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Cardiovascular Event Reduction and Adverse Events Among Subjects Attaining Low-Density Lipoprotein Cholesterol <50 mg/dl With Rosuvastatin

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

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Objectives The purpose of this study was to assess the impact on cardiovascular and adverse events of attaining low-density lipoprotein cholesterol (LDL-C) levels <50 mg/dl with rosuvastatin in apparently healthy adults in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial.

Background The safety and magnitude of cardiovascular risk reduction conferred by treatment to LDL-C levels below current recommended targets remain uncertain.

Methods A cohort of 17,802 apparently healthy men and women with high-sensitivity C-reactive protein ≥2 mg/l and LDL-C <130 mg/dl were randomly allocated to rosuvastatin 20 mg daily or placebo, and followed up for all-cause mortality, major cardiovascular events, and adverse events. In a post-hoc analysis, participants allocated to rosuvastatin were categorized as to whether or not they had a follow-up LDL-C level <50 mg/dl.

Results During a median follow-up of 2 years (range up to 5 years), rates of the primary trial endpoint were 1.18, 0.86, and 0.44 per 100 person-years in the placebo group (n = 8,150) and rosuvastatin groups without LDL-C <50 mg/dl (n = 4,000) or with LDL-C <50 mg/dl (n = 4,154), respectively (fully-adjusted hazard ratio: 0.76; 95% confidence interval: 0.57 to 1.00 for subjects with no LDL-C <50 mg/dl vs. placebo and 0.35, 95% confidence interval: 0.25 to 0.49 for subjects attaining LDL-C <50 mg/dl; p for trend <0.0001). For all-cause mortality, corresponding event rates were 0.67, 0.65, and 0.39 (p for trend = 0.004). Rates of myalgia, muscle weakness, neuropsychiatric conditions, cancer, and diabetes mellitus were not significantly different among rosuvastatin-allocated participants with and without LDL-C <50 mg/dl.

Conclusions Among adults with LDL-C <130 mg/dl and high-sensitivity C-reactive protein ≥2 mg/l, rosuvastatin-allocated participants attaining LDL-C <50 mg/dl had a lower risk of cardiovascular events without a systematic increase in reported adverse events. (J Am Coll Cardiol 2011;57:1666–75) © 2011 by the American College of Cardiology Foundation

Current guidelines suggest reducing low-density lipoprotein cholesterol (LDL-C) to <70 mg/dl in high-risk patients (1), and clinical trials have found the lowest cardiovascular event rates among patients with very low LDL-C (2–5). Although statin therapy is highly effective at lowering LDL-C and reducing vascular risk (2,6,7), concern persists that very low levels of cholesterol after aggressive use of statins may be associated with adverse clinical effects (8). For example, inadequate cholesterol levels have been proposed to affect serotonin and steroid hormone production, vitamin transport, and cell membrane function, with putative health consequences ranging from neuropsychiatric conditions to cancer (9–13). Conversely, paleolithic ancestors consuming a hunter-gatherer diet appeared largely free of degenerative cardiovascular disease (14,15), and persons with genetic mutations that affect LDL-C levels, such as PCSK9, have very low LDL-C levels during life, low vascular risk, and no apparent adverse effects (16).

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We examined the safety and magnitude of cardiovascular risk reduction among adults attaining LDL-C <50 mg/dl, a level below current recommended targets, in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial (17,18).

Methods

Study design and population. The JUPITER trial participants were men age 50 years or older (n = 11,001) and women age 60 years or older (n = 6,801) with LDL-C <130 mg/dl, high-sensitivity C-reactive protein (hsCRP) ≥2.0 mg/l, and no history of cardiovascular disease or diabetes mellitus (17,18). Current users of post-menopausal hormone therapy or immunosuppressive agents were excluded, as were those with chronic inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease, or with cancer within the preceding 5 years. Local institutional review boards approved the study, and all participants provided written, informed consent.

Potentially eligible subjects underwent a 4-week placebo run-in phase; those with compliance >80% were randomly allocated to rosuvastatin 20 mg daily or to placebo and followed up for occurrence of the primary endpoint, a composite of myocardial infarction (MI), stroke, arterial revascularization, unstable angina, or confirmed death from cardiovascular causes. An independent endpoint committee adjudicated primary endpoint events.

