walk-about life, he was convinced his wandering days were over. Nine homes, five states, a ton of frequent-flier miles, two vehicles, one ex-girlfriend, a lot of laughter, and a handful of amazing new friends later; Anthony has arrived as a graduating physician assistant and could not be happier. The future is full of promise and a dresser to call his own.
Abstract

**Background:** Secondary prevention of coronary events in patients with known CHD and dyslipidemia has traditionally been focused on decreasing LDL-C through the use of statins. However, significant risk remains in individuals whose LDL-C has been optimized but HDL-C remains low. A new class of medications, cholesteryl ester transfer protein inhibitors, is effective at significantly increasing HDL-C and potentially reducing cardiovascular risk in such patients. There are currently three CETP inhibitors being developed, two of which have been studied for safety and efficacy in patients with CHD or risk equivalents: anacetrapib and dalcetrapib. Following the safety concerns of torcetrapib, both study medications have demonstrated that they do not have the same off-target effects as those seen in the ILLUMINATE trial.

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**Conclusion:** Both anacetrapib and dalcetrapib have established themselves as safe and effective agents for increasing HDL-C, and to a lesser extent decreasing LDL-C. Although short-term data suggests a potential cardioprotective benefit with CETP inhibition, definitive conclusions regarding risk reduction in patients with CHD will be determined following the outcomes of the current phase III clinical trials.

**Keywords:** CETP inhibitor, anacetrapib, dalcetrapib, CHD
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List of Abbreviations

ACS……………………………………………………………..Acute coronary syndrome
AE…………………………………………………………………...Adverse event
ALP…………………………………………………………………..Alkaline phosphatase
CETP…………………………………………………….Cholesteryl ester transfer protein
CHD……………………………………………...Coronary Heart Disease
CPK………………………………………………………….….Creatinine phosphokinase
CVA……………………………………………………………...Cerebrovascular accident
CVD……………………………………………………….Cardiovascular Disease
FDG………………………………………………………………..….Fluorodeoxyglucose
HDL-C……………………………………...High-density lipoprotein cholesterol
hs-CRP…………………………………….high-sensitivity C-reactive protein
IDL-C……………………………………...Intermediate-density lipoprotein cholesterol
LDL-C……………………………………...Low-density lipoprotein cholesterol
MI………………………………………………………………...Myocardial Infarction
NCEP ATP III……National Cholesterol Education Program Adult Treatment Panel III

PAD………………………………………………………………..Peripheral arterial disease

SAE………………………………………………………………..Severe adverse event

VLDL-C……………………………………… Very low-density lipoprotein cholesterol
Cholesteryl Ester Transfer Protein Inhibition as a Safe and Effective Means of Treating Dyslipidemia and Potentially Reducing Cardiovascular Risk in Patients with CHD or Risk Equivalents: A Systematic Review

BACKGROUND

Although the rates of cardiovascular related deaths have declined significantly in recent decades the burden of disease remains high, accounting for one-third of all deaths in America, and is still the number one cause of death worldwide.¹ There are several established risk factors for coronary heart disease (CHD) in the general population, some of which are modifiable targets for medical therapy. Elevated low-density lipoprotein (LDL-C) and depressed high-density lipoprotein (HDL-C) are two such risk factors. Treating dyslipidemia as a means of secondary prevention to reduce the risk of coronary events in individuals with known CHD has traditionally been focused on decreasing LDL-C through the use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins). Multiple clinical trials have demonstrated the efficacy of statins in reducing LDL-C and to a varying extent secondary events in individuals with known CHD²⁻⁵ however, significant risk remains with individuals in whom HDL-C remains low despite treatment with statins.⁶,⁷,⁸ This phenomenon is further supported by a meta-analysis which demonstrated HDL-C to be predictive of cardiovascular events despite having an LDL-C of 70 mg/dl or less.⁸

Unfortunately, few options currently exist for clinicians to treat patients with CHD and dyslipidemia in whom HDL-C remains below the current recommended guidelines (≥40 mg/dl in men and ≥50 mg/dl in women).⁹ Statins, fibrates, and nicotinic acid have all been shown to modestly increase HDL-C.¹⁰ A recent meta-analysis demonstrated
nicotinic acid to be the most effective agent available for increasing HDL-C (an average increase of 16%) however, many patients are intolerant to its common side-effects of flushing and pruritus. The desire for a more effective and well-tolerated medication for increasing HDL-C has led to the development of a novel class of medications known as cholesteryl ester transfer protein (CETP) inhibitors.

**Mechanism of Action**

Cholesteryl ester transfer protein is a glycoprotein that is primarily secreted by the liver and is intimately involved in the cholesterol transport pathways, specifically in reverse cholesterol transport. In circulation, CETP is frequently bound to HDL-C molecules. The role of CETP is to facilitate the transfer of cholesterol esters from HDL-C to chylomicrons, very low-density lipoprotein (VLDL-C), and LDL-C in exchange for triglycerides. Following the transfer from HDL-C to LDL-C, cholesterol esters are bound for one of two fates: return to the liver or delivery to peripheral tissues following oxidation. It is through this second pathway in which CETP is thought to promote the atherosclerotic process and is the basis for CETP inhibition as a means of preventing the progression of atherosclerosis and reducing CHD risk. As CETP activity decreases, HDL-C increases, thereby increasing cholesterol efflux out of tissue cells to be returned to the liver for excretion into bile. In addition to its role in reverse cholesterol transport, HDL-C is believed to have anti-inflammatory, anti-oxidative, anti-thrombotic, anti-infectious, and vasodilatory effects, which contribute to its cardioprotective properties. The pathway of reverse cholesterol transport and basis for CETP inhibition are illustrated in figure 1.
Development

