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The Role of Niacin in Raising HDL-C to Reduce Cardiovascular Events in Patients with Atherosclerotic Cardiovascular Disease and Optimally Treated LDL-C AIM-HIGH: Rationale and Study Design*

The AIM-HIGH Investigators

Abstract

Background—To test the hypothesis that patients with atherosclerotic cardiovascular (CV) disease optimally treated on a statin but with residual atherogenic dyslipidemia (low HDL-C and high triglycerides) will benefit from addition of niacin with fewer CV events compared with placebo.

Statin monotherapy trials have found 25–40% CV risk reduction relative to placebo, leaving significant residual risk. Patients with *atherogenic dyslipidemia* have substantially increased CV risk.

Methods—Participants were men and women with established CV disease and atherogenic dyslipidemia. Lipid entry criteria varied by gender and statin dose at screening. All participants received simvastatin (or simvastatin plus ezetimibe) at a dose sufficient to maintain LDL-C 40 - 80 mg/dL (1.03 – 2.07 mmol/L). Participants were randomized to extended-release niacin or matching placebo. The primary end-point was time to occurrence of the first of: *coronary heart disease death, non-fatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization*. This event-driven trial will have 85% power to show a 25% reduction in primary event frequency after 850 patients have experienced a primary outcome event.

Results—AIM-HIGH completed enrollment in April 2010. Follow-up is expected to continue through 2012.

Summary—AIM-HIGH was designed to determine whether treating residual dyslipidemia with niacin further reduces cardiovascular events in patients with CVD on a statin at target levels of LDL-C.

BACKGROUND

Although atherosclerotic cardiovascular (CV) disease mortality has declined significantly over the past four decades, it remains the leading cause of death and disability among men and women in the western world.¹ Currently, over 13.2 million Americans have diagnosed *coronary heart disease (CHD)* and, despite profound advances in both pharmacologic and interventional management over the past 15 years, both morbidity and mortality remain

*A THEROTHROMBOSIS INTERVENTION IN METABOLIC SYNDROME WITH LOW HDL/HIGH TRIGLYCERIDES: IMPACT ON GLOBAL HEALTH OUTCOMES. (AIM-HIGH)

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appreciable. Elevated LDL-C is well-established as a major predictor of CHD risk and, importantly, multiple primary and secondary prevention trials with statins have convincingly demonstrated a 25–35% relative risk reduction in CHD mortality, all-cause mortality, non-fatal myocardial infarction (MI), and stroke;² however, the continuing risk for major CV events despite statin therapy remains unacceptably high, with cumulative 5-year CV event rates among statin-treated patients two-thirds to three-quarters that of placebo-treated patients.

Early population studies have demonstrated that LDL-C elevation is not the only lipid predictor of adverse CV outcomes.^{3,4} Low levels of HDL-C are also recognized as a major independent predictor of CHD risk, with a strong inverse association observed between HDL-C levels and incident CHD rates. The Veterans Affairs HDL Intervention Trial (VA-HIT) was the first study to provide some evidence that raising low levels of HDL-C in CHD patients with normal LDL-C levels was associated with significant reductions in CV events.⁵ An analysis of four large prospective trials demonstrated a 2–3% reduction in CHD risk for every 1 mg/dL increase in HDL-C.⁶ Additionally, the HDL-Atherosclerosis Treatment Study (HATS) demonstrated that treatment of the total lipid profile with a combination of simvastatin and niacin was associated with significant regression of coronary atherosclerosis and further reductions in clinical events during an average 2.5 year follow-up.⁷

