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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

and Bristol-Myers Squibb; and has a consulting agreement with Merck. Dr. Boekholdt has served as a consultant to Pfizer. Dr. Nordestgaard has served as a consultant for AstraZeneca, Abbott, Merck & Co., and Pfizer. Dr. Kastelein is a recipient of the Lifetime Achievement Award (2010T082) of the Dutch Heart Foundation; and is a consultant for and has received research grants from AstraZeneca. Dr. Ridker received research support from AstraZeneca, Novartis, Roche, and Sanofi-Aventis, and nonfinancial research support from Amgen. Dr. Ridker is coinventor on patents held by Brigham and Women's Hospital related to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Siemens and AstraZeneca; has served as a research consultant to Schering-Plough, Sanofi/Aventis, Isis, Siemens, Abbott, Merck, and Vascular Biogenics; and has received research grants from AstraZeneca.

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and other sources constituted proof beyond a reasonable doubt that rosuvastatin was indicated for a specified group of participants (after 1.9 years of median follow-up; maximal follow-up of 5.0 years). Follow-up included structured interviews assessing outcomes. The primary endpoint of the JUPITER trial was a composite endpoint (CVD), defined as the combined endpoint of myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death. For this analysis, we also examined the expanded secondary endpoint of CVD or death. Myocardial infarction, stroke, and CVD death were confirmed according to standard criteria. Unstable angina was ischemic chest pain at rest or with minimal exertion occurring within the preceding 48 hours requiring hospitalization and the presence of objective evidence of ischemia. Arterial revascularization was coronary artery bypass graft surgery, bypass grafting of any peripheral artery or carotid artery, or the performance of at least one percutaneous transluminal intervention. All reported primary endpoints that occurred through March 30, 2008, were adjudicated by an independent endpoint committee blinded to randomized treatment assignment.

Statistical analyses. Statistical analyses were performed with SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina). Medians, 25th, and 75th percentiles were calculated for continuous variables. Statistical comparisons were made with the sign tests for comparing the change from baseline with on-treatment values.

Statistical tests for outcomes were performed according to intention-to-treat analyses. The exposure time was calculated as the time from randomization to occurrence of the primary endpoint or the date of death, last study visit, withdrawal, loss to follow-up, or March 30, 2008, whichever came first. Absolute event rates were calculated per 100 person-years. Cox proportional hazards models were used to calculate the hazard ratios and 95% confidence intervals (CIs). All regression analyses were adjusted for age, sex, smoking status, family history of premature atherosclerosis, body mass index, systolic blood pressure, and fasting glucose. Each lipid measure was examined in tertiles and as continuous variables (per 1 SD). P values for linear trends were obtained using the median value for each tertile. All p values were 2-tailed. The likelihood ratio chi-square statistic was also used to evaluate the significance of individual lipid measures.

We conducted 2 additional exploratory analyses to evaluate the following: 1) whether any measure of on-treatment lipids was significantly related to residual risk after controlling for on-treatment LDL-C; and 2) whether on-treatment lipid measures remained associated with risk among individuals who achieved clinically accepted guideline-recommended cutoff points for LDL-C (≤100 or ≤70 mg/dl), non–HDL-C (≤130 or ≤100 mg/dl), or apolipoprotein B (≤90 or ≤80 mg/dl).

Results

The baseline characteristics for individuals randomly allocated to receive rosuvastatin and who had on-treatment lipid and lipoprotein measurements available for analysis at baseline and 1 year were similar to the overall JUPITER study population (17,20). The JUPITER patients were selected to have an LDL-C <130 mg/dl and triglycerides <500 mg/dl, and hence the total cholesterol, LDL-C, and non–HDL-C were all low (respective median baseline concentrations of 186, 108, and 134 mg/dl, respectively). The apolipoprotein B levels were not low (median baseline concentration 109 mg/dl). Random allocation to the rosuvastatin group in the JUPITER trial decreased median on-treatment concentrations of total cholesterol, LDL-C, and non–HDL-C to a similar extent on a mass concentration scale (−50 mg/dl, −50 mg/dl, and −54 mg/dl, respectively) and reduced apolipoprotein B by 41 mg/dl (Table 1). There was greater proportional LDL-C lowering (46.2%)