The first CETP inhibitor investigated was torcetrapib, manufactured by Pfizer®. Early clinical trials demonstrated promising results with significant increases in HDL-C and reductions of LDL-C.\textsuperscript{22,23} The ILLUMINATE trial was a phase III clinical trial designed to evaluate the safety and efficacy of torcetrapib in individuals with known cardiovascular disease (CVD) or who were at high-risk for CVD.\textsuperscript{24} In December 2006, the ILLUMINATE trial was terminated early due to an observed increase in morbidity and mortality in patients taking the study medication.\textsuperscript{24} Increases in systolic blood pressure, serum sodium, bicarbonate and aldosterone as well as decreases in potassium were noted in treatment patients. More importantly, there was an increased risk for cardiovascular events and death (hazard ratio 1.25 and 1.58, respectively).\textsuperscript{24} Initially there were concerns that the mechanism behind the deleterious effects of torcetrapib may have been mediated through its effects on CETP activity. It has since been determined that there were multiple off-target effects of torcetrapib unrelated to CETP inhibition, most significantly on the renin-angiotensin-aldosterone system (RAAS).\textsuperscript{25-28} There are currently three CETP-inhibitors in development: anacetrapib (Merck®), dalcetrapib (Roche®), and evacetrapib (Eli Lilly®). All three medications have demonstrated safety and efficacy in healthy populations,\textsuperscript{29-34} while anacetrapib and dalcetrapib have specifically been tested in individuals with CHD or risk equivalents. It is the purpose of this review article to evaluate the safety and efficacy of CETP inhibitors in treating dyslipidemia in patients with CHD or risk equivalents and their potential in reducing CV risk in such patients.
METHODS

A systematic search of the available literature was performed utilizing the databases Ovid/MEDLINE, EBSCOhost/CINAHL and the Evidence-Based Medicine Reviews Multifile using the MeSH terms and key words CETP inhibitor, cholesteryl ester transfer protein inhibitor, anacetrapib, dalcetrapib and evacetrapib combined with the modifier ‘or’. All searches were limited to articles published in the English language.

Randomized, double-blind, placebo-controlled clinical trials evaluating the safety and efficacy of various CETP inhibitors in individuals with known CHD or risk equivalents were included. Articles that were excluded were those evaluating the safety and efficacy of the medication torcetrapib due to the well known and established harmful effects of this medication. Studies that did not fit inclusion criteria were utilized solely for the background and discussion of this review.

RESULTS

The systematic search of the literature from three databases yielded a total of 284 articles. The resulting articles from the search were compiled and further screened for relevance to subject matter. Excluded were 276 articles, the remaining eight articles yielded four duplicates. Four randomized, double-blind, placebo-controlled clinical trials met inclusion and exclusion criteria and were evaluated for systematic review.

An additional randomized, double-blind, placebo-controlled clinical trial was cited several times throughout the literature search. The The dal-VESSEL\textsuperscript{35} article was however unavailable for review due to access constraints.
Safety of anacetrapib in patients with or at high risk for coronary heart disease

Cannon et al\textsuperscript{36} evaluated the safety and efficacy of anacetrapib in individuals with known CHD or who were at high risk for CHD. High risk was defined as those individuals with a Framingham Risk Score \(>20\%\) per ten years. Participants were 18 to 80 years old and had an LDL-C of 50-100 mg/dl while being treated with a statin (99.3\% of participants were being treated with a statin) with or without concomitant use of other lipid-lowering medications, had an HDL-C of less than 60 mg/dl and a plasma triglyceride concentration of 400 mg/dl or less. Patients were excluded if they had severe chronic heart failure, hypertension that was uncontrolled, any form of cardiac arrhythmia, an episode of acute coronary syndrome (ACS) or had underwent revascularization within the past three months, had active hepatobiliary disease, significantly impaired renal function, were receiving anticoagulation therapy with Coumadin or any other potent modifiers of the CYP3A4 pathway.\textsuperscript{36}

A total of 153 medical centers in 20 countries screened a total of 2757 patients for entry into the study. Of the 2757 patients screened, 1697 were accepted into a placebo run-in phase. Those individuals who had a 75\% adherence to treatment in the run-in phase were allowed to continue with the study. A total of 1623 patients were included in the study. Patients were prognostically balanced at baseline and throughout the course of the study. In a double-blinded fashion, participants were randomly assigned at a 1:1 ratio to receive either anacetrapib 100 mg or equivalent placebo orally once daily with food. Study participants were then evaluated every six to eight weeks in clinic for monitoring of possible adverse reactions, blood pressure measurements as well as venous blood draws for lipid measurements and other lab tests to assist in determining the safety of the
study medication. It was predetermined that if a patient’s LDL-C was found to be less than 25 mg/dl from two consecutive assays that the study medication would be discontinued. If a patient’s LDL-C was found to be elevated greater than 115 mg/dl on two consecutive assays and adherence was verified, investigators adjusted the patient’s non-study lipid-lowering medications (e.g. statins) accordingly. All patients, including those who did not complete treatment with the study medication were followed up twelve weeks after the termination of the 76 week trial to further assess safety of the study medication.36

The primary end points for the study included percentage change in LDL-C after 24 weeks of treatment and assessing the safety and side effect profile of the study medication. Of particular interest regarding indicators of possible adverse events was blood pressure; serum transaminases, creatinine kinase, sodium, potassium, chloride and bicarbonate. Predetermined adverse events that were monitored include myalgias, rhabdomyolysis, death attributable to cardiovascular causes, nonfatal myocardial infarction (MI) or cerebrovascular accident (CVA), unstable angina requiring hospitalization and all-cause death. Incidents of ACS requiring revascularization and heart failure were recorded but were not part of the predetermined cardiovascular end points. Secondary end points included percentage change of LDL-C from baseline to 76 weeks and HDL-C, calculated total cholesterol, apolipoprotein B and apolipoprotein A-1 at weeks 24 and 76.36

The 76 week trial lost 142 of the 811(17.6%) original anacetrapib patients due to LDL-C falling below the 25 mg/dl mark, while only one (0.1%) of the control patients was withdrawn secondary to low LDL-C. After considering the patients who were
withdrawn due to low LDL-C, the proportion of patients who discontinued the trial was balanced between the anacetrapib and placebo groups with 14.6% and 17.4%, respectively. Patients took anacetrapib for a mean of 424 days and placebo for a mean of 483 days. Follow-up in respect to clinical safety end-points was 99.1% and 99.4% for the anacetrapib and placebo groups.\textsuperscript{36}