Therapy for dyslipidemia reduces CV event frequency over periods of 3 – 8 years in rough proportion to the sum of treatment-induced percent reduction in LDL-C plus 1.3 times the percent increase in HDL-C.⁸ Thus, for example, a 30% LDL-C decrease and 6% HDL-C increase with a statin would predict a 38% event risk reduction compared to placebo. Recent studies have focused on more aggressive LDL-C reduction strategies using high doses of statins⁹ to achieve an LDL-C treatment target of ≤ 70 mg/dL in very high risk patients. Yet, in a post hoc analysis of the Treating to New Targets (TNT) Trial,¹⁰ it was noteworthy that even among those who attained LDL-C values < 70 mg/dL, patients in the highest quintile of HDL-C levels had a 25% lower 5-year rate of major CV events than those in the lowest quintile ($p=0.03$). Thus, HDL-C levels were independently predictive of major CV events in statin-treated patients regardless of LDL-C levels. Moreover, the growing numbers of patients with diabetes and metabolic syndrome, characterized by the atherogenic dyslipidemia triad of low HDL-C, elevated triglycerides, and small dense LDL, present an expanding reservoir of CHD patients who are at increased risk of vascular events compared to those without metabolic syndrome.¹¹

Despite these new insights, the evidence favoring treatment of atherogenic dyslipidemia is not considered sufficiently compelling by the National Cholesterol Education Program (NCEP) to merit a recommendation for specific HDL-C goals by Adult Treatment Panel III.¹² None-the-less, there is a growing evidence-based perception that treatment of atherogenic dyslipidemia will eventually become a proven adjunct to LDL-C-lowering, with a predicted near-doubling of current risk reduction¹³. Accordingly, alternative treatment strategies with combination therapies to address multiple lipid abnormalities in CHD patients are needed. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) Trial will test the hypothesis that niacin added to optimal statin therapy will reduce the risk of CV events compared to statins alone in patients with atherosclerotic CV disease and atherogenic dyslipidemia.

METHODS AND STUDY DESIGN

Participating clinical sites

Participating sites, identified based on successful recruitment in prior trials, were selected from outpatient internal medicine, cardiology, and diabetes clinics, and catheterization and vascular laboratories. Study participants were recruited from 69 sites from the United States and 23 from Canada. Institutions included 33 private, 27 university, 18 community hospitals, 12 Veterans Administration facilities and 1 managed care clinic. Predominant recruitment strategies included surveillance and solicitation from coronary care, catheterization and cardiac rehabilitation logs, and review of databases and mass mailing. As recruitment lagged for minorities and women (target 27% minority and 30% women) supplemental funding was provided to eight carefully selected sites in hopes of enriching the proportions of these groups in the final cohort.

Patient entry requirements

Participants were men and women, age 45 years or older with atherogenic dyslipidemia and documented, clinically established atherosclerotic CV disease (Table I). Participants could present with more than one qualifying diagnosis. The trial was approved by the ethics committee from each participating institution. All study participants provided written informed consent.

For the great majority of patients screened on a steady dose of a given statin $\pm$ ezetimibe, eligibility was determined using their measured (on-treatment) lipid profile, with adjustments based on the predicted effects of a given statin and dose ($\pm$ ezetimibe) on LDL-C (according to published prescribing information), and assuming modest statin-induced increases in HDL-C and decreases in triglycerides for both genders. Patients were allowed to be rescreened for lipid measures up to two times.

Drug protocol, Run-in, Randomization, and Blinding Methods

Extended-release niacin (Niaspan®), its placebo, and ezetimibe (Zetia®), were provided by Abbott Laboratories. In order to maintain the blind, placebo matching extended-release niacin contained 50 mg per tablet of immediate release niacin, sufficient to provoke a discernible flush in most patients. Supplies of simvastatin were provided by Merck.

Patients meeting entry requirements were given open-label active therapy with simvastatin 40 mg daily at bedtime, plus extended-release niacin on a dosage schedule advancing weekly by 500 mg qhs for four successive weeks, to a final dose of 2,000 mg qhs (as four 500 mg tablets). This run-in phase could be extended to 8 weeks, as needed to demonstrate tolerance of at least 1,500 mg/day of niacin. Those choosing to continue after the 4–8 week active run-in were given simvastatin 40 mg/day (“**standard therapy**”) and were randomly assigned to either extended-release niacin at 1,500 mg – 2,000 mg per day (“**combination therapy**”) as tolerated, or to its active placebo. Randomization was stratified by history of diabetes and clinical site. An application on a secure Web site provided the randomization assignment as a numbered drug kit, blinded to niacin/placebo. For those limited to a niacin dose of 1,500 mg/day during the run-in, there was a subsequent attempt to increase dosage to 2,000 mg/day (or its equivalent placebo dose) over the first year. Patients were educated about ways to minimize flushing, including taking the medication at bedtime with a low-fat snack and, if allowed by their private physician, taking 325 mg aspirin up to 30 minutes before taking blinded study medication.