Table 1 Lipids, Apolipoproteins, and Ratios Among 7,832 Rosuvastatin-Treated Individuals With Baseline and 1-Year Measures of All Lipid Variables Examined

Variables	Baseline	Year 1	Change	p Value
Lipids (mg/dl)				
TC	186 (169, 200)	133 (116, 155)	−50 (−67, −27)	<0.0001
LDL-C	108 (94, 119)	55 (44, 71)	−50 (−63, −29)	<0.0001
Non–HDL-C	134 (118, 147)	76 (64, 96)	−54 (−70, −31)	<0.0001
Triglycerides	118 (85, 169)	99 (74, 137)	−17 (−48, 5)	<0.0001
HDL-C	49 (40, 60)	52 (43, 64)	3 (−2, 8)	<0.0001
Apolipoproteins (mg/dl)				
Apolipoprotein A-I	163 (144, 185)	165 (145, 188)	2 (−12, 16)	<0.0001
Apolipoprotein B	109 (95, 122)	66 (56, 81)	−41 (−54, −24)	<0.0001
Ratios				
TC/HDL-C	3.67 (3.06, 4.41)	2.50 (2.10, 3.05)	−1.11 (−1.65, −0.61)	<0.0001
LDL-C/HDL-C	2.14 (1.69, 2.64)	1.05 (0.78,1.46)	−1.02 (−1.44, −0.57)	<0.0001
Apolipoprotein B/A-I	0.66 (0.55, 0.80)	0.40 (0.32,0.52)	−0.25 (−0.35, −0.14)	<0.0001

Values are median (25th, 75th percentile).
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

compared with non–HDL-C (40.3%) or apolipoprotein B (37.6%) with rosuvastatin therapy. Triglycerides were also reduced but to a lesser extent.

The primary endpoint was reduced with rosuvastatin by 44% ($p < 0.001$) (17). Table 2 displays CVD incidence rates and associations for each of the on-treatment lipids, apolipoproteins, and ratios (examined in tertiles) with incident events obtained from separate Cox regression models that adjusted for nonlipid risk factors. Generally similar and significant associations were obtained for on-treatment concentrations of LDL-C, non–HDL-C, and apolipoprotein B with CVD. By contrast, on-treatment triglycerides, HDL-C, and apolipoprotein A-I showed no associations with CVD risk. Similar results were noted for the expanded secondary endpoint of CVD or death, except that apolipoprotein A-I now became statistically significant and the apolipoprotein B/A-I ratio now had a greater magnitude of association (2.12 [95% CI: 1.44 to 3.12]).

When lipids, apolipoproteins, and ratios were examined as standardized continuous variables, results were generally similar for LDL-C, non–HDL-C, apolipoprotein B, and the ratios (Table 3), as were the goodness-of-fit likelihood ratio chi-square statistics that added each of these variables to a model with only nonlipid risk factors. Specifically, for on-treatment LDL-C, non–HDL-C, apolipoprotein B, and the ratios (total cholesterol/HDL-C, LDL-C/HDL-C, and apolipoprotein B/A-I), the respective adjusted standardized hazard ratios (95% CIs) 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).

Two exploratory analyses were also conducted. First, we assessed whether any of the measures (non–HDL-C, apolipoprotein B, total cholesterol/HDL-C, LDL-C/HDL-C, or apolipoprotein B/A-I) was significantly related to residual risk after controlling for on-treatment LDL-C. In models that included on-treatment LDL-C, none of the other lipid measures remained statistically significant.