At week 24, LDL-C had decreased from 81 mg/dl to 45 mg/dl in the anacetrapib group compared to placebo which had a decrease from 82 mg/dl at baseline to 77 mg/dl, demonstrating a decrease in LDL-C that was 39.8% greater with anacetrapib than that with placebo (P<0.001). HDL-C was increased from 41 mg/dl to 101 mg/dl in the anacetrapib group as compared to placebo which had an increase from 40 mg/dl at baseline to 46 mg/dl, demonstrating an increase in HDL-C that was 138.1% greater with anacetrapib than that with placebo (P<0.001). Non-HDL cholesterol decreased from 109.7 mg/dl to 69.7 mg/dl in the anacetrapib group compared to placebo which had a decrease from 111.1 mg/dl at baseline to 104.8 mg/dl, demonstrating a decrease in non-HDL cholesterol that was 31.7% greater with anacetrapib than that with placebo (P<0.001). Apolipoprotein A-1 plasma concentration increased from 142.5 mg/dl to 208.0 mg/dl in the anacetrapib group compared to placebo which had an increase from 142.8 mg/dl at baseline to 144.9 mg/dl, demonstrating an increase in apolipoprotein A-1 plasma concentration that was 44.7% greater with anacetrapib than that with placebo (P<0.001). Apolipoprotein B plasma concentration decreased from 88.4 mg/dl to 70.1 mg/dl in the anacetrapib group compared to placebo which had an increase from 88.9 mg/dl at baseline to 89.2 mg/dl, demonstrating a decrease in apolipoprotein B that was
21.0% greater with anacetrapib than that with placebo (P<0.001). All of the changes in serum lipid biomarkers were sustained throughout the 76 week trial.36

There were no significant differences between anacetrapib and placebo in adverse events thought to be related to the study medications that resulted in treatment discontinuation. There also were no differences in mean change of systolic or diastolic blood pressures in the two groups. No significant differences were noted between the anacetrapib and placebo groups in regard to serum sodium, potassium, chloride, bicarbonate or aldosterone.36 There were no reported cases of rhabdomyolysis in either the treatment or placebo groups. There was no significant difference between groups in the incidence of reported myalgias or elevations in creatinine kinase. There was however significantly fewer cases of elevated transaminases in the anacetrapib group compared to placebo (1 vs. 8 respectively). There were a total of 16 (2.0%) cardiovascular adverse events in the anacetrapib group during the 76 week trial compared to 21 (2.6%) in the placebo group. There was no evidence of an associated 25% increase in cardiovascular events that was noted with torcetrapib.24 There were 11 all-cause deaths in the anacetrapib group compared with 8 in the placebo group during the 76 week trial. In the three months following completion of the trial there was 1 reported death in the anacetrapib group and 4 reported in the placebo group, making the total for both groups twelve. Although not a predetermined end-point, of particular interest, there were significantly fewer patients in the anacetrapib group than placebo that underwent revascularization (8 vs. 28 respectively).
Safety and tolerability of dalcetrapib (2009)

Stein et al\textsuperscript{37} evaluated the safety and tolerability of the investigational CETP inhibitor dalcetrapib in patients with dyslipidemia, CHD or CHD risk equivalents. This phase II clinical trial enrolled a total of 838 patients who participated in five randomized, double-blind, placebo-controlled trials. Four of the trials (conducted in the Netherlands), had a four-week treatment period and the remaining trial (conducted in the United States), had a twelve-week treatment period. Two of the five trials specifically were designed to evaluate the study medication in individuals with CHD or CHD risk equivalents, as established by the NCEP ATP III guidelines. Two of the three remaining trials were designed to evaluate the study medication in individuals with Type II hyperlipidemia, while the final trial which had a twelve-week treatment period, evaluated the study medication in individuals with low or average HDL-C. Inclusion criteria can be found listed in table 1 of the specified study. Exclusion criteria were a BMI of 35 or greater (40 or greater in the 12-week trial), hypertension that was uncontrolled; diabetes (except for the two CHD studies in which it was considered a risk equivalent); significant disease of kidneys, liver, heart, brain or arteries; elevated transaminases; active pregnancy, breast feeding or a significant likelihood of becoming pregnant; current medical treatment with corticosteroids, thiazide diuretics, oral contraceptives containing 30 \textmu g or greater of estrogen, immunosuppressive therapy, macrolides, antiepileptics, lipid-modifying agents or plant sterols. Patients were prognostically balanced at baseline with the following exceptions: the incidence of patients with CHD or atherosclerotic disease was significantly lower in the dalcetrapib 900 mg group compared to placebo (P<0.05) in the twelve-week study, patients in the dalcetrapib 300 and 900 mg groups
had statistically significant greater BMI and age (P<0.05) as well as a greater mean lipid level (P<0.001) when compared to the placebo group in the four week trials.37

Following a four to eight week run-in period in which 113 patients were excluded for various reasons, the four, four-week studies evaluating dalcetrapib in individuals with either Type II hyperlipidemia or CHD or risk equivalents randomized 551 patients with intent to treat. Patients in the Type II hyperlipidemia monotherapy trial were randomized in 1:1 fashion to receive placebo or dalcetrapib 300, 600, or 900 mg/day. In the Type II hyperlipidemia combination therapy trial, patients were randomized in a 1:1:1 fashion to receive placebo or dalcetrapib 300 or 600 mg/day with 40 mg/day of pravastatin. In the CHD combination therapy trial with atorvastatin, patients were randomized in a 1:1 fashion to receive placebo or dalcetrapib 600 mg/day with atorvastatin 20 mg/day. In the CHD combination therapy trial with simvastatin, patients were randomized in a 1:1 fashion to receive placebo or dalcetrapib 600 mg/day with simvastatin 40 mg/day.37

Following a six to ten week run-in period in which 153 patients were excluded for various reasons, a total of 292 patients were randomized to receive treatment in the twelve-week study evaluating dalcetrapib in patients with low or average HDL-C. Patients taking pravastatin 40 mg/day were randomized in a 1:1:1:1 fashion to receive placebo or dalcetrapib 300, 600, or 900 mg/day.37

Outcome measures were focused on efficacy and safety of dalcetrapib. Efficacy was evaluated by assessing LDL-C, HDL-C, apolipoprotein A-1, triglycerides, CETP activity and CETP mass. The efficacy of dalcetrapib in combination therapy in the four-week trials was pooled for analysis and included the data from the twelve-week trial up to four weeks with the exception of LDL-C because the patients were treated to LDL-C
target. Laboratory data was measured at baseline and weeks four and twelve. The safety of dalcetrapib was evaluated by recording and assessing any adverse events (AE). Adverse events were assessed on severity, intensity, outcome, and relation to treatment. An AE was considered a serious AE (SAE) if it resulted in death, was life-threatening, resulted in hospitalization or prolonged hospitalization, resulted in serious disability or incapacity or required serious medical intervention including surgery to prevent one of the aforementioned outcomes.  

