

Rationale and design of the dal-OUTCOMES trial: Efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome

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Background Despite contemporary therapies for acute coronary syndrome (ACS), morbidity and mortality remain high. Low levels of high-density lipoprotein (HDL) cholesterol are common among patients with ACS and may contribute to ongoing risk. Strategies that raise levels of HDL cholesterol, such as inhibition of cholesterol ester transfer protein (CETP), might reduce risk after ACS. Dal-OUTCOMES is a multicenter, randomized, double-blind, placebo-controlled trial designed to test the hypothesis that CETP inhibition with dalcetrapib reduces cardiovascular morbidity and mortality in patients with recent ACS.

Design The study will randomize approximately 15,600 patients to receive daily doses of dalcetrapib 600 mg or matching placebo, beginning 4 to 12 weeks after an index ACS event. There are no prespecified boundaries for HDL cholesterol levels at entry. Other elements of care, including management of low-density lipoprotein cholesterol, are to follow best evidence-based practice. The primary efficacy measure is time to first occurrence of coronary heart disease death, nonfatal acute myocardial infarction, unstable angina requiring hospital admission, resuscitated cardiac arrest, or atherothrombotic stroke. The trial will continue until 1,600 primary end point events have occurred, all evaluable subjects have been followed for at least 2 years, and 80% of evaluable subjects have been followed for at least 2.5 years.

Summary Dal-OUTCOMES will determine whether CETP inhibition with dalcetrapib, added to current evidence-based care, reduces cardiovascular morbidity and mortality after ACS. (Am Heart J 2009;158:896-901.e3.)

Despite evidence-based therapeutic strategies including prompt coronary revascularization,¹ intensive statin therapy,^{2,3} and thienopyridine antiplatelet agents,⁴ patients hospitalized with acute coronary syndrome

(ACS) are at high risk for recurrent cardiovascular events. In approximately 10% of patients with ACS, cardiovascular death, recurrent myocardial infarction, or stroke occurs within 1 year.⁴ With >1 million cases of ACS occurring annually in the United States alone,⁵ the high residual risk after ACS presents an imperative to identify new therapeutic approaches to improve these outcomes.

In epidemiologic analyses, both high levels of low-density lipoprotein (LDL) cholesterol and low levels of high-density lipoprotein (HDL) cholesterol predict cardiovascular risk.^{6,7} Statin drugs effectively lower LDL cholesterol and attenuate cardiovascular risk after ACS,^{2,3} but low HDL cholesterol remains a predictor of risk on a background of statin therapy.⁸⁻¹⁰ Even among patients treated with atorvastatin to achieve the optional American Heart Association/American College of Cardiology goal of LDL cholesterol <70 mg/dL,¹¹ low HDL cholesterol remains a predictor of risk in chronic coronary heart disease¹² and after ACS.^{13,14} Moreover, low HDL cholesterol is common among patients with ACS. When defined

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Submitted July 24, 2009; accepted September 22, 2009.

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0002-8703/\$ - see front matter

Published by Mosby, Inc.

doi:10.1016/j.ahj.2009.09.017

as a level <40 mg/dL in men or <45 mg/dL in women, approximately half of patients who present with ACS have low HDL cholesterol^{2,3,13,14} and the proportion in this category has increased in recent years.¹⁵ The frequency of ACS in the population, the prevalence of low HDL among patients with ACS, and the association between low HDL and adverse outcomes beg the question of whether interventions that increase the concentration or mimic the function of HDL would reduce cardiovascular risk after ACS.

Studies using intracoronary ultrasonography have suggested that infusion of HDL-mimetic agents promote favorable remodeling of coronary atherosclerotic plaques within a few weeks after an ACS event.¹⁶⁻¹⁸ To date, however, no investigation has determined whether cardiovascular morbidity and mortality after ACS can be favorably modified by an HDL-based intervention.