Clinic physicians reported adverse events as verbatim terms, which were coded to Medical Dictionary for Regulatory Activities preferred terms (19) by an automated system, over-read by trained coders. We report treatment-emergent adverse events, that is, events that either began or worsened after randomization. Adverse events were not adjudicated, except for hemorrhagic stroke, which was a subcategory of stroke, a component of the primary endpoint.

Abbreviations and Acronyms

ALT = alanine aminotransferase
CHD = coronary heart disease
CI = confidence interval
eGFR = estimated glomerular filtration rate
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio
hsCRP = high-sensitivity C-reactive protein
LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction

The trial's pre-specified monitoring plan called for 2 interim efficacy analyses with O'Brien-Fleming stopping boundaries determined by means of the Lan-DeMets approach. The stopping boundary was crossed at the first pre-specified efficacy evaluation in September 2007; however, the independent data and safety monitoring board conservatively sought "proof beyond a reasonable doubt" and voted to continue the trial at

Table 1 Baseline Characteristics by Treatment Group and Attained LDL-C

		Rosuvastatin	
	Placebo	No LDL-C <50 mg/dl	LDL-C <50 mg/dl
n	8,150	4,000	4,154
Age, yrs	66 (60–71)	66 (60–71)	66 (61–72)
Women	3,081 (38)	1,604 (40)	1,520 (37)
Ethnicity			
White	5,854 (72)	2,793 (70)	3,106 (75)
Black	1,012 (12)	515 (13)	476 (12)
Hispanic	1,012 (12)	514 (13)	456 (11)
Asian	119 (2)	88 (2)	44 (1)
Other/unknown	153 (2)	90 (2)	72 (2)
Body mass index, kg/m^2	28 (25–32)	28 (25–32)	29 (26–32)
Systolic BP, mm Hg	134 (124–145)	134 (124–145)	135 (124–147)
Diastolic BP, mm Hg	80 (75–87)	80 (75–87)	80 (75–88)
Current smoker	1,283 (16)	646 (16)	623 (15)
Family history of CHD	969 (12)	431 (11)	499 (12)
LDL-C, mg/dl	109 (94–119)	113 (101–122)	103 (87–115)
HDL-C, mg/dl	49 (40–60)	49 (41–60)	48 (40–59)
Triglycerides, mg/dl	118 (86–170)	115 (82–164)	122 (88–175)
Total cholesterol, mg/dl	185 (169–199)	190 (175–203)	181 (163–196)
Glucose, mg/dl	94 (88–102)	93 (87–101)	95 (88–102)
Hemoglobin A1C, %	5.7 (5.5–5.9)	5.7 (5.4–5.9)	5.7 (5.4–5.9)
eGFR, ml/min/1.73 m^2	74 (65–84)	75 (65–87)	73 (64–83)
Impaired fasting glucose	2,581 (32)	1,133 (28)	1,402 (34)
hsCRP, mg/l	4.3 (2.8–7.1)	4.3 (2.8–7.1)	4.2 (2.8–7.0)

Data are presented as n, median (interquartile range), or n (%).

BP = blood pressure; CHD = coronary heart disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol.

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Table 2 Independent Predictors of Attaining LDL-C <50 mg/dl at Any Visit Among Rosuvastatin-Allocated Patients

Variable	Odds Ratio	95% CI	p Value
Age	1.023	1.017–1.030	<0.0001
Men (women, referent)	1.190	1.069–1.324	0.002
Impaired fasting glucose	1.251	1.129–1.385	<0.0001
Adherence to study medication	1.025	1.022–1.029	<0.0001
Body mass index	1.027	1.018–1.036	<0.0001
Baseline LDL-C	0.968	0.965–0.971	<0.0001
Baseline HDL-C	0.996	0.993–1.000	0.023
Baseline hsCRP	0.990	0.985–0.996	0.001

Sex and impaired fasting glucose were categorical variables in the multivariable logistic regression model; all others were continuous variables.
CI = confidence interval; other abbreviations as in Table 1.

that point. At its next meeting in March 2008, 328 confirmed primary endpoints had occurred (nominal hazard ratio [HR]: 0.57, 95% confidence interval [CI]: 0.46 to 0.72), and the board voted unanimously to recommend termination of the trial. The steering committee accepted that recommendation, and only major cardiovascular events occurring before March 30, 2008, are included in the primary endpoint analysis. Reporting of adverse events and all-cause mortality continued in a blinded manner until each participant appeared for a close-out visit and discontinued study medication.