Of the 551 patients randomized to the four-week trials, 546 were treated and analyzed in their respective groups. Of the 292 patients randomized to the twelve-week trial, 287 were treated and analyzed. A dose-dependent increase in HDL-C (P<0.001) and apolipoprotein A-1 (P<0.05) was observed in the monotherapy group at four weeks as well as in the combination therapy groups at four and twelve weeks. There was a significant decrease in LDL-C in the dalcetrapib 900 mg treatment group at the end of four weeks (-7.4 mg/dl, P<0.05). CETP activity was significantly decreased and CETP mass significantly increased by dalcetrapib at all doses at weeks four and twelve (P<0.001). All efficacy results from this trial can be found in table 3 of the specified study.  

Safety analyses of dalcetrapib revealed no significant differences between dalcetrapib 300 or 600 mg and placebo in the combination four-week trial in patients reporting one or more AE. Patients taking dalcetrapib 900 mg/day did report significantly more adverse events than placebo and dalcetrapib 600 mg (58% vs 42% vs 42% respectively, P<0.05). In the monotherapy group, there were no differences in reported AEs from placebo to all dalcetrapib dose groups. There were six SAEs reported in the
four-week trial with no significant difference between the treatment groups and placebo. No deaths were reported during any of the trials. In the twelve-week trial there were significantly more SAEs reported in the dalcetrapib 900 mg group (n=5, 7%) compared to dalcetrapib 300 or 600 mg or placebo (n=1, 1%; n=2, 3%, n=1, 1%, respectively). There were no differences between all dalcetrapib dose groups as compared to placebo with the most commonly reports AEs (diarrhea, nasopharyngitis, HA, URI, cough, nausea, back pain, myalgias, pain in extremity, muscle spasm, abdominal distension). Withdrawal from treatment in the dalcetrapib groups were considered to be possibly or probably related to treatment, while the placebo group withdrawals were considered to be unrelated or remotely related. There was no dose response and a low incidence of reported cardiac and vascular AEs in both placebo and dalcetrapib groups. Only one cardiac AE (palpitations) was considered to be possibly related to treatment. There was no significant increase in transaminases or blood pressure in all dalcetrapib dose groups as compared to placebo. None of the trials were stopped early secondary to observed adverse events.\textsuperscript{37}

**Safety and tolerability of dalcetrapib (RO4607381/JTT-705): results from a 48-week trial (2010)**

Stein et al\textsuperscript{38} evaluated the safety and efficacy of the investigational CETP inhibitor dalcetrapib in patients with CHD or CHD risk equivalents as determined by NCEP ATP III guidelines. Specifically, researchers were interested in further evaluating dalcetrapib in patients receiving longer-term, high-dose treatment and its potential effects on mesenteric lymph nodes through imaging with MRI. The study was conducted in
fifteen medical centers located in the United States and Germany. This was a randomized, double-blind, placebo-controlled, parallel-group phase II clinical trial. Inclusion criteria were patients aged 18-75 years old; had CHD or CHD risk equivalents; had an LDL-C ≤100 mg/dl and triglycerides ≤600 mg/dl while on atorvastatin; body weight less than 125 kg (275 lbs). Exclusion criteria were systolic BP ≥180 mmHg; diastolic BP ≥ 100 mmHg; HbA1c > 10%; recent ACS or revascularization; serious disease of the liver, kidneys, blood, brain, or digestive tract; elevated transaminases; elevated creatinine phosphokinase (CPK); contraindications to MRI; mesenteric lymph node abnormalities; medical treatment with corticosteroids, thiazide diuretics, oral contraceptives containing 30 µg or greater of estrogen, immunosuppressive therapy, macrolides, antiepileptics, antivirals, or azole antifungals. Patients were prognostically balanced at baseline between the treatment and placebo groups with the exception that the dalcetrapib group had a significantly greater proportion of patients with coronary disease and atherosclerosis compared to placebo (55% vs 41% and 39% vs 33%, respectively). These differences were maintained at the beginning of the twenty-four week extension phase.38

There were 266 patients enrolled into a five to twelve week run-in phase in which patients were treated with atorvastatin 10 to 80 mg/d to achieve an LDL-C less than 100 mg/dl. Of the 266 patients in the run-in phase, 131 patients were excluded for various reasons. The remaining 135 patients continued treatment with atorvastatin 10-80 mg/day and were randomized 1:2 with intent-to-treat, to receive either placebo or dalcetrapib 900 mg/d for twenty-four weeks, followed by an optional twenty-four week extension period.
Double-blinding was maintained from the initial twenty-four week treatment period through the end of the extension period. 

Patients were evaluated in clinic at baseline, weeks 2, 6, 12, 18, 24, 36, and 48, and at follow-up to assess efficacy and safety. Primary outcome measures for efficacy of dalcetrapib were changes in HDL-C from baseline at twenty-four and forty-eight weeks. Secondary outcomes for efficacy included the biomarkers apolipoprotein A-1, CETP activity and mass, and high-sensitivity C-reactive protein (hs-CRP) as well as changes in lipids. A primary safety outcome of this trial was to assess the effect of long-term, high-dose dalcetrapib on mesenteric lymph node size through MRI. Patients underwent unenhanced, high-resolution MRI without contrast at baseline, weeks 12, 24, 36, and 48. The MRI scans were interpreted by a local radiologist as well as two blinded, independent reviewers with the primary intention of determining the size of lymph nodes as measured by the shortest axis. Undetectable nodes were considered to be less than 2 mm. Lymph node sizes were recorded and compared to earlier images. Patient safety was assessed by monitoring reported and observed AEs and evaluating vital signs, physical exam and laboratory tests. Lab tests for safety included transaminases, CPK, alkaline phosphatase (ALP), sodium, potassium, and aldosterone levels.