Protocol Clinic Procedures and Time Course: (clinic visits, phone contact, blood samples, lipid drug titration)

The principal goals of the first year, which included 5 visits and 3 telephone contacts, were to teach the patient the trial expectations, to encourage long-term commitment, to assist with drug adherence, and to adjust the simvastatin dosage, with the possible addition of ezetimibe 10 mg, in order to achieve a target LDL-C in the range 40 – 80 mg/dl (1.0 – 2.1 mmol/L). The starting simvastatin dose for virtually all patients was 40 mg/day. At four of the first year visits (1 mo, 3 mo, 6 mo, 12 mo), a blood sample was obtained. Based on the LDL-C level relative to the goal range, the statin dose might remain unchanged, or doubled or halved within the dosing range of 10 mg – 80 mg. If a patient achieved an LDL-C level of 80–100 mg/dL (2.1–2.6 mmol/L) while receiving 40 mg simvastatin plus 10 mg ezetimibe, for safety reasons a dosage increase to 80 mg simvastatin plus 10 mg ezetimibe was not required. Absent symptomatic or enzymatic evidence for statin toxicity, all patients were encouraged to remain on at least 10 mg simvastatin despite very low LDL-C levels.

After the first year, participants were seen every six months in clinic, where blood samples were obtained for safety and possible adjustment of statin dose annually. Participants were contacted by phone at 3 and 9 months thereafter. ECGs were obtained annually to assess for potential silent MI.

Clinical endpoints and their adjudication

All primary, secondary, and tertiary events after randomization were reviewed by an independent Clinical Events Committee (CEC). Only events confirmed by the CEC will be included in the final analysis. Events occurring during the run-in phase were recorded, but not included in the final analysis.

The primary endpoint in AIM-HIGH was time from randomization to the first occurrence of CHD death, non-fatal MI, ischemic stroke, admission for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. A symptom driven revascularization procedure for restenosis was not considered part of the primary endpoint.

Secondary endpoints included the composite end-points of (i) CHD death, non-fatal MI, ischemic stroke, high-risk acute coronary syndrome, or (ii) coronary heart disease death, non-fatal MI, and ischemic stroke, or (iii) any cardiovascular death

The tertiary endpoints included: (i) all-cause death (ii) the composite of all-cause death, admission for acute coronary syndrome, ischemic stroke or any arterial revascularization, and (iii) the individual components of the endpoints.

Statistical considerations

The trial will be analyzed under the principle of intention to treat. All participants will be followed to a common termination date or death (estimated average follow-up 4.6 years; minimum follow-up 30 months and maximum approximately 7 years).

As originally designed, the primary endpoint was specified as a composite endpoint consisting of CHD death, non-fatal MI, ischemic stroke or hospitalization for high risk acute coronary syndrome. Under this design, with an estimated sample size of 3,300, the trial had 99% power to detect a 25% reduction in primary outcome events among patients randomized to the combination of extended-release niacin + simvastatin (“combination therapy”), assuming a 0.089 hazard rate in patients randomized to placebo + simvastatin (“standard therapy”), using an unadjusted one-sided p-value of 0.025. The Interim Analysis Plan allowed for one adjustment to sample size if the overall primary event rate was lower

than expected. Because of a lower than expected overall primary endpoint rate, protocol amendment 5, adopted April 2010, modified the primary endpoint to the expanded composite described above. Expansion of the trial sample size and extension of follow-up were considered, but for budgetary reasons not implemented. This modification was proposed by the AIM-HIGH Executive Committee, which was blinded to by-treatment-arm results, and approved by the NHLBI following the recommendations of an Independent Review Committee appointed by the NHLBI, which was also blinded to by-treatment-arm outcome data.