Participants provided fasting blood samples for lipid profiles at baseline, annually thereafter, and at the final visit. Alanine aminotransferase (ALT) was measured, and urinalysis was performed at baseline, at 3 and 6 months after randomization, semiannually thereafter, and at the final visit. Creatine kinase was measured at baseline and final visit, and at physician discretion for muscle symptoms. We estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease study equation (20).

Statistical analyses. This post-hoc analysis includes all randomized JUPITER participants with at least 1 post-randomization lipid profile (n = 16,304). Subjects were categorized according to their allocated treatment group and, within the rosuvastatin group, by attained LDL-C level. Those with 1 or more post-randomization LDL-C levels <50 mg/dl were categorized as having attained LDL-C <50 mg/dl; the remaining rosuvastatin-allocated subjects were categorized as not having attained LDL-C <50 mg/dl. Clinical event rates of placebo-allocated subjects were compared with rosuvastatin-allocated participants attaining LDL-C <50 mg/dl and, separately, to participants not attaining LDL-C <50 mg/dl. In addition, events were compared between rosuvastatin-allocated participants who did and did not attain LDL-C <50 mg/dl.

Within the rosuvastatin group, we identified independent predictors of attaining LDL-C <50 mg/dl by multivariable logistic regression. The HR and 95% CI were calculated from Cox proportional hazard models; because a primary interest for this analysis was in nonrandomized comparisons of subjects with or without LDL-C <50 mg/dl, all HRs

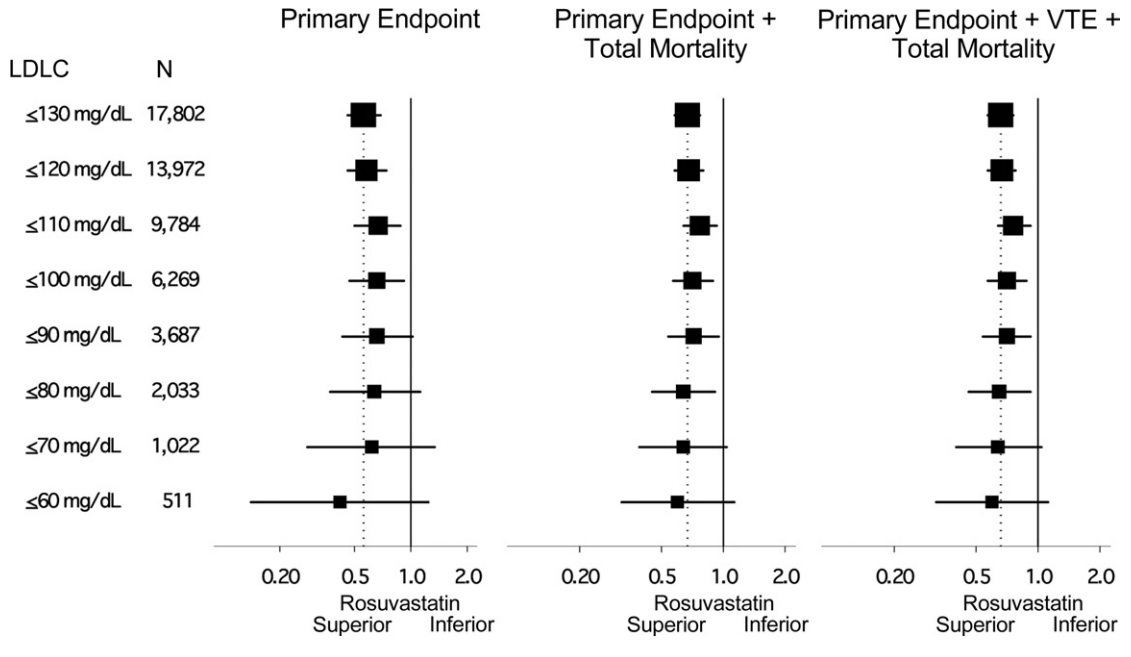

Figure 1 Cardiovascular Events and All-Cause Mortality by Baseline LDL-C Level

Numbers of patients with baseline low-density lipoprotein cholesterol (LDL-C) in each category, hazard ratios, and 95% confidence intervals for time to occurrence of the primary endpoint, the primary endpoint or death, and the composite of the primary endpoint, venous thromboembolism (VTE), or death are shown by baseline LDL-C level.