In this regard, inhibition of cholesterol ester transfer protein (CETP) may be an attractive strategy.^{19,20} Cholesterol ester transfer protein promotes transfer of cholesterol esters from HDL to triglyceride-rich lipoprotein particles, in exchange for triglyceride, thereby reducing the circulating HDL cholesterol concentration. Most animal and human data support the idea that inhibition of CETP retards the development or progression of atherosclerosis. Ordinarily, mice do not express CETP and are resistant to the development of atherosclerosis. In transgenic mice expressing simian or human CETP, an increased propensity to develop atherosclerosis has been demonstrated in some^{21,22} but not all studies.²³ Rabbits naturally express CETP, and treatment of cholesterol-fed rabbits with CETP inhibitors reduces the extent of atherosclerosis.^{24,25} In humans, deficiency or pharmacologic inhibition of CETP is associated with greater HDL-mediated macrophage cholesterol efflux,^{26,27} and CETP polymorphisms associated with reduced CETP activity or mass and increased HDL cholesterol concentration are associated with decreased cardiovascular risk in most²⁸ but not all²⁹ analyses.

The first CETP inhibitor to enter phase III clinical development, torcetrapib, failed to attenuate the progression of atherosclerosis and increased cardiovascular morbidity and mortality.³⁰⁻³² However, torcetrapib had adverse neurohumoral and hemodynamic effects that confound testing the hypothesis of whether CETP inhibition improves outcomes in atherosclerotic cardiovascular disease.²⁹ Activation of the renin-angiotensin-aldosterone system and elevation of blood pressure by torcetrapib were observed in clinical trials and reproduced by torcetrapib treatment in rats,³³ a species that does not express CETP. The latter finding indicates that these adverse effects are not attributable to CETP inhibition per se. Moreover, in post hoc analysis of a trial that investigated the effects of torcetrapib on progression of coronary atherosclerosis, larger treatment-associated increases in HDL cholesterol were

associated with more favorable changes in coronary atheroma volume, as measured by intravascular ultrasound.³⁴ These observations suggest that HDL formed in response to CETP inhibition may retard progression of atherosclerosis and that a CETP inhibitor without the off-target effects of torcetrapib might afford clinical benefit.

Dalcetrapib is a CETP inhibitor that differs from torcetrapib in several ways: Dalcetrapib is structurally dissimilar, is less lipophilic, and does not form a stable drug-CETP-HDL complex at clinically relevant plasma concentrations.³⁵ Importantly, dalcetrapib appears to be devoid of the undesirable neurohumoral and hemodynamic effects of torcetrapib.^{33,36} In phase II clinical trials, dalcetrapib 600 mg daily raised HDL cholesterol concentration by 25% to 31% without significant effects on LDL cholesterol, triglycerides, or blood pressure, and was well tolerated.³⁶ The differences between dalcetrapib and torcetrapib provide a strong rationale to use the former agent to retest the hypothesis that CETP inhibition exerts protective cardiovascular effects. Accordingly, the DAL-OUTCOMES trial was designed to determine whether dalcetrapib reduces cardiovascular morbidity and mortality among patients with recent ACS.

Methods

Study objective

Dal-OUTCOMES (www.clinicaltrials.gov identifier NCT00658515) is an investigator-initiated, international, multicenter, randomized, double-blind, placebo-controlled study in approximately 15,600 patients with recent ACS. The protocol was developed by an independent academic Executive Committee (Appendix) in conjunction with the sponsor. The study is approved in each participating center by the responsible Institutional Review Board or Ethics Committee. The primary study objective is to evaluate whether dalcetrapib 600 mg daily, initiated 4 to 12 weeks after an index ACS event, reduces the incidence of the composite end point of coronary heart disease death, major nonfatal coronary events (acute myocardial infarction, hospitalization for ACS, or resuscitated cardiac arrest), or stroke.