Subsequently, we compared associations with residual risk among the subgroups of individuals who achieved the clinical recommendations for LDL-C targets or the alternative recommended targets for non–HDL-C or apolipoprotein B. As shown in Table 4, among the subgroups of individuals achieving the lower clinical targets (LDL-C ≤70 mg/dl, non–HDL-C ≤100 mg/dl, or apolipoprotein B ≤80 mg/dl), the magnitude of residual risk was small, and the residual risk associated with these measures became attenuated and mostly no longer statistically significant. Apolipoprotein B/A-I retained its association with the expanded secondary endpoint of CVD or death, but this finding was also attenuated in the subgroup of individuals who achieved apolipoprotein B ≤80 mg/dl on therapy.

Discussion

In the JUPITER trial of primary prevention nondiabetic individuals with low LDL-C and high hsCRP, measuring on-treatment LDL-C was as valuable as measuring non–HDL-C or apolipoprotein B, or the ratios (total cholesterol/HDL-C, LDL-C/HDL-C, and apolipoprotein B/A-I) in relation to residual risk of CVD. The magnitude of the overall residual risk and the risk associated with these measures decreased after achieving on-treatment concentrations of LDL-C ≤70 mg/dl, non–HDL-C ≤100 mg/dl, or apolipoprotein B ≤80 mg/dl. Furthermore, the current findings do not support the hypothesis that on-treatment triglycerides are related to residual risk among nondiabetic primary prevention individuals with baseline triglyceride levels <500 mg/dl and elevated hsCRP who are treated with potent statin therapy; however, median on-treatment triglycerides was low (118 mg/dl).

Optimal targets of statin therapy. It has been a matter of controversy whether measuring non–HDL-C or apolipoprotein B concentrations are useful among primary prevention individuals treated with statin therapy, and whether either measure—or both—should be used as an alternative or in addition to LDL-C. Among primary prevention populations, 2 prior trials (AFCAPS/TexCAPS and CARDS) evaluated this question. On-treatment apolipoprotein B was better as a predictor of events compared with LDL-C in asymptomatic individuals with low HDL-C in AFCAPS/TexCAPS, although non–HDL-C was not evaluated in that study (12). Among diabetic patients in CARDS, none of the on-treatment lipids or apolipoproteins were statistically significantly associated with risk in the statin-allocated arm (although LDL-C and the LDL-C/HDL-C ratio were borderline significant) (9,13). The present JUPITER analysis, which was conducted among primary prevention individuals who were nondiabetic and without dyslipidemia, adds to the prior literature in finding that measuring LDL-C alone was as valuable as measuring non–HDL-C, apolipoprotein B, or the ratios (total cholesterol/HDL-C, LDL-C/HDL-C, and apolipoprotein B/A-I) in relation to residual risk.

Data from secondary prevention trials that evaluated the predictive value of LDL-C, non–HDL-C, and apolipoprotein B in relation to recurrent events also have been mixed and inconclusive (14,21,22). In the 4S (Scandinavian Simvastatin Survival Study) study (21), on-treatment LDL-C was comparable with non–HDL-C or the total cholesterol/HDL-C ratio, whereas apolipoprotein B had weaker association with recurrent events. In the LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) Trial (22), on-treatment apolipoprotein B had a stronger association than LDL-C, although non–HDL-C was not reported. In the combined analysis from the TNT (Treating to New Targets) trial and IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) trials, which compared potent versus less intensive statin therapy for the secondary prevention of cardiovascular disease (14), non–HDL-C and apolipoprotein B were comparable in relation to risk. Compared with TNT/IDEAL, the JUPITER on-statin arm achieved lower levels of lipids and

Table 2 Risk of First CVD Event or Death for On-Treatment Lipids, Apolipoproteins, and Ratios According to Tertiles