Significant increases in HDL-C and apolipoprotein A-1 were observed in the dalcetrapib treatment group compared to placebo at weeks twenty-four and forty-eight. The increases in HDL-C and apolipoprotein A-1 in the dalcetrapib group at week twenty-four were 12.8 mg/dl (33.4%, P<0.001) and 14.8 mg/dl (11.4%, P=0.002), respectively compared to 0.5 mg/dl (3.5%, P<0.001) and 4.2 mg/dl (4.4%, P=0.002), respectively in the placebo group. Week forty-eight saw similar differences with increases in HDL-C
and apolipoprotein A-1 in the dalcetrapib group at week forty-eight were 13.8 mg/dl (33.8%, P<0.001) and 22.0 mg/dl (16.4%, P=0.002), respectively compared to 1.4 mg/dl (3.7%, P<0.001) and 9.8 mg/dl (8.2%, P=0.002), respectively in the placebo group. Of interest, there were small but statistically significant increases in hs-CRP levels in the dalcetrapib groups compared to placebo at week twenty-four, but not week forty-eight. Changes in hs-CRP at week twenty-four in the dalcetrapib group were 0.05mg/L (5.7%) compared to -0.24 mg/L (-24.2%), (P=0.010) in the placebo group. There were a total of 70 patients in the dalcetrapib group and 33 patients in the placebo group that had a detectable lymph node at randomization. At week forty-eight in the placebo group, 56% of lymph nodes decreased in size, 41% increased in size and 3% did not change. Similar results were found in the dalcetrapib group, 56% decreased in size and 42% increased in size. There was no significant difference in the proportion of enlarged mesenteric lymph nodes in the two groups.38

There was no significant difference between the percentages of patients reporting at least one AE in the dalcetrapib group (85%) compared to placebo (83%). There were also similarities in reported common AEs between the two groups. The exception would be a significantly greater incidence of reported diarrhea with the treatment group compared to placebo (17% vs 11%, respectively). Treatment-related AEs were also similar between dalcetrapib and placebo (39% vs 33%, respectively). Rates of serious AEs were similar between dalcetrapib and placebo groups as well (11% vs 9%). Of note, there was one report of CAD that was considered to be possibly related to dalcetrapib by the investigator. There were significantly more withdrawals due to AEs (12% vs 7%) and treatment-related AEs (9% vs 4%) in the dalcetrapib group compared to placebo. There
was no significant difference in blood pressure between the two groups throughout the forty-eight week study. There were no significant differences between the two groups in regard to changes in any of the secondary safety biochemical measurements (transaminases, CPK, ALP, sodium, potassium, or aldosterone). There were no deaths throughout the forty-eight week trial.38

**Safety and efficacy of dalcetrapib on atherosclerotic disease using non-invasive multimodality imaging (dal-PLAQUE): a randomized clinical trial**

Fayad et al39 examined the safety and efficacy of the novel CETP inhibitor dalcetrapib in patients with CHD or CHD risk equivalents as determined by the NCEP ATP III guidelines. Specifically, researchers were interested in the effects of long-term therapy with dalcetrapib on structural and inflammatory indices of atherosclerosis as measured with MRI and PET/CT imaging, respectively. This was a randomized, double-blind, placebo-controlled phase IIb trial, conducted in eleven medical centers in the U.S. and Canada. Inclusion criteria were patients aged 18-75 years old; had known CHD or risk equivalents; plasma triglyceride concentration of 400 mg/dl or less; had LDL-C of 100 mg/dl or less while being treated with a statin or other cholesterol-lowering medication unless receiving maximal dose therapy or were intolerant to statins; had a carotid or aortic wall to background ratio (TBR) of 1.6 or higher upon screening. Exclusion criteria were treatment with nicotinic acid or fibrates; uncontrolled hypertension or diabetes (HbA1c >10%); coronary or cerebrovascular event within past three months; known familial hypercholesterolemia; impaired renal function with a glomerular filtration rate of less than 30 ml/min; contraindications to MRI/CT/PET.
Patients were prognostically balanced at baseline with the following exceptions: patients in the placebo group had more patients with peripheral artery disease (PAD) than those in the dalcetrapib group (15% vs 9%); there was a higher rate of CHD in the dalcetrapib group than in the placebo group (89% vs 82%); and although LDL-C was balanced, there was a higher rate of statin use in the placebo group than in the dalcetrapib group (92% vs 81%).

There were 189 patients entered into a pre-randomization phase that lasted up to eight weeks in which patients’ LDL-C was optimized to less than 100 mg/dl unless they were taking maximum dose therapy. Patients were screened with \(^{18}\)F-Fluorodeoxyglucose (FDG)-PET/CT during pre-randomization. Those who met the required TBR of 1.6 or greater in the right carotid, left carotid or ascending aorta were eligible for randomization. A total of 59 individuals were excluded during pre-randomization, leaving 130 eligible patients to be randomized in a 1:1 fashion. There were 64 patients randomized to treatment with dalcetrapib 600 mg/day and 66 patients randomized to matching placebo utilizing a computer-generated global randomization code. Patients remained on statin therapy and/or other lipid-lowering medications throughout the twenty-four month clinical trial. Double-blinding was maintained throughout the twenty-four month trial.

Co-primary end-points for the trial were MRI and PET/CT imaging. MRI was used to assess structural changes in the carotid arteries from baseline as measured by total vessel area, wall area, wall thickness, and wall area/total vessel area ratio (normalized wall index) as the average of left and right carotids at twenty-four months. Secondary MRI end-points were changes from baseline to six and twelve months in the
aforementioned indices. PET/CT was used to assess change in carotid or ascending aorta wall uptake of $^{18}$F-FDG from baseline to six months, as the primary end-point change in TBR was measured in the most diseased 1.5 cm segment. An additional PET/CT study was performed solely on the carotid arteries (as an average of the carotids) for comparison to MRI-derived structural end-points. Secondary PET/CT endpoints were changes in TBR in the most diseased as determined at baseline at three and six months and other surrogates. Images from MRI and PET/CT were read by masked radiologists, two for MRI and two for PET/CT. HDL-C, LDL-C, total cholesterol, triglyceride, apolipoprotein A-1, and apolipoprotein B plasma concentrations were measured at baseline, three, six, twelve, and twenty-four months as secondary end-points. Multiple biomarkers assessing inflammation, oxidative stress and cardiovascular risk were measured at baseline, three, twelve, and twenty-four months as secondary end-points. Safety was assessed by monitoring reports of AEs, vital signs, electrocardiograms, and lab values.