Study population

The trial will enroll male and female patients ≥ 45 years of age who are hospitalized for *acute myocardial infarction* defined by abnormal troponin or creatine kinase (CK)-MB mass and at least one of the following: symptoms of acute myocardial ischemia, new or presumed new ischemic electrocardiographic (ECG) findings (ST depression or elevation, T wave inversion, pathologic Q waves, or left bundle-branch block), or imaging evidence of loss of viable myocardium. Patients may also qualify for the trial on the basis of *myocardial infarction related to percutaneous coronary intervention* (defined by normal levels of cardiac biomarkers before the procedure and elevation of biomarkers to >3 times upper limit of normal after the procedure) or *biomarker-negative ACS* (defined by symptoms of myocardial ischemia with an accelerating pattern or occurring at rest with new or presumed new ischemic ECG findings and at

Table I. Principal inclusion and exclusion criteria

Inclusion criteria

- Hospitalization for ACS, defined by symptoms of unstable myocardial ischemia, elevated cardiac biomarkers, new or presumed new ischemic ECG changes, and/or evidence of myocardial ischemia or infarction by imaging criteria
- Age ≥ 45 y
- Any baseline level of HDL cholesterol is acceptable
- Evidence-based management of LDL cholesterol
- Clinically stable for at least 1 wk before randomization

Exclusion criteria

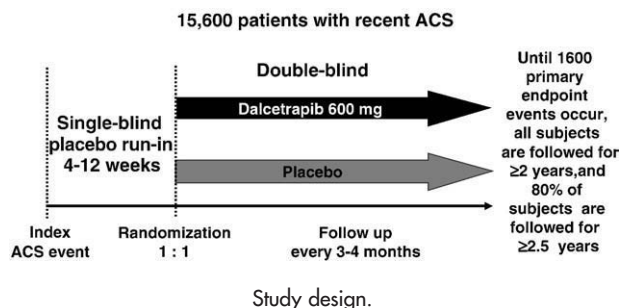
- Index event due to uncontrolled hypertension and/or blood pressure remaining $\geq 180/110$ mm Hg despite treatment
- New York Heart Association class III or IV congestive heart failure irrespective of ejection fraction, or New York Heart Association class II heart failure with left ventricular ejection fraction $\leq 40\%$, persisting at end of run-in period despite treatment
- Laboratory values outside specified limits at end of run-in period: hepatic transaminase, alkaline phosphatase, or total bilirubin >1.5 times upper limit of normal; creatine phosphokinase >3 times upper limit of normal; hemoglobin ≤ 10 g/dL; hemoglobin $A_{1c} >10\%$; triglycerides ≥ 400 mg/dL (4.5 mmol/L); creatinine >2.2 mg/dL (194.5 μ mol/L)
- Clinically apparent liver disease
- Concurrent treatment with niacin, fibrates, bile acid sequestrants, or any other drug administered for the purpose of raising HDL cholesterol
- Previous exposure to a CETP inhibitor
- Malignancy (except for nonmelanoma skin cancer) within the preceding 3 y
- Inability to provide informed consent or comply with study requirements, unreliability, substance abuse within the preceding 5 y, life expectancy shorter than trial duration, pregnancy, lactation, or childbearing potential without use of effective contraception

least one of the following: 50% stenosis of an epicardial coronary artery by angiography, reversible ischemia indicated by stress testing, or pathologic Q waves by ECG). Each of these categories identifies high-risk coronary heart disease patients who might benefit from an increase in HDL cholesterol concentration.

Study procedures

Patients meeting these criteria and offering informed consent may enter a single-blind placebo run-in period (Figure 1). The run-in period is intended to provide sufficient time to determine if patients fulfill all eligibility criteria and meet no exclusion criteria (Table I), to complete all planned coronary revascularization procedures, to allow a metabolic steady state to be restored after the acute phase response to ACS, and to implement evidence-based management of LDL cholesterol. At a minimum, the last includes medical and dietary treatment to an LDL target level <100 mg/dL (<2.6 mmol/L) and ideally to a target level <70 mg/dL (<1.8 mmol/L). Patients with moderate to severe hypertriglyceridemia (≥ 400 mg/dL or 4.5 mmol/L) are excluded because of the likelihood that such patients will require treatment with niacin or fibrate. There are no specific inclusion/exclusion criteria for baseline HDL cholesterol levels. Patients with uncontrolled hypertension or advanced heart failure are excluded.