Variable	Tertile 1	Tertile 2	Tertile 3	p Value for linear trend
Lipids				
TC (mg/dl)	<123	123–145	>145	
No. CVD/no. CVD or death/total N	37/60/2,726	22/36/2,498	42/69/2,608	
CVD incidence rate	0.60	0.40	0.78	
CVD $HR_{adjusted}$ (95% CI)	1.00	0.75 (0.44–1.28)	1.53 (0.96–2.45)	0.04
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.72 (0.47–1.09)	1.47 (1.02–2.11)	0.02
LDL-C (mg/dl)	<48	48–64	>64	
No. CVD/no. CVD or death/total N	30/53/2,628	23/40/2,618	48/72/2,586	
CVD incidence rate	0.51	0.39	0.91	
CVD $HR_{adjusted}$ (95% CI)	1.00	0.83 (0.48–1.43)	1.99 (1.25–3.19)	0.0007
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.78 (0.52–1.18)	1.63 (1.13–2.34)	0.002
Non–HDL-C (mg/dl)	<69	69–88	>88	
No. CVD/no. CVD or death/total N	31/52/2,713	31/46/2,595	39/67/2,524	
CVD incidence rate	0.52	0.53	0.75	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.11 (0.67–1.84)	1.64 (1.01–2.66)	0.03
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.98 (0.66–1.46)	1.72 (1.19–2.48)	0.001
Triglycerides (mg/dl)	<83	83–121	>121	
No. CVD/no. CVD or death/total N	35/53/2,663	30/52/2,581	36/60/2,588	
CVD incidence rate	0.61	0.54	0.62	
CVD $HR_{adjusted}$ (95% CI)	1.00	0.94 (0.58–1.55)	1.06 (0.65–1.73)	0.76
CVD/death $HR_{adjusted}$ (95% CI)	1.00	1.12 (0.76–1.66)	1.31 (0.89–1.93)	0.16
HDL-C (mg/dl)	<47	47–59	>59	
No. CVD/no. CVD or death/total N	41/67/2,770	27/48/2,522	33/50/2,540	
CVD incidence rate	0.66	0.50	0.60	
CVD $HR_{adjusted}$ (95% CI)	1.00	0.80 (0.48–1.33)	1.04 (0.63–1.71)	0.84
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.85 (0.56–1.24)	0.83 (0.56–1.23)	0.36
Apolipoproteins				
Apolipoprotein A-I (mg/dl)	<152	152–179	>179	
No. CVD/no. CVD or death/total N	36/64/2,612	40/62/2,649	25/39/2,571	
CVD incidence rate	0.64	0.69	0.44	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.06 (0.66–1.68)	0.76 (0.44–1.30)	0.33
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.92 (0.64–1.31)	0.59 (0.39–0.90)	0.01
Apolipoprotein B (mg/dl)	<60	60–75	>75	
No. CVD/no. CVD or death/total N	29/48/2,660	30/46/2,628	42/71/2,544	
CVD incidence rate	0.50	0.50	0.78	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.01 (0.60–1.68)	1.60 (0.98–2.59)	0.04
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.91 (0.61–1.37)	1.64 (1.13–2.38)	0.003
Ratios				
TC/HDL-C	<2.23	2.23–2.83	>2.83	
No. CVD/no. CVD or death/total N	31/48/2,613	32/49/2,613	38/68/2,606	
CVD incidence rate	0.54	0.55	0.68	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.04 (0.63–1.73)	1.27 (0.77–2.10)	0.31
CVD/death $HR_{adjusted}$ (95% CI)	1.00	1.10 (0.73–1.65)	1.63 (1.11–2.39)	0.008
LDL-C/HDL-C	<0.87	0.87–1.29	>1.29	
No. CVD/no. CVD or death/total N	25/45/2,611	33/54/2,611	43/66/2,610	
CVD incidence rate	0.43	0.56	0.79	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.20 (0.70–2.03)	1.82 (1.10–3.02)	0.01
CVD/death $HR_{adjusted}$ (95% CI)	1.00	1.15 (0.77–1.73)	1.64 (1.11–2.42)	0.008
Apolipoprotein B/A-I	<0.35	0.35–0.47	>0.47	
No. CVD/no. CVD or death/total N	25/42/2,611	29/42/2,611	47/81/2,610	
CVD incidence rate	0.43	0.49	0.86	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.15 (0.66–1.98)	1.96 (1.18–3.25)	0.004
CVD/death $HR_{adjusted}$ (95% CI)	1.00	1.02 (0.66–1.57)	2.12 (1.44–3.12)	<0.0001

Incidence rates are per 100 person-years. HRs were adjusted for sex, age, smoking status, family history of premature atherosclerosis, body mass index, systolic blood pressure, and fasting glucose.