were adjusted for baseline variables (age, sex, body mass index, systolic blood pressure, smoking status, impaired fasting glucose status, and baseline levels of LDL-C, high-density lipoprotein cholesterol [HDL-C], and hsCRP) (17). Linear trends were analyzed. Change in eGFR was compared between groups by analysis of covariance including baseline eGFR as a covariate and fully adjusted for the covariates listed in the preceding text. Analyses were performed using SAS version 8.2 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics of the placebo group and rosuvastatin group are summarized in Table 1, the latter according to attained LDL-C concentration. Median follow-up was 2.0 years in the placebo group, and 1.9 and 2.0 years, respectively, in rosuvastatin-allocated subjects without and with LDL-C levels <50 mg/dl. Baseline and 1-year LDL-C levels (median) were 109 and 110 mg/dl in the placebo group, 113 and 70 mg/dl in rosuvastatin-allocated subjects with no LDL-C <50 mg/dl, and 103 and 44 mg/dl in rosuvastatin-allocated patients with LDL-C <50 mg/dl.

Medication adherence, defined as taking at least 80% of the prescribed study medication, was 88.3% in the placebo group and 82.6% and 94.9% in rosuvastatin-allocated subjects without and with LDL-C <50 mg/dl, respectively. Among rosuvastatin-allocated JUPITER study participants, independent predictors of attaining LDL-C <50 mg/dl included slightly older age, greater medication adherence, higher body mass index, impaired fasting glucose status, and lower baseline levels of LDL-C, HDL-C, and hsCRP (Table 2). Ethnicity was not an independent determinant of attaining LDL-C <50 mg/dl.

We have previously reported that rosuvastatin reduced the primary study endpoint, a composite of cardiovascular death, MI, stroke, arterial revascularization, and unstable angina, by 44% (HR: 0.56, 95% CI: 0.46 to 0.69; $p < 0.0001$) (18). This treatment effect was consistent regardless of baseline LDL-C level (Fig. 1). In contrast, the magnitude of clinical benefit was directly related to attained LDL-C level (Fig. 2). Compared with placebo, rosuvastatin-allocated patients with no LDL-C <50 mg/dl had a smaller risk reduction for the primary endpoint (fully-adjusted HR: 0.76 vs. placebo, 95% CI: 0.57 to 1.00) compared with patients with LDL-C <50 mg/dl (HR:

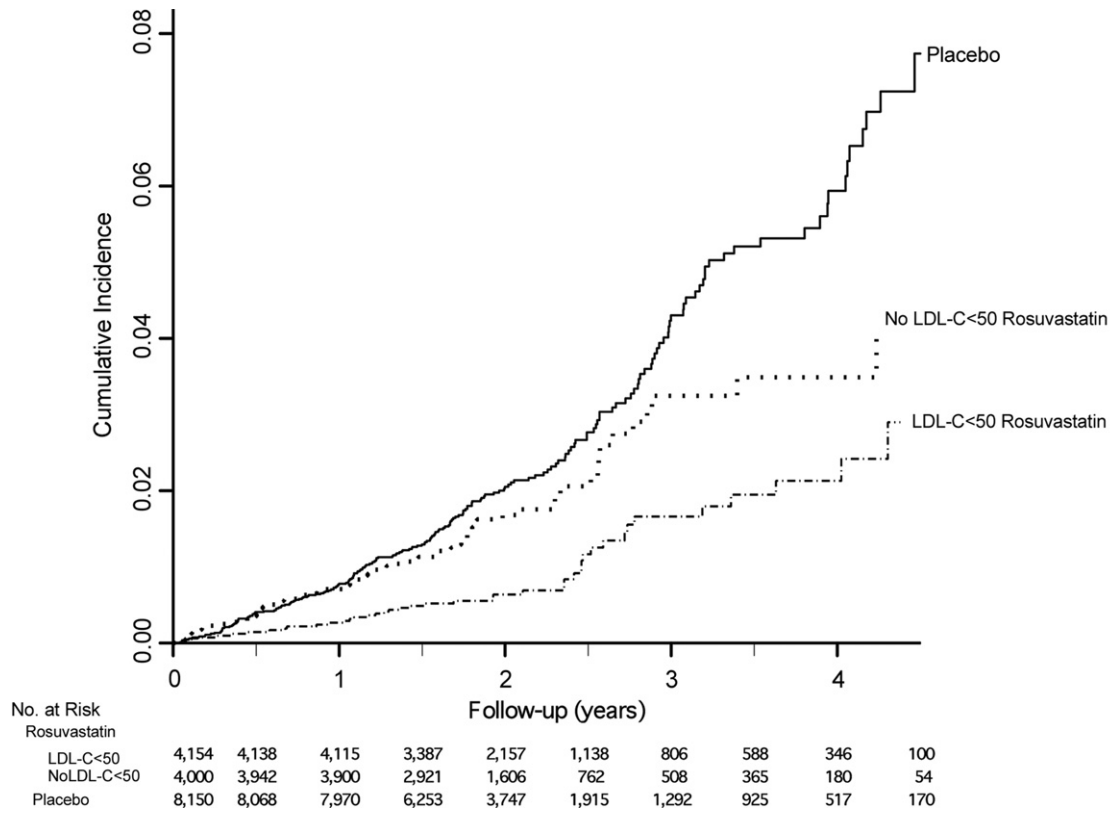

Figure 2 **Time to Occurrence of Major Cardiovascular Events According to Treatment Group and Achieved LDL-C Concentrations**

Kaplan-Meier curves for the primary study endpoint, time to first occurrence of cardiovascular death, myocardial infarction, stroke, arterial revascularization, or hospitalized unstable angina for subjects allocated to placebo **(solid line)**, rosuvastatin with no low-density lipoprotein cholesterol (LDL-C) <50 mg/dl **(dashed line)**, and rosuvastatin with LDL-C <50 mg/dl **(dotted line)**; p for trend <0.0001.

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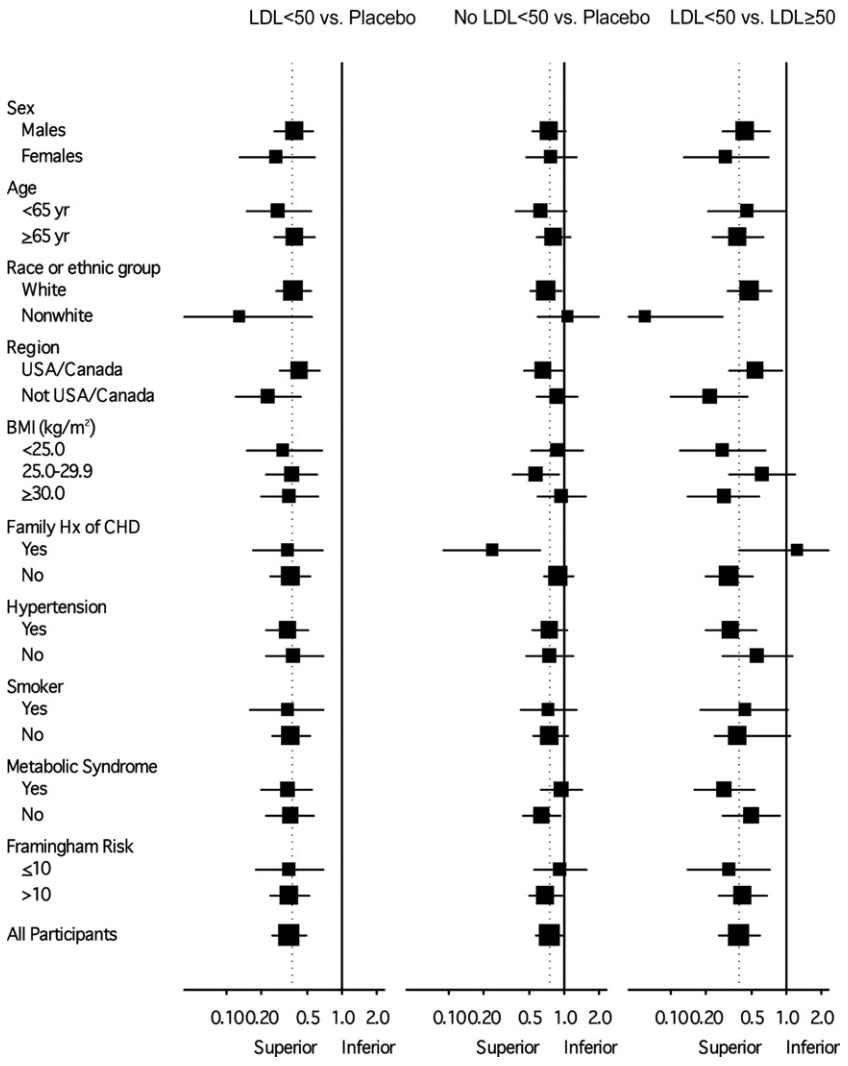