After a minimum of 4 weeks and a maximum of 12 weeks in the placebo run-in phase, patients who fulfill all inclusion and no exclusion criteria are randomly assigned in a 1:1 ratio to double-blind treatment with dalcetrapib 600 mg daily or matching placebo, administered with the largest meal of the day.

Figure 1

Randomization is stratified by country and by type of index ACS event (biomarker positive or negative). After randomization, follow-up visits occur at the end of 1, 3, 6, 9, and 12 months, and every 4 months thereafter. At randomization and at multiple time points after randomization, fasting blood glucose, hemoglobin A_{1c} , creatinine, electrolytes, liver function, creatine phosphokinase, triglycerides, and LDL cholesterol are measured and reported to investigators. Investigators are encouraged to adjust statin treatment as needed to maintain evidence-based target levels of LDL cholesterol throughout the trial. In addition, serial blinded measurements of HDL cholesterol, apolipoproteins, lipid subfractions, markers of lipid metabolism, and high-sensitivity C-reactive protein are performed. Aldosterone is measured at randomization, 3 months of treatment, and end of study in the first 2,000 patients randomized. Biomarkers of inflammation, oxidation, and cardiovascular risk are measured in 2,000 patients recruited at sites capable of storing samples at -70°C . A 12-lead ECG is obtained at randomization, after 1, 3, 6, and 12 months of treatment, and annually thereafter until end of trial. All ECGs are interpreted in a blinded fashion by a core ECG laboratory located at St Louis University.

Study outcomes

The primary efficacy measure is the time to first occurrence of coronary heart disease death, major nonfatal coronary event (myocardial infarction, hospitalization for unstable angina, or resuscitated cardiac arrest), or stroke. Detailed criteria for each type of primary end point event are provided in Table II. The analysis plan also prespecifies examination of individual components of the primary end point, total mortality, and other secondary and tertiary efficacy measures, as listed in Table III. Safety of dalcetrapib treatment is assessed by reporting of adverse events, laboratory tests, vital signs, ECG, and occurrence of new malignancies and infections.

Statistical considerations

Assumptions include a projected median baseline HDL cholesterol level of 40 mg/dL (1.04 mmol/L), a 25% to 30% increase in HDL cholesterol with dalcetrapib (corresponding to approximately 11 mg/dL), and a 1.5% relative risk reduction for each milligram-per-decilitr increment in HDL cholesterol, resulting in a 15% relative risk reduction with dalcetrapib. Based on these assumptions, a primary end point event rate in the placebo group of 7.2% in the first year of treatment and 2.4% per year thereafter based on other contemporary trials,^{3,37} and a

Table II. Definitions of primary end points

Coronary heart disease death

- Any death with a clear relationship to underlying coronary heart disease (including death secondary to acute myocardial infarction, sudden death, unobserved and unexpected death, resuscitated out-of-hospital cardiac arrest that does not survive to hospital discharge, and other death that cannot definitely be attributed to a nonvascular cause.

Myocardial infarction

- Abnormal levels of cardiac biomarkers, defined as values above the decision threshold considered diagnostic of myocardial infarction at the local laboratory. Hierarchy of biomarkers is cardiac troponin, CK-MB mass, and CK-MB activity.

