Efficacy and Safety of *Ezetimibe* Added to *Atorvastatin* Versus *Atorvastatin* Uptitration or Switching to *Rosuvastatin* in Patients With Primary Hypercholesterolemia

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Hypercholesterolemic patients (n = 1,547) at high atherosclerotic cardiovascular disease risk with low-density lipoprotein cholesterol (LDL-C) levels ≥100 and ≤160 mg/dl while treated with atorvastatin 10 mg/day entered a multicenter, randomized, double-blind, active-controlled, clinical trial using two 6-week study periods. Period I compared the efficacy/safety of (1) adding ezetimibe 10 mg (ezetimibe) to stable atorvastatin 10 mg, (2) doubling atorvastatin to 20 mg, or (3) switching to rosuvastatin 10 mg. Subjects in the latter 2 groups who persisted with elevated LDL-C levels (≥100 and ≤160 mg/dl) after period I, entered period II; subjects on atorvastatin 20 mg had ezetimibe added to their atorvastatin 20 mg, or uptitrated their atorvastatin to 40 mg; subjects on rosuvastatin 10 mg switched to atorvastatin 20 mg plus ezetimibe or uptitrated their rosuvastatin to 20 mg. Some subjects on atorvastatin 10 mg plus ezetimibe continued the same treatment into period II. At the end of period I, ezetimibe plus atorvastatin 10 mg reduced LDL-C significantly more than atorvastatin 20 mg or rosuvastatin 10 mg (22.2% vs 9.5% or 13.0%, respectively, p <0.001). At the end of period II, ezetimibe plus atorvastatin 20 mg reduced LDL-C significantly more than atorvastatin 40 mg (17.4% vs 6.9%, p <0.001); switching from rosuvastatin 10 mg to ezetimibe plus atorvastatin 20 mg reduced LDL-C significantly more than uptitrating to rosuvastatin 20 mg (17.1% vs 7.5%, p <0.001). Relative to comparative treatments, ezetimibe added to atorvastatin 10 mg (period I) or atorvastatin 20 mg (period II) produced significantly greater percent attainment of LDL-C targets <100 or <70 mg/dl, and significantly greater percent reductions in total cholesterol, non−high-density lipoprotein cholesterol, most lipid and lipoprotein ratios, and apolipoprotein B (except ezetimibe plus atorvastatin 20 vs atorvastatin 40 mg). Reports of adverse experiences were generally similar among groups. In conclusion, treatment of hypercholesterolemic subjects at high cardiovascular risk with ezetimibe added to atorvastatin 10 or 20 mg produced significantly greater improvements in key lipid parameters and significantly greater attainment of LDL-C treatment targets than doubling atorvastatin or switching to (or doubling) rosuvastatin at the compared doses. **(Am J Cardiol 2013;112:1885−1895)**

Few studies have used treat-to-target designs that compare sequential "real-life" treatment options in lipid management among the most challenging patients, including those at high cardiovascular disease (CVD) risk with intensive low-density lipoprotein cholesterol (LDL-C) treatment targets. This 2-period study (each 6 weeks) examined patients at high CVD risk who did not achieve LDL-C targets while treated with a commonly prescribed statin at a commonly used dose (atorvastatin 10 mg/day). The primary objective of period I was to compare the LDL-C-lowering efficacy of ezetimibe 10 mg add-on to atorvastatin 10 mg versus doubling atorvastatin to 20 mg or switching to rosuvastatin 10 mg. The main objective of period II was to examine subjects who did not achieve an LDL-C target of <100 mg/dl after period I, compare the LDL-C-lowering efficacy of adding ezetimibe 10 mg to atorvastatin 20 mg versus doubling the atorvastatin dose from 20 mg (period I) to 40 mg, and compare switching from rosuvastatin 10 mg (period I) to ezetimibe 10 mg plus atorvastatin 20 mg versus doubling rosuvastatin to 20 mg. Finally, this study evaluated these sequential treatment options with regard to achievement of LDL-C treatment targets of <100 or <70 mg/dl, consistent with National

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This study (MK653C in High Cardiovascular Risk Patients with High Cholesterol) is registered at ClinicalTrials.gov (NCT01154036).

See page 1894 for disclosure information.