Figure 3 **Primary Endpoint in Pre-Specified Subgroups Within JUPITER Trial, Stratified by Achieved LDL-C**

Hazard ratios and 95% confidence intervals for the primary endpoint are shown for patients without and with low-density lipoprotein cholesterol (LDL-C) <50 mg/dl compared with placebo and for rosuvastatin-allocated patients with versus without LDL-C <50 mg/dl. Among the 30 subgroups assessed, p values for interaction were all >0.05, except for family history (Hx) of premature coronary heart disease (CHD) in the rosuvastatin-allocated group without LDL <50 mg/dl versus placebo (p for interaction = 0.003) and white versus nonwhite ethnicity for rosuvastatin-allocated patients with versus without LDL-C <50 mg/dl (p for interaction = 0.03). BMI = body mass index.

0.35, 95% CI: 0.25 to 0.49; p for trend <0.0001). This relationship between attained LDL-C and cardiovascular risk reduction was consistent among pre-specified subgroups of patients categorized by baseline characteristics (Fig. 3).

We observed similar relationships between attained LDL-C and clinical event reduction for the pre-specified endpoint of MI, stroke, or cardiovascular death (fully-adjusted HR: 0.78, 95% CI: 0.55 to 1.12 vs. HR: 0.26, 95% CI: 0.16 to 0.43 for patients without and with LDL-C <50 mg/dl, respectively; p for trend <0.0001), for all-cause mortality (fully-adjusted HR: 1.15, 95% CI: 0.83 to 1.58 vs. HR: 0.54, 95% CI: 0.37 to 0.78 for patients without and with LDL-C <50 mg/dl, respectively; p for trend = 0.004), and for the post-hoc composite of the primary endpoint, venous thromboembolism, and death (fully-adjusted HR: 0.85, 95% CI: 0.68 to 1.04 vs. HR: 0.41, 95% CI: 0.32 to 0.53 for patients without and with LDL-C <50 mg/dl, respectively; p for trend <0.0001) (Fig. 4).

We also directly compared clinical outcomes in analyses limited to patients treated with rosuvastatin who did or did not attain LDL-C <50 mg/dl during follow-up. As also shown in Figure 4, compared with patients who did not attain LDL-C <50 mg/dl, patients who did had a fully-adjusted HR for the primary trial endpoint of 0.39 (95% CI: 0.26 to 0.59; p < 0.0001). A similar relationship was observed for the pre-specified endpoint of MI, stroke, and cardiovascular death (fully-adjusted HR: 0.29, 95% CI: 0.16 to 0.52; p < 0.0001), for all-cause mortality (fully-adjusted