CVD = cardiovascular disease; HR = hazard ratio; other abbreviations as in Table 1.

Table 3 Risk of First CVD Event or Death for Standardized On-Treatment Lipids, Apolipoproteins, and Ratios

Variable	SD	Standardized $HR_{adjusted}$ (95% CI)	p Value	Likelihood Ratio Chi-Square* (p Value)
Lipids				
TC (mg/dl)	33.1			
CVD		1.19 (0.98–1.45)	0.08	2.84 (0.09)
CVD/death		1.21 (1.04–1.41)	0.02	5.45 (0.02)
LDL-C (mg/dl)	27.4			
CVD		1.31 (1.09–1.56)	0.004	7.64 (0.006)
CVD/death		1.29 (1.12–1.49)	0.0004	11.44 (0.0007)
Non–HDL-C (mg/dl)	30.8			
CVD		1.25 (1.04–1.50)	0.02	5.18 (0.02)
CVD/death		1.28 (1.11–1.47)	0.0005	10.69 (0.001)
Triglycerides (mg/dl)	62.7			
CVD		0.93 (0.74–1.17)	0.56	0.36 (0.55)
CVD/death		1.04 (0.90–1.21)	0.57	0.30 (0.58)
HDL-C (mg/dl)	16.3			
CVD		0.89 (0.70–1.12)	0.29	1.15 (0.28)
CVD/death		0.86 (0.72–1.03)	0.10	2.90 (0.09)
Apolipoproteins				
Apolipoprotein A-I (mg/dl)	32.4			
CVD		0.81 (0.65–1.01)	0.06	3.50 (0.06)
CVD/death		0.77 (0.65–0.92)	0.003	9.15 (0.002)
Apolipoprotein B (mg/dl)	22.1			
CVD		1.27 (1.06–1.53)	0.009	6.13 (0.01)
CVD/death		1.30 (1.13–1.49)	0.0003	12.05 (0.0005)
Ratios				
TC/HDL-C	0.86			
CVD		1.22 (1.03–1.44)	0.02	4.59 (0.03)
CVD/death		1.24 (1.09–1.41)	0.0009	9.41 (0.002)
LDL-C/HDL-C	0.65			
CVD		1.29 (1.09–1.52)	0.002	7.85 (0.005)
CVD/death		1.29 (1.14–1.46)	<0.0001	13.11 (0.0003)
Apolipoprotein B/A-I	0.17			
CVD		1.27 (1.09–1.49)	0.003	7.37 (0.007)
CVD/death		1.30 (1.16–1.46)	<0.0001	15.85 (<0.0001)

Standardized HRs were adjusted for sex, age, smoking status, family history of premature atherosclerosis, body mass index, systolic blood pressure, and fasting glucose. *Likelihood ratio chi-square and p values obtained from the Cox proportional hazards regression comparing models that added the lipid variable to a referent model (nonlipid covariates only). A higher chi-square value indicates a better model fit.

Abbreviations as in Tables 1 and 2.

apolipoproteins but had magnitude of associations with CVD that were generally similar to TNT/IDEAL (Online Table 1). Among acute coronary syndrome patients in the PROVE IT–TIMI 22 trial, on-treatment apolipoprotein B was equivalent to LDL-C or non–HDL-C (23).

An unresolved important question relates to the optimal treatment targets of statin therapy for primary prevention. Subgroup analyses from the current study suggest that the magnitude of overall residual risk is small, and that most of the associations with CVD were attenuated below levels of LDL-C, non–HDL-C, or apolipoprotein B that corresponded to established targets previously derived from secondary prevention trials (LDL-C ≤70, non–HDL-C ≤100 mg/dl, or apolipoprotein B ≤80 mg/dl). The current data also do not support obtaining more than one of these measures in addition to LDL-C for assessing residual risk. These results, however, should be considered exploratory because they were derived from subgroup analysis and remain to be tested in a prospective clinical trial in the primary prevention setting.

