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On-Treatment Non–High-Density Lipoprotein Cholesterol, Apolipoprotein B, Triglycerides, and Lipid Ratios in Relation to Residual Vascular Risk After Treatment With Potent Statin Therapy

JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin)

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Objectives The goal of this study was to determine whether residual risk after high-dose statin therapy for primary prevention individuals with reduced levels of low-density lipoprotein cholesterol (LDL-C) is related to on-treatment apolipoprotein B, non–high-density lipoprotein cholesterol (non–HDL-C), triglycerides, or lipid ratios, and how they compare with on-treatment LDL-C.

Background Guidelines focus on LDL-C as the primary target of therapy, yet residual risk for cardiovascular disease (CVD) among statin-treated individuals remains high and not fully explained.

Methods Participants in the randomized placebo-controlled JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial were adults without diabetes or CVD, with baseline LDL-C levels <130 mg/dl, high-sensitivity C-reactive protein levels ≥2 mg/l, and triglyceride concentrations <500 mg/dl. Individuals allocated to receive rosuvastatin 20 mg daily with baseline and on-treatment lipids and lipoproteins were examined in relation to the primary endpoint of incident CVD (nonfatal myocardial infarction or stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death).

Results Using separate multivariate Cox models, statistically significant associations of a similar magnitude with residual risk of CVD were found for on-treatment LDL-C, non–HDL-C, apolipoprotein B, total cholesterol/HDL-C, LDL-C/HDL-C, and apolipoprotein B/A-I. The respective adjusted standardized hazard ratios (95% confidence intervals) for each of these measures were 1.31 (1.09 to 1.56), 1.25 (1.04 to 1.50), 1.27 (1.06 to 1.53), 1.22 (1.03 to 1.44), 1.29 (1.09 to 1.52), and 1.27 (1.09 to 1.49). The overall residual risk and the risk associated with these measures decreased among participants achieving on-treatment LDL-C ≤70 mg/dl, on-treatment non–HDL-C ≤100 mg/dl, or on-treatment apolipoprotein B ≤80 mg/dl. In contrast, on-treatment triglycerides showed no association with CVD.

Conclusions In this primary prevention trial of nondiabetic individuals with low LDL-C and elevated high-sensitivity C-reactive protein, on-treatment LDL-C was as valuable as non–HDL-C, apolipoprotein B, or ratios in predicting residual risk. (JUPITER—Crestor 20mg Versus Placebo in Prevention of Cardiovascular [CV] Events; NCT00239681) (J Am Coll Cardiol 2012;59:1521–8) © 2012 by the American College of Cardiology Foundation

Statins are the most widely used lipid-lowering agents and the standard of care for individuals with dyslipidemia or prior cardiovascular disease (CVD) or who are at high-risk for CVD (1,2). Current guidelines focus on reducing low-density lipoprotein cholesterol (LDL-C) as the primary target of therapy, tailoring the level of optimal LDL-C reduction to the individual's level of cardiovascular risk. Nonetheless, the risk among statin-treated individuals remains high and has been

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Abbreviations and Acronyms

CI = confidence interval

CVD = cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

hsCRP = high-sensitivity C-reactive protein

LDL-C = low-density lipoprotein cholesterol

termed "residual risk." The 5-year incidence rate of a major CVD event occurring among statin-treated patients in randomized clinical trials is 1 in 5 (22%) for individuals with prior CVD and 1 in 10 (10%) for individuals with no prior CVD (3,4).

Residual risk after statin treatment may be related to the on-treatment concentrations of lipids, apolipoproteins, or other biomarkers beyond LDL-C (5). In a recent analysis from the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, on-treatment concentrations of high-sensitivity C-reactive protein (hsCRP) were predictive of residual risk among primary prevention individuals treated with potent statin therapy (6), but on-treatment high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I were not (7). It is possible that other lipid or apolipoprotein measures, such as the LDL-C/HDL-C ratio or apolipoprotein B/A-I ratio, may provide better risk information than HDL-C or apolipoprotein A-I alone (8).

Furthermore, apolipoprotein B has been proposed as a therapeutic target for lipid lowering (9,10). Apolipoprotein B reflects the number of potentially atherogenic lipoprotein particles, because each very-low-density lipoprotein and LDL particle carries on its surface one apolipoprotein B molecule (11). On-treatment apolipoprotein B has been compared with LDL-C in asymptomatic individuals for the primary prevention of CVD among statin-treated individuals with low HDL-C in the AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) trial (12) and among patients with diabetes in the CARDS (Collaborative Atorvastatin Diabetes Study) trial (13). In AFCAPS/TexCAPS, on-treatment apolipoprotein B was a better predictor of events compared with LDL-C, but comparison with non–HDL-C was not reported (9,12). In contrast, among statin-treated patients in CARDS, none of the on-treatment lipids or apolipoproteins were statistically significantly associated with events (13).

Among patients with stable coronary disease treated with potent statin therapy, apolipoprotein B and non–HDL-C were comparable as predictors of residual risk (14). But it is uncertain if apolipoprotein B or non–HDL-C are better targets of therapy compared with LDL-C for the primary prevention of CVD among nondiabetic individuals with low LDL-C treated with potent statin therapy.

This analysis of the JUPITER trial cohort addressed, in a primary prevention setting of nondiabetic individuals with baseline low LDL-C but elevated hsCRP, whether residual risk after high-dose statin therapy was related to on-treatment levels of apolipoprotein B, non–HDL-C, trigylcerides, or lipid ratios, and how they compared with on-treatment LDL-C. A secondary goal was to explore residual risk associations of these measures among the subgroup of individuals who achieved very low cholesterol targets while undergoing statin therapy.

Methods

Study population. The JUPITER design has been previously published (15–17). Asymptomatic individuals (women age ≥60 years, men age ≥50 years) with no history of coronary disease, stroke, or diabetes and who had LDL-C levels <130 mg/dl, hsCRP levels ≥2.0 mg/l, and triglyceride concentrations <500 mg/dl were randomized. Those patients currently using hormone therapy or with previous or current use of lipid-lowering therapy or immunosuppressant agents were excluded. Family history of premature atherosclerosis was defined as coronary disease in a first-degree relative (men age <55 years or women age <65 years). Of the 8,901 individuals randomized to receive rosuvastatin therapy, individuals were included who had both baseline and on-treatment 1-year measures for all the lipid and lipoprotein variables examined, resulting in a sample size of 7,832.

Laboratory measurements. Measurements were performed in a central laboratory on blood samples collected after patient fasting of at least 8 h (18). Concentrations of apolipoproteins B and A-I were measured via immunonephelometry by using a Behring nephelometric assay (Marburg, Germany). An enzymatic procedure (cholesterol esterase) with a colorimetric endpoint was used to assess total cholesterol. Triglycerides were measured with an enzymatic hydrolysis procedure to obtain a colorimetric endpoint triglyceride value. HDL-C was measured in the resulting supernatant after heparin–manganese precipitation of apolipoprotein B–containing proteins. LDL-C concentrations were calculated by using the Friedewald equation when triglycerides were <400 mg/dl (19) and measured by ultracentrifugation when triglycerides were ≥400 mg/dl. A high-sensitivity assay (Behring) nephelometer was used for measurement of hsCRP.

Outcomes. The trial was expected to last approximately 5 years, but on March 30, 2008, the Independent Data and Safety Monitoring Board terminated the trial early upon determination that the accumulated evidence from the trial

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