At twenty-four months, significant increases in HDL-C and apolipoprotein A-1 were observed in the dalcetrapib group as compared to placebo (30.9% vs 4.0% and 10.0% vs 3.2%, respectively). There was a significant increase in hs-CRP in the dalcetrapib group as compared to placebo at twenty-four weeks (33.3% vs 0.0%). As measured by MRI, there were no observed pro-atherogenic effects on vascular plaque burden with dalcetrapib. As compared to placebo, in the dalcetrapib group there was a decrease from baseline in total vessel area (-4.01 mm$^2$, 90% CI -7.23 to -0.80), a decrease in wall area (-2.20 mm$^2$, 90% CI -4.54 to 0.13), and an increase in normalized wall index (0.60%, 90% CI -1.2 to 2.5). As measured by PET/CT data, there were no observed pro-
inflammatory effects within the vascular system as compared to placebo after six months. Absolute change in the most diseased segment TBR was greater in placebo than in the dalcetrapib group (-0.26 vs -0.19). There was a decrease in the absolute and percentage changes in the dalcetrapib group as compared to placebo in the carotid arteries analysis, which can be found in table 5 and figure 3 of the specified study. Withdrawal from treatment was similar in rate and cause in both placebo and dalcetrapib groups. There was a total of 10 (16%) withdrawals in the dalcetrapib group and 14 (22%) in the placebo group. There were two deaths in the placebo group (CHD and electromechanical dissociation) and one in the dalcetrapib group (metastatic cancer). Treatment discontinuation secondary to drug-related AEs and SAEs were similar in the two groups. Transaminase and CPK elevations were similar in both groups. There were no significant differences in vital signs, specifically blood pressures between the two groups.39

DISCUSSION

Safety

Due to the results of the ILLUMINATE trial which demonstrated an increase in cardiovascular events and all-cause death,24 safety concerns for CETP inhibitors remain at the forefront of current and ongoing research. The mechanisms in which torcetrapib was shown to assert its deleterious effects on patients are believed to have been mediated through off-target activation of the RAAS.25-28 As such, all clinical trials evaluating the safety of the CETP inhibitors are particularly interested in monitoring patients’ blood pressures, serum electrolytes and aldosterone concentrations as well as rates of CV events. In addition to these critical safety measures it is also important to identify and
quantify the most common AEs as well as any other potentially harmful effects the investigational medications may have.

**Anacetrapib** - A single study published to date evaluates the safety of anacetrapib in patients with known CHD or risk equivalents. The safety results from Cannon et al demonstrated that there were no differences in systolic or diastolic blood pressures between anacetrapib and placebo. There also were no differences in serum electrolytes or aldosterone between the two treatment groups. An increase in cardiovascular AEs was not observed with treatment, in fact there were more CV events in the placebo group (n=21, 2.6%) compared to the treatment group (n=16, 2.0%). Revascularization rates were also significantly decreased with patients treated with anacetrapib (n=8) compared to placebo (n=28). All-cause mortality was the same between the anacetrapib and placebo groups (12 deaths each) at the end of the twelve-week follow-up period.

Previous studies of anacetrapib have determined the most common adverse events associated with the study medication to be gastrointestinal complaints (diarrhea, constipation and dyspepsia) as well as myalgias. There were no reported cases of rhabdomyolysis with treatment, and reports of myalgias were similar between the two groups. There were no differences in transaminases or CPK in the two groups. The safety and tolerability of anacetrapib appears to be comparable to that of statins and justifies further evaluation in larger populations with CHD.

**Dalcetrapib** - There are three published studies that have outlined the safety of dalcetrapib in patients with CHD or risk equivalents. In all studies and all dose-
groups, there were no significant increases in systolic or diastolic blood pressures as compared to placebo. There also were no clinically significant differences in serum electrolytes or aldosterone in all dose-groups of dalcetrapib as compared to placebo. There were no significant differences and no dose-response effect on CV events with dalcetrapib as compared to placebo. There were however, a handful of CV events reported that may have been related to treatment with dalcetrapib. A myocardial infarction that was considered to be remotely related or unrelated to treatment with dalcetrapib occurred in the Stein et al (2009).\textsuperscript{37} In the same study, there was one CV event, palpitations, thought to be possibly related to treatment. The Stein et al (2010) trial\textsuperscript{38} identified a single case of CAD and two cases of hypertension thought to be possibly related to treatment with dalcetrapib. In contrast, there was a higher incidence of CV events in the placebo group as compared to the dalcetrapib group (11% vs 3%) in the dal-PLAQUE trial.\textsuperscript{39} Safety results from Stein et al (2009)\textsuperscript{37} found the incidence of AEs was significantly greater in individuals taking the highest dose of dalcetrapib (900 mg/day). There were no deaths in either of the two Stein et al trials.\textsuperscript{37,38} The dal-PLAQUE trial reported two deaths in the placebo group (CHD and electromechanical dissociation) and one death in the dalcetrapib group (metastatic cancer).\textsuperscript{39}

The most commonly reported AEs from the three studies included: diarrhea, headache, nasopharyngitis, URI, myalgias, and other muscle related symptoms.\textsuperscript{37-39,39} In the Stein et al (2009) trial\textsuperscript{37} there was a higher incidence of SAEs in the dalcetrapib 900 mg/day group compared to the other dose-groups and placebo. There were no significant differences in the rate of common AEs and SAEs in the Stein et al (2010) trial\textsuperscript{38} where patients received dalcetrapib 900 mg/day compared to placebo. The dal-PLAQUE trial\textsuperscript{39}
reported similarly with no differences in the rate of common AEs and SAEs in patients receiving dalcetrapib 600 mg/day compared to placebo.