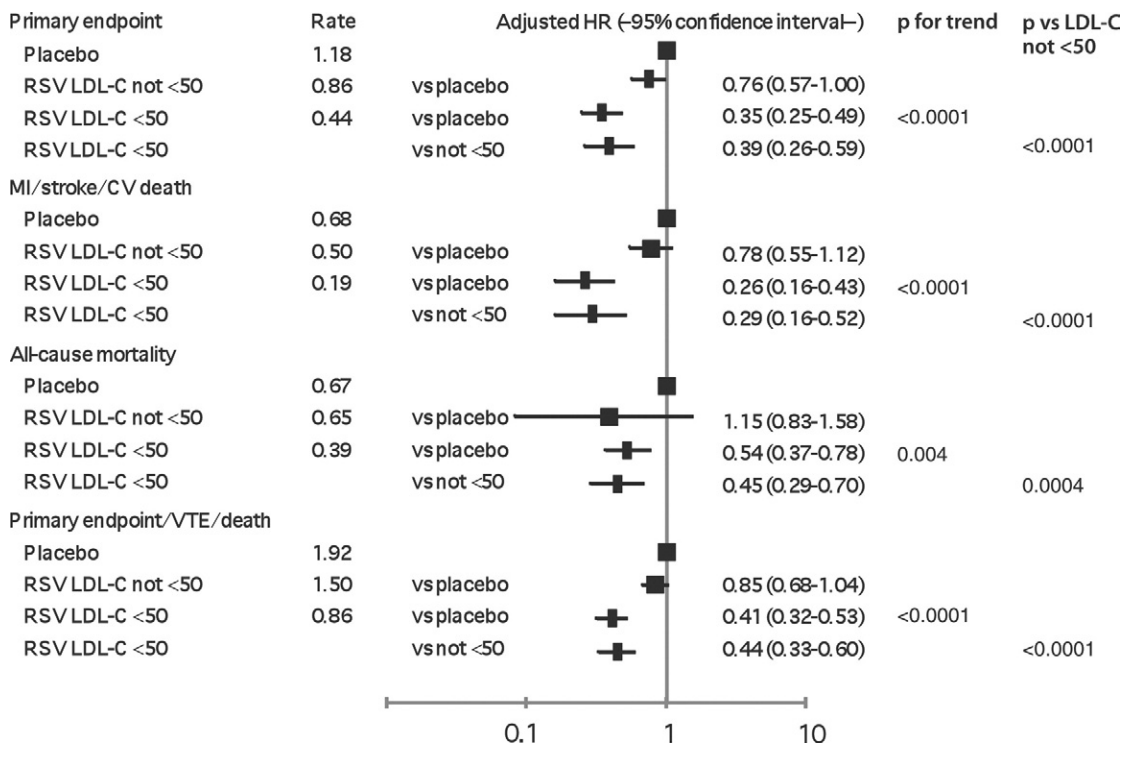

Figure 4 **Fully-Adjusted Hazard Ratios for Incident Cardiovascular Events and All-Cause Mortality According to Treatment Group and Achieved Concentrations of LDL-C**

Event rates are per 100 person-years. Low-density lipoprotein cholesterol (LDL-C) not <50 indicates rosuvastatin (RSV) group without LDL-C level <50 mg/dl; LDL-C <50 indicates rosuvastatin group with at least 1 LDL-C level <50 mg/dl. The p for trend indicates trend across placebo group, LDL-C not <50 group, and LDL-C <50 mg/dl group. CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; VTE = venous thromboembolism.

HR: 0.45, 95% CI: 0.29 to 0.70; p = 0.0004), and for the net clinical benefit endpoint that included the primary endpoint, venous thromboembolism, and total mortality (fully-adjusted HR: 0.44, 95% CI: 0.33 to 0.60; p < 0.0001). These effects were generally consistent across pre-specified subgroups (Fig. 3).

Rates of adverse events were similar in the placebo and rosuvastatin groups except for a slightly higher rate of muscle symptoms with rosuvastatin (Table 3). Rates of myalgia, muscle weakness, and myopathy were not significantly different among rosuvastatin-allocated patients with and without LDL-C <50 mg/dl. Diabetes mellitus as an adverse event was reported more frequently among rosuvastatin-allocated patients attaining LDL-C <50 mg/dl than among rosuvastatin-allocated patients who did not attain LDL-C <50 mg/dl, but this difference was not significant (1.6 vs. 1.2 per 100 person-years, p = 0.70). Rates of psychiatric adverse events, fatigue, peripheral neuropathy, cancer, hematuria, proteinuria, and renal failure did not differ between the rosuvastatin and placebo groups. Reports of hematuria were more frequent (p = 0.03) in rosuvastatin-allocated patients with LDL-C <50 mg/dl when compared with placebo, whereas depression (p = 0.005) and colon cancer (p = 0.04) were reported less frequently.