AND at least 1 of the following:

- Ischemic symptoms within the prior 48 h
- Imaging evidence of loss of viable myocardium
- ECG findings (new or presumed new if no prior ECG available) consistent with myocardial infarction, based upon ACC/ESC/AHA criteria³⁷

In addition, the following categories are considered:

- Silent Q wave myocardial infarction, detected on routine ECGs collected at baseline and annually during follow-up, is included in the definition of MI.
 - Fatal myocardial infarction
- Death within 28 d of myocardial infarction, as defined above, or autopsy evidence within 28 d of myocardial infarction, or death in hospital >28 d of myocardial infarction with clear causal relationship between myocardial infarction and death

Unstable angina (hospitalization for ACS without biomarker elevation)

- Admission to hospital or emergency department (exceeding 23 h) with symptoms presumed to be caused by myocardial ischemia and an accelerating tempo in the prior 48 h and/or prolonged (at least 20 min) rest chest discomfort

AND at least 1 of the following:

- ECG evidence of myocardial ischemia
- Angiographic progression of coronary artery disease (if prior coronary angiogram is available)
- At least 50% stenosis of an epicardial coronary artery (if no prior coronary angiogram is available)
- Abnormal exercise or pharmacologic stress test indicating new or presumed new territory of reversible ischemia

Resuscitated cardiac arrest

- Successful resuscitation after documented cardiac arrest
- Patient admitted to hospital and subsequently discharged

Stroke

- Acute neurologic vascular event with focal neurologic signs lasting >24 h, with or without evidence of intracranial hemorrhage.
- If the event represents a worsening of a previous deficit, it must either have persisted for >1 wk or have persisted > 24 h and be accompanied by appropriate new CT or MRI findings.
- Strokes are subclassified as ischemic, hemorrhagic, or uncertain type based on clinical and neuroimaging data.
- Fatal stroke is defined by death occurring after confirmed stroke and due to stroke-related deficit, cerebral edema, herniation, or hemorrhage, or to medical complications or withdrawal of life support that would not have occurred had it not been for the stroke. Death within 30 d of confirmed stroke is determined to be fatal stroke in the absence of another clearly identified cause.

ACC, American College of Cardiology; ESC, European Society of Cardiology; AHA, American Heart Association; CT, computed tomography; MRI, magnetic resonance imaging.

2-sided $\alpha \leq .05$, the trial will have 90% power with 1,600 primary end point events, corresponding to a sample size of 15,600 patients followed for at least 2 years. To allow sufficient duration of exposure to dalcetrapib for a thorough assessment of both safety and efficacy, the trial will continue until 1,600 primary end point events have occurred, all evaluable surviving subjects have been followed for at least 2 years, and 80% of surviving evaluable subjects have been followed for at least 2.5 years. The primary efficacy analysis will be performed on an intention-to-treat basis using a stratified Cox proportional hazards model. For secondary and tertiary end points, Cox regression, Cochrane-Mantel-Haenzel, and analysis of variance tests will be used as applicable. Analysis of subpopulations defined by categorical and continuous variables will be performed according to a prespecified statistical analysis plan. Characteristics to be examined include age; gender; renal function; presence or absence of diabetes, hypertension, and metabolic syndrome; and baseline levels of HDL and LDL cholesterol, triglycerides, and apolipoproteins. Proportional hazard regression models will also be constructed to include changes in or actual values of HDL and LDL cholesterol as covariates.

Every 2 months, the Data and Safety Monitoring Board (DSMB) reviews interim data to assess safety. Interim analyses for efficacy will be performed by the DSMB when 50% and 70% of expected total primary events have been adjudicated. After either analysis, the DSMB may recommend stopping the trial if a significant benefit of dalcetrapib treatment is seen for the primary efficacy analysis at $P < .001$, with consistency in both morbidity and mortality findings. At the 70% interim analysis, the DSMB may also elect to terminate the trial for futility. As a result of α spending for interim analyses, the final analysis will require $P < .048$ to be declared significant at the .05 level. Details for the interim analyses are provided in the DSMB charter.