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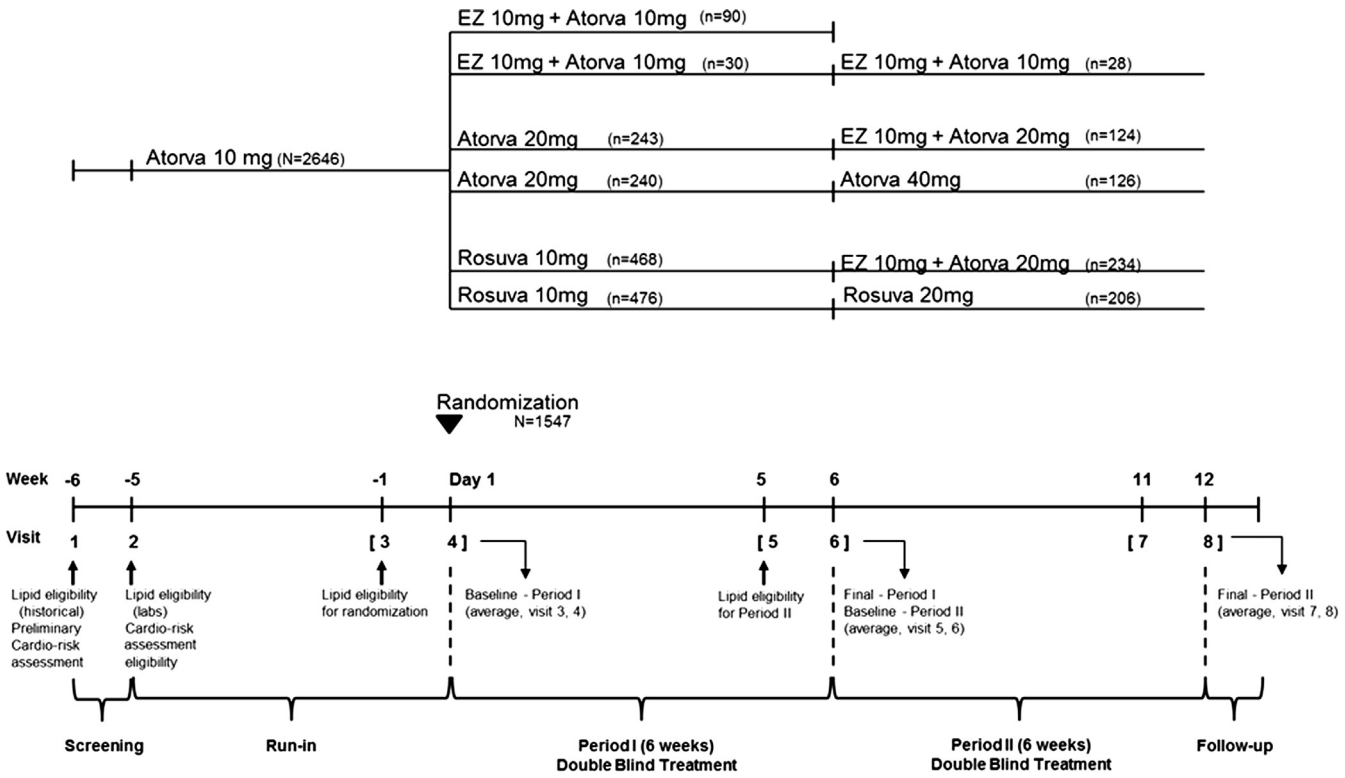

Figure 1. Study design. Atorva = atorvastatin; EZ = ezetimibe; Rosuva = rosuvastatin.

Cholesterol Education Program, Adult Treatment Panel III and European Society of Cardiology/European Atherosclerosis Society guidelines.[1,2]

Methods

This clinical trial entitled A Randomized, Double-Blind, Active-Controlled, Multicenter Study of Patients with **P**rimary Hypercholesterolemia and High Cardiovascular Risk Who Are Not Adequately Controlled with **A**torvastatin 10 mg: A **C**omparison of the Efficacy and Safety of Switching to Coadministration **E**zetimibe and Atorvastatin Versus Doubling the Dose of Atorvastatin or Switching to Rosuvastatin (PACE), was conducted from September 29, 2010 to October 17, 2012 (study MK653C-162, *http://clinicaltrials.gov*, identifier NCT01154036) and included subjects evaluated from 296 research sites across 29 countries (Argentina [18], Belgium [2], Bulgaria [11], Canada [15], Chile [7], Columbia [5], Croatia [4], Czech Republic [19], Denmark [5], Estonia [4], Finland [5], France [7], Germany [9], Hungary [13], Israel [14], Italy [8], Lithuania [8], the Netherlands [4], Norway [4], Poland [14], Portugal [4], Romania [18], Slovakia [12], Slovenia [3], Spain [11], Sweden [6], Turkey [8], the United Kingdom [12], and the United States [46]). The study was conducted in accordance with principles of the ICH Good Clinical Practice and all local and/or national regulations and directives. The appropriate institutional review boards approved the protocol, and all subjects documented their agreement to participate by written informed consent.

Subjects included in the present study were men and women of nonchildbearing potential and aged $\geq$18 and $<$80 years with primary hypercholesterolemia. Subjects were required to be at high CVD risk and meet prespecified lipid entry criteria. The high CVD risk study entry criteria included subjects without CVD who had type 2 diabetes mellitus or $\geq$2 CVD risk factors and a 10-year risk for coronary heart disease $>$20% (as determined by the Framingham risk calculation) or subjects with known CVD, including patients with established coronary and other atherosclerotic vascular diseases.[2–4] The lipid study entry criteria included subjects naive to lipid-lowering therapy (never treated or no therapy for $\geq$6 weeks before the prescreen visit) with an LDL-C level in the predetermined range of 166 to 190 mg/dl or subjects on a stable dose of statin, ezetimibe, or statin plus ezetimibe having LDL-C-lowering efficacy equivalent to or less than atorvastatin 10 mg and with historic lipid values within a range that might reasonably meet randomization lipid criteria (described later).

Main exclusion criteria included alanine aminotransferase or aspartate aminotransferase levels $>2\times$ the upper limit of normal (ULN); creatine kinase $>3\times$ the ULN; a history of significant myopathy or rhabdomyolysis with any statin or ezetimibe; hypersensitivity or intolerance to ezetimibe, atorvastatin, rosuvastatin, or any component of these medications; congestive heart failure (New York Heart Association class III or IV); previous myocardial infarction, coronary artery bypass surgery, angioplasty, or acute coronary syndrome within 3 months before screening; uncontrolled cardiac arrhythmias or recent significant changes on an electrocardiogram within 6 months before screening; homozygous familial hypercholesterolemia or LDL-C apheresis; partial ileal bypass, gastric bypass, or other significant intestinal malabsorption; uncontrolled hypertension; poorly controlled type 1 or 2 diabetes