The Interim Analysis Plan allows for two examinations of the efficacy data by the DSMB when approximately 50% and 75% of the projected primary events have occurred.

Substudies

A number of integrated substudies provide additional opportunity to elucidate mechanism(s) of action and effects of niacin in patient subpopulations. A carotid magnetic resonance imaging (MRI) study has enrolled and obtained baseline MRI scans on 231 participants. This study will evaluate plaque lipid composition and burden in carotid arteries assessed by multi-contrast MRI and determine whether MRI-based plaque characterization predicts future clinical cardiovascular events. An HDL proteomics/functionality and plaque inflammation substudy has enrolled 332 participants, of whom 159 are also enrolled in the MRI substudy, and will investigate the relative effects of each treatment strategy on inflammatory changes in atherosclerotic plaques and HDL particles. Both of these substudies are funded by the NHLBI. A cost-effectiveness/health economics study is ongoing. Other substudies include investigations of biomarkers/pharmacogenomics, apolipoproteins, nuclear magnetic resonance analyses of lipoproteins, LpPLA2, and effects on renal function, glucose control/onset of diabetes, and phosphorus/calcium homeostasis.

Management

An Executive Committee, consisting of the trial co-principal investigators, directors of the Coordinating Center, chair of the Substudies, Ancillary Studies and Publications Committee, key investigators involved in the design of the trial and the lead clinical research associate from the Coordinating Center plus representatives from the sponsor, the National Heart, Lung, and Blood Institute (NHLBI) provided overall direction for the trial. All laboratory results were provided by a core laboratory, Northwest Lipid Metabolism and Diabetes Research Laboratories (University of Washington) and ECGs read by a core ECG facility, St. Louis University. Drug packaging, labeling and distribution was provided by Abbott Laboratories. A Protocol Review Committee appointed by NHLBI reviewed the initial protocol and made minor suggestions for additional safety labs. An independent Data and Safety Monitoring Board (DSMB) was appointed by the NHLBI to periodically monitor the trial for participant safety and recommend possible early termination based on pre-specified efficacy and lack of efficacy boundaries.

A Substudies, Ancillary Studies and Publications Committee reviewed and made recommendations to the Executive Committee regarding a variety of substudy and ancillary study proposals. This committee will be responsible for assigning authorship to all AIM-HIGH publications according to an adopted publications policy.

The Coordinating Center (Axio Research and Clinical Trials Monitoring Unit of the University of Washington) provided day-to-day oversight for the trial and support of the clinical sites. Trained Clinical Research Associates visited each clinical site during the early phase of recruitment to confirm accurate protocol implementation and to correct any misinterpretations. Sites having difficulty implementing the protocol were visited as

frequently as needed to resolve problems. Data were collected using an electronic data capture system and the password-protected study Web site provided access to a variety of study documents and study management reports as well as randomization and drug dispensing applications.

Results

AIM-HIGH completed enrollment in April 2010 (Figure 1). Participants were recruited from the United States, 1871 (55%) from non-Veterans Administration facilities and 475 (14%) from Veterans Administration facilities, and from Canada, 1,068 (31%). Of the 8,162 participants who signed informed consent, 2,825 were excluded because they did not meet lipid criteria. The most common reason for exclusion of patients meeting lipid and CV disease entry requirements was unwillingness to discontinue current lipid-altering therapies other than statins and/or ezetimibe.

Of 4,275 patients entering the open label run-in, 3,414 (80%) successfully completed the run-in and agreed to be randomized. Principal reasons for declining further participation were niacin intolerance due to flushing (6%) or itching (2%), or due to loss of interest (9%).

Discussion

Beginning with the Scandinavian Simvastatin Survival Study in 1994¹⁴, clinical trials with statins have shown major coronary events to decrease in rough proportion to the on-treatment percent reduction in LDL-C, and overall by about 30% of the placebo-treated rates². Thus, while statins, which principally lower LDL-C, reflect an important therapeutic advance, additional treatment measures are needed to further diminish the health impact of atherosclerotic vascular disease. AIM-HIGH is the first large study to assess the clinical benefit associated with the addition of niacin to an intensive statin ± ezetimibe regimen when both groups are treated to an aggressive LDL-C target of 40–80 mg/dl (1.0–2.1 mmol/L).