The safety and tolerability of dalcetrapib appears similar to that of anacetrapib. Although there were a small number of reported CV events that may to some degree have been related to treatment with dalcetrapib, these findings lack statistical significance and require further trials in larger populations to determine the relevance of these findings.\textsuperscript{37,38} Both medications have demonstrated that they do not induce the same off-target effects observed with torcetrapib,\textsuperscript{24,37-39} however they both require further testing in patients with CHD to further demonstrate their safety in this population under long-term therapy.

**Efficacy and Limitations**

Both anacetrapib and dalcetrapib have demonstrated that they are effective in significantly increasing HDL-C and to a lesser extent in decreasing LDL-C. However, the effects of anacetrapib appear to be more pronounced than those of dalcetrapib. Anacetrapib at a daily dose of 100 mg effectively decreased LDL-C by 39.8\% and increased HDL-C 138.1\%.\textsuperscript{36} The lipid-modifying effects of dalcetrapib were one-quarter to one-half of those seen with anacetrapib.\textsuperscript{36-39} The primary lipid end-points of the three dalcetrapib studies can be seen in Table**. Through their lipid-modifying actions alone, CETP inhibitors may confer their greatest potential for reducing CV risk in individuals with CHD.

**Anacetrapib**- Independent of lipid-modification, anacetrapib appears to show more promise in effectively reducing CV risk in patients with known CHD. The results
from Cannon et al.\textsuperscript{36} suggests that patients treated with anacetrapib may be less likely to require revascularization, possibly secondary to the increased efflux of cholesterol from the vascular wall due to an increase in circulating anti-atherogenic HDL-C molecules. There were also fewer reported CV events in the anacetrapib group compared to placebo. Unfortunately, due to the sample size (n=1,612), one cannot definitively say that anacetrapib reduces the need for revascularization and or the rate of CV events.\textsuperscript{36}

In addition to sample size, there were several other limiting factors in the anacetrapib trial conducted by Cannon et al.\textsuperscript{36} First, a majority of the study participants were white. A more expansive study population including patients of other ethnic backgrounds should be completed to evaluate safety and drug metabolism in these populations. Second, the length of the trial stands as another limitation in this study’s design. Longer trials will be needed in the future to establish long-term safety and efficacy data on patients taking anacetrapib. Third, the study participants were receiving concomitant treatment with several different statins. The study adjusted for this by matching the number of participants taking each of the various types of statins in the placebo and treatment groups. This study was likely designed as such due to previous studies having already described the safety and efficacy of anacetrapib when paired with specific statins.\textsuperscript{29,42} While this method of testing the efficacy of anacetrapib in conjunction with various types of statins is more reflective of how the medication will be used in practice, more control over the types of statins that patients were taking would have produced a study with less confounding variables. Fourth, the study protocol required any patient with LDL-C below the 25 mg/dl threshold to be withdrawn from the study medication, with patients expected to complete safety follow-up through the
twelve-week post-treatment phase. There is no long-term data evaluating the possible safety concerns associated with individuals with LDL-C below 25 mg/dl. Finally, the study is industry sponsored by Merck® thereby introducing possible bias into data collection and analysis.\textsuperscript{36}

**Dalcetrapib**- The most promising evidence for dalcetrapib in reducing CV risk independent of its lipid-modifying properties comes from the dal-PLAQUE study\textsuperscript{39}.\textsuperscript{30} Fayad,Z.A. 2011}} An absolute difference of -4.01 mm (-7.23 to -0.80, 90% CI) in total vessel area, a decrease in wall area (-2.20 mm\textsuperscript{2}, 90% CI -4.54 to 0.13), and an increase in normalized wall index (0.60%, 90% CI -1.2 to 2.5) were observed in the dalcetrapib group as compared to placebo after twenty-four months of treatment. This suggests a possible anti-atherogenic effect of dalcetrapib with reversal of atherosclerosis via the reverse cholesterol transport pathway. There was also a decrease in the absolute and percentage changes in the dalcetrapib group as compared to placebo in the carotid artery analysis. However, there was a more pronounced decrease in metabolic activity in the most diseased segment of patients’ index vessels with placebo than with anacetrapib at six months (-0.26 and -0.19 respectively). Although this data was underpowered (P=0.51) and considered to be within the predetermined limits of no harm by the study’s design, it is of concern due to the correlation between inflammation in the vascular system and the progression of atherosclerotic plaques.\textsuperscript{43,44} The results of the dal-PLAQUE trial\textsuperscript{39} are promising, however due to the size of the study population (n=130), definitive conclusions cannot be drawn regarding the efficacy of dalcetrapib in reducing the atherosclerotic burden in patients with CHD.
The dal-PLAQUE trial\textsuperscript{39} had several other significant limitations in addition to the lack of a large sample population. First and most notably, it is important to recognize that this study is significantly underpowered and lacks statistically significant confidence intervals; this again is a product of the small sample size. Second, the primary end-points of this study are based solely on non-invasive imaging techniques. There is the potential for inter and intra-user variability in interpreting results from images. The study designers tried to limit this variability by utilizing two different, blinded readers for each of the imaging modalities. Additionally, the study report did not address how differences in image interpretations were accounted for. Third, the favorable results from the PET/CT scan were identified on comparison of carotid artery analysis, but not seen in images taken from the index vessels. The authors make a note of the possibility of MRI being more sensitive in detecting structural changes in the smaller carotid arteries as compared to the larger ascending aorta which was the predominant index vessel. Fourth, the study participants were receiving concomitant treatment with several different statins and other lipid-lowering medications. The study report did not address this issue, as such there is no way to know whether participants were matched based on the type of statin they were taking. This confounding variable could have potential effects on study outcomes as there may be variability among statins in their ability to reduce vascular inflammation.\textsuperscript{45-47} Finally, the study is industry sponsored by Roche\textsuperscript{®} thereby introducing possible bias into data collection and analysis.