Triglycerides and residual risk. Another area of recent controversy has been whether triglycerides contribute to risk among statin-treated individuals compared with untreated individuals. The lack of association for on-treatment triglycerides with residual risk in JUPITER is supported by most previous statin trials, which also found no significant associations for on-treatment triglycerides (12,21,24,25), as well as data from a meta-analysis (26). Importantly, however, in the current JUPITER trial as well as in former statin trials, those with the highest triglyceride levels were excluded, and most included individuals had relatively low on-treatment triglyceride levels. Therefore, we cannot exclude the possibility that higher on-treatment triglycerides may be important for predicting residual risk.

Table 4 Risk of First CVD Event or Death for Standardized On-Treatment Lipids, Apolipoproteins, and Ratios According to Subgroups

Variable	CVD		CVD/Death	
	Standardized $HR_{adjusted}$ (95% CI)	p Value	Standardized $HR_{adjusted}$ (95% CI)	p Value
LDL-C ≤100 mg/dl (no. CVD/no. CVD or death/total N: 86/140/6,970)				
LDL-C	1.70 (1.22–2.36)	0.002	1.47 (1.13–1.91)	0.004
Non–HDL-C	1.31 (0.97–1.79)	0.08	1.34 (1.05–1.71)	0.02
Apolipoprotein B	1.40 (1.05–1.86)	0.02	1.35 (1.08–1.70)	0.009
TC/HD-C	1.15 (0.90–1.48)	0.26	1.18 (0.97–1.42)	0.10
LDL-C/HDL-C	1.43 (1.09–1.88)	0.01	1.34 (1.07–1.67)	0.01
Apolipoprotein B/A-I	1.31 (1.07–1.61)	0.009	1.30 (1.12–1.51)	0.001
LDL-C ≤70 mg/dl (no. CVD/no. CVD or death/total N: 61/103/5,793)				
LDL-C	0.96 (0.56–1.73)	0.96	0.88 (0.58–1.36)	0.57
Non–HDL-C	0.66 (0.39–1.12)	0.13	0.85 (0.57–1.28)	0.44
Apolipoprotein B	0.88 (0.56–1.37)	0.56	1.00 (0.71–1.40)	0.96
TC/HDL-C	0.92 (0.61–1.37)	0.67	1.05 (0.79–1.40)	0.73
LDL-C/HDL-C	1.17 (0.72–1.89)	0.52	1.15 (0.80–1.66)	0.46
Apolipoprotein B/A-I	1.18 (0.86–1.62)	0.31	1.24 (1.01–1.53)	0.04
Non–HDL-C ≤130 mg/dl (no. CVD/no. CVD or death/total N: 87/141/7,035)				
LDL-C	1.58 (1.18–2.13)	0.002	1.37 (1.08–1.74)	0.01
Non–HDL-C	1.36 (0.99–1.88)	0.06	1.36 (1.06–1.76)	0.02
Apolipoprotein B	1.40 (1.04–1.87)	0.03	1.35 (1.07–1.70)	0.01
TC/HDL-C	1.15 (0.87–1.53)	0.33	1.20 (0.97–1.49)	0.10
LDL-C/HDL-C	1.41 (1.07–1.86)	0.02	1.32 (1.05–1.65)	0.02
Apolipoprotein B/A-I	1.29 (1.05–1.60)	0.02	1.29 (1.11–1.51)	0.001
Non–HDL-C ≤100 mg/dl (no. CVD/no. CVD or death/total N: 70/114/6,108)				
LDL-C	1.26 (0.79–2.01)	0.33	1.11 (0.77–1.59)	0.58
Non–HDL-C	0.98 (0.59–1.62)	0.93	1.05 (0.71–1.57)	0.79
Apolipoprotein B	1.14 (0.74–1.73)	0.56	1.10 (0.79–1.53)	0.58
TC/HDL-C	1.05 (0.71–1.56)	0.79	1.12 (0.83–1.50)	0.45
LDL/HDL-C	1.29 (0.85–1.97)	0.24	1.22 (0.88–1.70)	0.24
Apolipoprotein B/A-I	1.23 (0.93–1.63)	0.14	1.26 (1.03–1.52)	0.02
Apolipoprotein B ≤90 mg/dl (no. CVD/no. CVD or death/total N: 76/125/6,511)				
LDL-C	1.44 (0.98–2.11)	0.06	1.25 (0.92–1.69)	0.15
Non–HDL-C	1.12 (0.74–1.69)	0.60	1.23 (0.89–1.68)	0.21
Apolipoprotein B	1.29 (0.86–1.91)	0.22	1.30 (0.96–1.78)	0.09
TC/HDL-C	1.03 (0.73–1.47)	0.86	1.14 (0.88–1.48)	0.34
LDL-C/HDL-C	1.31 (0.90–1.89)	0.16	1.24 (0.93–1.66)	0.14
Apolipoprotein B/A-I	1.23 (0.94–1.60)	0.12	1.28 (1.06–1.53)	0.009
Apolipoprotein B ≤80 mg/dl (no. CVD/no. CVD or death/total N: 66/107/5,798)				
LDL-C	1.38 (0.86–2.23)	0.18	1.15 (0.80–1.67)	0.45
Non–HDL-C	1.05 (0.62–1.76)	0.86	1.08 (0.72–1.62)	0.72
Apolipoprotein B	1.27 (0.77–2.09)	0.36	1.18 (0.80–1.75)	0.41
Total/HDL-C	0.96 (0.62–1.47)	0.84	1.05 (0.76–1.44)	0.78
LDL-C/HDL-C	1.20 (0.76–1.92)	0.44	1.15 (0.80–1.65)	0.45
Apolipoprotein B/A–I	1.18 (0.85–1.63)	0.32	1.22 (0.98–1.51)	0.08