Study organization

An independent academic Executive Committee, composed of 10 voting members and an independent nonvoting statistician and sponsor representative, designed the protocol and is responsible for oversight and guidance of the study. A National Leaders Committee, composed of lead investigators from each participating country, works in tandem with the Executive

Table III. Efficacy measures

Primary

- Time to first occurrence of coronary heart disease death, major nonfatal coronary event (myocardial infarction, hospitalization for biomarker-negative ACS, resuscitated cardiac arrest), or stroke of presumed atherothrombotic etiology

Secondary

Time to first occurrence of:

- All-cause mortality
- A composite of all-cause mortality, major nonfatal coronary events, or stroke
- Individual components of the primary efficacy measure
- Unanticipated coronary revascularization (not due to restenosis at previous intervention site)

Change from baseline of:

- Blood lipids, lipoproteins, apolipoproteins
- Biomarkers of inflammation, oxidation, and cardiovascular risk

Tertiary

Time to first occurrence of:

- Procedure-related myocardial infarction
- Coronary revascularization due to restenosis at previous intervention site
- Noncoronary revascularization
- All strokes, irrespective of etiology (ie, atherothrombotic, embolic, or hemorrhagic)

Incidence of:

- The primary end point and its components at 6, 12, and 24 m
- The primary end point and its components occurring after 6 and 12 m of treatment
- Hospitalization for congestive heart failure other than in conjunction with a primary end point event
- All cardiovascular events listed above, including multiple occurrences of events in a patient.

Committee. The Clinical Events Committee, composed of 5 cardiologists and 2 neurologists, reviews and adjudicates each suspected clinical end point in a blinded fashion. The DSMB, composed of 4 physicians and a statistician, monitors the accumulating safety data within the trial and conducts interim analyses of efficacy and futility as indicated above.

Discussion

Dal-OUTCOMES was designed to test the hypothesis that inhibition of CETP reduces cardiovascular risk. Dalcetrapib is a suitable agent to test this hypothesis because it appears to be devoid of the undesired, off-target effects of torcetrapib.^{33,36} Dal-OUTCOMES evaluates dalcetrapib in a large cohort of patients with recent ACS because those patients face a high risk of recurrent cardiovascular events and may derive a large absolute benefit from an effective new therapy. At the same time, potential adverse cardiovascular effects of dalcetrapib are likely to be detected most readily and rapidly in a population at high cardiovascular risk. With an expected average duration of treatment of several years, dal-OUTCOMES will also provide information regarding the utility of CETP inhibition in the chronic phase of coronary heart disease. It is uncertain whether an inverse relationship between circulating HDL cholesterol concentration and cardiovascular risk extends over the entire physiologic range of HDL concentration. For this reason, dal-OUTCOMES places no upper bound on baseline HDL cholesterol concentration. Full recruitment of subjects for dal-OUTCOMES is expected in 2010, with completion of the trial in 2013.

It is useful to consider dal-OUTCOMES in context with other randomized controlled trials that are investigating whether niacin (www.clinicaltrials.gov NCT00461630 and NCT00120289), fenofibrate (NCT00000620), or pioglitazone (NCT00212004 and NCT00091949) reduces cardiovascular morbidity and mortality in patients with coronary heart disease or stroke. Although each of these agents raises HDL cholesterol, each also has multiple other actions. Thus, it may be difficult to ascribe any benefit observed in these trials to effects of treatment on HDL cholesterol per se. Moreover, each of these trials either excludes or is not limited to patients with recent ACS. Thus, dal-OUTCOMES is expected to provide unique information, in terms of both therapeutic strategy and target population.

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Appendix A. Committees

Executive Committee: Gregory G. Schwartz (Chair), Anders G. Olsson (Co-Chair), Christie M. Ballantyne, Phillip J. Barter, Ingar Holme, David Kallend, Lawrence Leiter, Eran Leitersdorf, John J. V. McMurray, Stephen J. Nicholls, Prediman K. Shah, Jean-Claude Tardif, Bernard R. Chaitman (ex officio).

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Clinical Events Committee: Bernard R. Chaitman (Chair), Richard Bach, Salvador Cruz-Flores, Daniel Fintel, Gilbert Gosselin, Cathy A. Sila, Kristian Thygesen.

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