Niacin has been used for over 50 years in the management of cholesterol disorders.¹³ Niacin is most noted for its effects on HDL-C, with HDL-C increases in the 15% to 35% range. It also lowers triglycerides (20% to 50%) and is one of few drugs to lower lipoprotein (a) [Lp(a)]¹². In the Coronary Drug Project, a five year, double-blind, placebo-controlled trial conducted in the 1970's, niacin reduced the incidence of non-fatal MI by 24% and stroke by 22%, with a late benefit on overall mortality at 15 years, 10 years after the study ended.^{15,16} More recent imaging studies of niacin in combination with colestipol^{17,18} or a statin^{7,19,20,21} have also consistently shown a benefit on atherosclerosis burden; however, the evidence has generally not been considered sufficiently robust to support the more widespread use of niacin or the adoption into clinical practice guidelines of therapeutic target levels for HDL-C.

The mechanism of action of niacin on lipid biology is not well understood and appears to be quite complex.^{22,23} Niacin favorably affects levels of all lipoprotein fractions associated with atherosclerosis, decreasing apolipoprotein B-containing lipoproteins, including lipoprotein (a), while increasing HDL-C. Niacin inhibits lipolysis in adipose tissue and lowers plasma levels of free fatty acids, an effect mediated through the recently discovered nicotinic acid receptor HM74A, or the G_i-protein-coupled orphan membrane receptor (GPR109A), and modulation of hormone-sensitive TG lipase activity. It has been postulated that reduced flux of free fatty acids to the liver, by limiting substrate availability for hepatic synthesis of triglycerides, results in decreased output of VLDL by the liver and thus decreases plasma levels of triglycerides and LDL-C. Levels of HDL-C are increased

secondarily and indirectly via cholesterol ester transfer protein. Other evidence points to a direct hepatic site of action of niacin. In vitro studies show that niacin directly inhibits hepatic diacylglycerolacyltransferase 2, the rate limiting step in hepatic triglyceride synthesis. These studies also show that niacin inhibits hepatic HDL holoparticle uptake, effectively increasing the plasma residence time of HDL particles²³. More recently, in vivo metabolic clearance studies show that niacin stimulates receptor-mediated uptake of apoB100 and B48 from triglyceride-rich lipoproteins and increases hepatic apoAI synthesis.

Fibrates are another option for treatment of dyslipidemia. While fibrate-induced reduction of triglycerides is comparable to that of niacin, fibrates increase HDL-C significantly less than does niacin²². Despite these favorable effects of fibrates, the clinical trial evidence for a benefit on major coronary events is mixed. In VA-HIT⁵, a secondary prevention trial, gemfibrozil decreased the risk of non-fatal MI or CHD death by 22% among patients with low HDL-C (<40 mg/dL [1.0 mmol/L]) but without significantly elevated LDL-C. This study was widely regarded as a test of the HDL-C hypothesis. Gemfibrozil also decreased the risk of cardiovascular events in the primary prevention Helsinki Heart Study²⁴; however, more recently, trials with other fibrates including BIP²⁵ (secondary prevention, bezafibrate), and two studies among patients with diabetes (FIELD²⁶ - fenofibrate versus placebo; and ACCORD²⁷ - fenofibrate versus placebo on a background of simvastatin), failed to meet their primary endpoints and did not confirm a significant benefit on cardiovascular risk reduction. Thus, AIM-HIGH provides an important test for what may become the preferred treatment for residual dyslipidemia after successful treatment with a statin.

In summary, AIM-HIGH was designed to provide a rigorous test of the HDL hypothesis, to show that niacin treatment of residual dyslipidemia among CHD patients on a statin at their LDL-C goal will further decrease the incidence of major CV events compared to statin alone. The trial's results will have far ranging implications for current medical practice and the public health.