Limitations of the two clinical trials evaluating the safety and tolerability of dalcetrapib have similar limitations to the aforementioned studies. First, both studies are limited by the small sample sizes (n=833 and n=135).\textsuperscript{**} Second, both studies are too
CONCLUSION

Cardiovascular disease remains an unequivocal burden on health care systems worldwide. As such, interest in developing new strategies and medications for the prevention of CVD remains important as ever. Current treatment guidelines recommend the use of statins to treat dyslipidemic patients with low HDL-C, yet significant risk remains in those individuals who achieve ideal LDL-C levels and whose HDL-C remains low. The new class of CETP inhibitors has established itself as being exceedingly more efficacious at increasing HDL-C levels than the current options of statins, fibrates and nicotinic acid. Phase I and II clinical trials in both anacetrapib and dalcetrapib have demonstrated that both medications have a good safety profile and are potent inhibitors of CETP however, the results from Phase III clinical trials will be the deciding factor as to whether either of these medications will be approved for treatment of the general population.

There are two ongoing Phase III clinical trials evaluating the long-term safety and efficacy of anacetrapib and dalcetrapib in large populations. The REVEAL (Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification) trial is currently enrolling an estimated 30,000 participants with known vascular disease. The trial is designed to evaluate how effective anacetrapib 100 mg/daily is at preventing CV events (coronary death, MI or revascularization) in individuals with preexisting CVD over a mean follow-up period of four years. The estimated completion date of the REVEAL trial
is January 2017. The dal-OUTCOMES trial is an ongoing study which has enrolled an estimated 15,600 participants with stable CHD who have recently experienced ACS. The trial is designed to evaluate how effective dalcetrapib 600 mg/daily is at preventing secondary events (any CV morbidity or mortality) in individuals with recent ACS over a mean follow-up period of two years. The estimated completion date of the dal-OUTCOMES trial is May 2013. In addition to the ongoing clinical trials with anacetrabin and dalcetrapib, a third CETP inhibitor evacetrapib is being developed by Eli Lilly® and is currently recruiting for early phase clinical trials.

The promising results from phase I and II clinical trials have made CETP inhibitors a novel therapy in treating dyslipidemia however; their role is yet to be determined. As monotherapy they are impressively effective at augmenting HDL-C, which makes them ideal pharmaceutical agents for treating individuals with isolated low HDL-C. Although CETP inhibitors have a much less pronounced effect on LDL-C than do statins, they make ideal agents for adjunct therapy. There is however a possibility of achieving dangerously low LDL-C with co-administration and further research must elucidate the possible sequelae and or ideal dosing regimens with statins to maintain patient safety. Ultimately, the goal of pharmacotherapy in patients with CHD is to prevent CV events. If the ongoing phase III clinical trials demonstrate a decrease in CV risk, CETP inhibitors may revolutionize the way in which clinicians treat dyslipidemic patients.
References


# Table I. Characteristics of Reviewed Studies

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<tr>
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*Sample size of n=125 resulted in underpowered P values and insignificant confidence intervals.*
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<td>-</td>
<td>21 (28%) vs 22 (30%)</td>
</tr>
<tr>
<td>Stein et al[38]</td>
<td>900 mg</td>
<td>24 weeks</td>
<td>N=89; Placebo N=46</td>
<td>-0.5% vs 5.6%</td>
<td>33.4% vs 3.5%</td>
<td>n/a [8]</td>
<td>-</td>
<td>No clinically or statistically significant changes in node size. 35 (39%) vs 15 (33%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48 weeks</td>
<td>N=52; Placebo N=25</td>
<td>4.8% vs -3.0%</td>
<td>33.8% vs 3.7%</td>
<td>n/a [8]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Fayad et al[39]</td>
<td>600 mg</td>
<td>6 months</td>
<td>N=63; Placebo N=65</td>
<td>3.8% vs 3.9%</td>
<td>33.9% vs -0.8%</td>
<td>2 (3%) vs 7 (11%)</td>
<td>MRI carotid total vessel area absolute change compared to placebo: -0.041 [9]</td>
<td>11 (17%) vs 18 (28%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 months</td>
<td>N=63; Placebo N=65</td>
<td>0.1% vs 7.3%</td>
<td>30.9% vs 4.0%</td>
<td>-</td>
<td>PET/CT 18F-FDG uptake absolute change index vessel: -0.19 vs -0.26</td>
<td></td>
</tr>
</tbody>
</table>

\[\] *Includes cardiac AEs and SAEs, respectively. †Results from monotherapy studies not included. §Reported cardiac and vascular AEs possibly related to treatment with dalcetrapib 900 mg/d were: one case of CAD and two cases of hypertension. ‡Number of patients (N) reported as measured at time of statistical analysis of end-points.
Figure 1: Diagram of lipid transport and the action of CETP

Figure 1. Triglycerides derived from the intestine are transported via chylomicrons, or synthesized de novo in the liver and transported via VLDL. Triglyceride-rich VLDL is hydrolyzed via lipoprotein lipase (LPL) and other lipolytic enzymes and subsequently converted into LDL, which is rich in cholesterol esters (CE). Cholesterol-rich LDL particles can then bind to cell LDL receptors (LDL-R) in hepatic or peripheral tissues (including arterial wall macrophages) to transfer cholesterol esters into these cells. Cholesterol that is transferred to peripheral tissues via LDL is frequently oxidized during this process. Reverse cholesterol transport allows free cholesterol (FC) to be removed from peripheral tissues (including arterial wall macrophages) via a number of mechanisms, including ATP binding cassette A1 (ABC A1), ATP binding cassettes G1 and G4 (ABC G1 and ABC G4), and via the scavenger pathway through scavenger receptor B1 (SR B1). Free cholesterol is then transferred to either a mature α-HDL molecule, or a nascent pre β-HDL molecule. Pre β-HDL molecules are rich in free cholesterol and phospholipids (PL). The free cholesterol bound to pre β-HDL is esterified via lecithin cholesterol acyltransferase (LCAT) which will force the maturation of the discoid molecule into a spherical α-HDL. Mature α-HDL can then transfer cholesterol from the periphery back to the liver via SR B1 receptors, where cholesterol can be recycled or excreted into bile. Cholesteryl ester transfer protein (CETP) mediates the transfer of lipoproteins by exchanging triglycerides from VLDL to HDL in exchange for cholesterol esters from HDL to VLDL and LDL. The net effect of CETP activity is the loss of CEs from the antiatherogenic HDL molecules to the proatherogenic LDL and VLDL molecules, whereby cholesterol can undergo oxidation and contribute to the vascular plaque burden.