Standardized HRs were adjusted for sex, age, smoking status, family history of premature atherosclerosis, body mass index, systolic blood pressure, and fasting glucose.
Abbreviations as in Tables 1 and 2.

Study limitations. The current study has potential limitations. Median duration of follow-up in JUPITER was 1.9 years (maximum 5.0 years) due to early termination of the trial for benefit, and data for events occurring long-term could not be assessed. JUPITER excluded individuals with known CVD, diabetes, or high triglyceride levels or who did not meet entry criteria for LDL-C and hsCRP, and it is unclear if our results would be applicable to other individuals from primary or secondary prevention who were excluded from the trial. JUPITER was a randomized clinical trial that tested a fixed dose of a potent statin and did not test the efficacy of different doses of statins nor did it test a strategy based on achieving different lipid targets. Finally, although standardized regression coefficients provide some ability to compare effect sizes across biomarkers, they are dependent on the study-specific variability of these biomarkers, which is influenced by the trial eligibility criteria.

Study strengths. Strengths of the current study are the large number of individuals with baseline and on-treatment

lipid and lipoprotein measures as well as detailed information on cardiovascular risk factors. Finally, few previous studies have examined individuals from primary prevention who had baseline low or average LDL-C levels and who attained even lower LDL-C concentrations with potent therapy.

Conclusions

In this large randomized, primary prevention trial of nondiabetic individuals with elevated hsCRP and low LDL-C, on-treatment LDL-C was as valuable as non–HDL-C, apolipoprotein B, and several ratios in the prediction of residual risk. Among participants achieving on-treatment concentrations of LDL-C ≤70 mg/dl, non–HDL-C ≤100 mg/dl, or apolipoprotein B ≤80 mg/dl, the overall magnitude of residual risk was small, and the risk associated with these measures decreased and was no longer statistically significant. Finally, the current study does not support the routine measurement of triglycerides among nondiabetic individuals without significant dyslipidemia who are treated with potent statin therapy.

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Key Words: apolipoproteins ■ lipids ■ lipoproteins ■ primary prevention ■ trials.

APPENDIX

For a supplementary table of study data, please see the online version of this article.