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APPENDIX

Executive Committee

B. Gregory Brown, MD, PhD, University of Washington (Co-Principal Investigator); William E. Boden, MD, FACC, University of Buffalo (Co-Principal Investigator); Jeffrey R. Probstfield, MD, FACC, University of Washington (Co-Director, Coordinating Center); Ruth McBride, Axio Research (Co-Director, Coordinating Center); Todd Anderson, MD, University of Calgary and Libin Cardiovascular Institute (Chair, Substudies, Ancillary Studies and Publications Committee); Bernard Chaitman, MD, FACC, St. Louis University (Director, Central Electrographic Laboratory and Chair, Clinical Events Committee); Santica Marcovina, PhD, ScD, University of Washington (Director, Northwest Lipid Metabolism and Diabetes Research Laboratory); William Weintraub, MD, FACC, Christiana Care Health Services (Principal Investigator, Economics Substudy), Xue-Qiao Zhao, MD, University of Washington (Principal Investigator Carotid MRI Substudy); Koon Teo, MB, PhD, FACC, McMaster University (Canadian Investigator Representative); Judith Kaiser, BSN, RN, University of Washington (Lead CRA, Coordinating Center); Patrice Desvignes-Nickens, MD, NIH/NHLBI (Project Officer, NHLBI); Jerome L. Fleg, MD, FACC NIH/NHLBI (Project Officer, NHLBI); Mark E. McGovern, MD, FACC, Miami FL (Cardiovascular Clinical Trials Consultant and Industry Liaison). Ex-officio: James C. Stolzenbach, PhD and Robert J. Padley, MD, Abbott Laboratories (Industry Representatives).

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Data and Safety Monitoring Board

Janet Wittes, PhD (Chair), Donna Arnett, PhD, MSPH; John LaRosa, MD; Trevor Orchard, MD; Karol E. Watson, MD; Eric M Meslin, PhD (Judith Hsia, MD served as chair until 2007).

Core Laboratories

Northwest Lipid Metabolism and Diabetes Research Laboratory

Santica Marcovina, PhD, ScD, Director.

St. Louis University Electrocardiographic Laboratory

Bernard Chaitman, MD, Director.

Recruiting Clinical Sites

Given in a separate appendix.

AIM-HIGH Methods and Baseline

Figure 1.
Study Flow

Table 1**Inclusion and Exclusion Criteria*****Inclusion Criteria***

Men and women aged 45 and older with established vascular disease and atherogenic dyslipidemia, defined in the following ways:

- 1** Established Vascular Disease satisfying at least one of the following:
 - a.** Documented CAD with $\geq$ one of the following:
 - i.** Documented multi-vessel CAD, with one or more $\geq$ 50% stenoses in $\geq$ two major epicardial coronary arteries by angiography. Patients with prior successful percutaneous coronary intervention (PCI), even with no residual stenosis, were eligible.
 - ii.** Documented prior MI satisfying $\geq$ two of the following:
 - Characteristic ischemic chest pain or pain in associated referral areas
 - Elevation of CK ($\geq$ twice the upper limit of normal) and/or CK-MB ($\geq$ twice the upper limit of normal) and/or troponin T or I ($\geq$ twice the upper limit of normal)
 - New Q waves in adjacent ECG leads, or new dominant R wave in V1
 - iii.** Hospitalization for non-ST segment elevation acute coronary syndrome with objective evidence of ischemia (ST-segment deviation or biomarker positivity), stable $\geq$ 4 weeks following hospital discharge.
 - b.** Documented cerebrovascular or carotid disease with at least one of the following:
 - i.** Documented ischemic stroke within the past 5 years but not $<$ 8 weeks prior to enrollment
 - ii.** Symptomatic carotid artery disease with $\geq$ 50% stenosis
 - iii.** Asymptomatic carotid stenosis $\geq$ 70%
 - iv.** History of carotid revascularization (surgical or catheter based)
 - c.** Documented PAD with $\geq$ one of the following:
 - i.** Ankle-brachial index $<$ 0.85 with or without claudication
 - ii.** History of aorto-iliac or peripheral arterial intervention (surgical or catheter based)
- 2** AND Atherogenic Dyslipidemia defined as:
 - a.** If off statins at entry, all of the following:
 - i.** LDL-C $\leq$ 180 mg/dL (4.7 mmol/L)
 - ii.** HDL-C $\leq$ 40 mg/dL (1.0 mmol/L) for men or $\leq$ 50 mg/dL (1.3 mmol/L) for women
 - iii.** Triglycerides 150 – 400 mg/dL (1.7 – 4.5 mmol/L)
 - b.** If on a statin with or without ezetimibe at entry, the equivalent lipid criteria satisfied*:
 - i.** Upper limit for LDL-C adjusted according to dose and published effect of particular statin
 - ii.** HDL-C $\leq$ 42 mg/dL (1.1 mmol/L) for men or $\leq$ 53 mg/dL (1.4 mmol/L) for women
 - iii.** Triglycerides 100 – 400 mg/dL (1.1 – 4.5 mmol/L)

Exclusion Criteria:

- 1** Hospitalization for acute coronary syndrome and discharge within 4 weeks prior to planned enrollment
- 2** Coronary Artery Bypass Graft (CABG) surgery within 1 year of planned enrollment (run-in phase), unless there has been a new, intercurrent acute coronary syndrome event or recurrent angina, associated with angiographic evidence of disease progression ($\geq$ 50% stenosis) in 1 or more native vessels or bypass grafts, regardless of whether subsequently treated with PCI/stenting
- 3** Planned percutaneous coronary intervention (PCI) within 4 weeks prior to planned enrollment
- 4** Stroke within 8 weeks prior to enrollment
- 5** Fasting glucose $>$ 180 mg/dL (10 mmol/L) or hemoglobin A1C $>$ 9.0%
- 6** Inability or refusal to use a glucometer for home glucose monitoring (diabetic patients)
- 7** CHD associated with unstable angina and symptoms refractory to maximal medical therapy

- 8 Patients with left main coronary disease $\geq 50\%$ and no prior CABG
- 9 Ejection fraction $< 30\%$
- 10 Cardiogenic shock, pulmonary edema or CHF unresponsive to standard medical therapy
- 11 Concomitant valvular heart disease likely to require surgery or adversely affect prognosis during follow-up
- 12 Congenital or primary cardiomyopathy likely to adversely affect prognosis during follow-up
- 13 Resuscitated out-of-hospital sudden death or symptomatic sustained or non-sustained ventricular tachycardia without an implantable cardioverter-defibrillator (ICD)
- 14 Significant systemic hypertension (blood pressure $> 200/100$ mmHg) unresponsive to medical therapy
- 15 Active peptic ulcer disease
- 16 AST or ALT > 2 times upper limit of normal or active liver disease
- 17 Recent history of acute gout. (For patients with baseline uric acid > 7.0 mg/dL [415 $\mu\text{mol/L}$], treatment with allopurinol is recommended but not mandated)
- 18 Chronic renal insufficiency with creatinine ≥ 2.5 mg/dL (220 $\mu\text{mol/L}$)
- 19 Patients who cannot discontinue the following excluded concomitant medications:
 - Drugs with a high probability of increasing the risk for hepatotoxicity or myopathy, such as those predominantly metabolized by cytochrome P450 system 3A4, including, but not limited to: cyclosporine, itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, verapamil, amiodarone
 - Lipid-lowering drugs (other than the investigational drugs), such as statins, bile-acid sequestrants, fish oils, cholesterol absorption inhibitors, fibrates
 - High-dose, antioxidant vitamins (vitamins C, E, or beta-carotene)
- 20 Pregnant (or likely to become pregnant) women or pre-menopausal women not using adequate contraception
- 21 Significant co-morbidity likely to cause death in the 3–5 year follow-up
- 22 Patients with AIDS/active HIV infection, due to potential confounding drug interactions
- 23 Significant active history of substance abuse within 5 years
- 24 Unwillingness/inability to give informed consent or follow study protocol
- 25 Current participation in another clinical study or trial that involves a study drug or intervention
- 26 Unwillingness of patient's physician to allow participation in the study

* Except for statin and/or ezetimibe, all other drugs affecting lipid levels, such as fibrates, niacin, bile acid sequestrants, fish oils were washed out for ≥ 4 weeks prior to the baseline.