Hemorrhagic stroke, an adjudicated component of the primary efficacy endpoint, was identified in 8 subjects in the placebo group and 5 in the rosuvastatin group (rates of 0.04 and 0.03 per 100 person-years, respectively). Within the rosuvastatin group, hemorrhagic stroke was identified in 4 patients without and 1 patient with LDL-C <50 mg/dl.

ALT elevation to 3 times the upper limit of normal was more frequent with rosuvastatin than with placebo (p < 0.01), as were 2 category increases (e.g., negative/trace to ++) in urine dipstick for protein (p = 0.01) and blood (p < 0.01) (Table 4). Within the rosuvastatin group, ALT elevation and dipstick proteinuria and hematuria occurred with similar frequency in participants without and with LDL-C <50 mg/dl. The eGFR fell in both the placebo group and the rosuvastatin group during the follow-up period; there was no evidence that rosuvastatin or attainment of LDL-C <50 mg/dl adversely affected eGFR.

Discussion

Rosuvastatin reduced major cardiovascular events by 44% compared with placebo for the entire JUPITER study cohort, and by 65% among those attaining LDL-C <50 mg/dl. Similarly, all-cause mortality was reduced by 20% for the entire cohort (18) and by 46% among patients attaining

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Table 3 Numbers and Rates (per 100 Person-Years) of Treatment-Emergent Adverse Events by Treatment Group and Attained LDL-C

	Placebo (n = 8,150)		Rosuvastatin: No LDL-C <50 mg/dl (n = 4,000)			Rosuvastatin: LDL-C <50 mg/dl (n = 4,154)			p Value vs. No LDL-C <50 mg/dl
System Organ Class Preferred Term(s)	n	Rate	n	Rate	p Value vs. Placebo	n	Rate	p Value vs. Placebo	
Any adverse event	6,509	103.1	3,126	104.0	0.84	3,424	108.1	0.01	0.004
Musculoskeletal/connective tissue disorders	2,930	21.7	1,489	24.4	0.006	1,691	24.3	0.0001	0.23
Myalgia	559	3.2	317	4.0	0.03	326	3.5	0.08	0.49
Muscular weakness	61	0.3	43	0.5	0.03	30	0.3	0.75	0.11
Rhabdomyolysis*/myopathy/myositis	9	0.05	3	0.04	0.61	7	0.07	0.56	0.56
Gastrointestinal disorders	2,106	14.0	980	14.0	0.62	1,142	14.4	0.26	0.32
Respiratory, thoracic, and mediastinal disorders	1,360	8.3	611	8.0	0.43	766	8.9	0.10	0.08
Nervous system disorders	1,431	8.8	628	8.3	0.10	720	8.3	0.27	0.60
Peripheral neuropathy†	40	0.2	18	0.2	0.79	20	0.2	0.53	0.72
Amyotrophic lateral sclerosis	2	0.01	0	0	0.10	1	0.01	—	—
Parkinson's disease	13	0.1	5	0.1	0.78	8	0.1	0.80	0.63
Memory impairment‡	33	0.2	21	0.2	0.13	12	0.1	0.23	0.041
General disorders/administration site conditions									
Fatigue	297	1.7	133	1.6	0.51	176	1.8	0.09	0.12
Renal and urinary disorders	782	4.5	344	4.3	0.56	439	4.8	0.54	0.30
Hematuria	175	1.0	86	1.0	0.63	123	1.3	0.03	0.05
Proteinuria§	111	0.6	55	0.6	0.82	73	0.75	0.12	0.41
Renal failure‖	70	0.4	32	0.4	0.74	39	0.40	0.78	0.75
Eye disorders									
Cataract	195	1.1	72	0.9	0.11	104	1.1	0.91	0.20
Cancer	269	1.5	128	1.5	0.56	131	1.4	0.36	0.36
Prostate cancer¶	53	0.3	12	0.1	0.08	26	0.3	0.69	0.06
Breast cancer#	23	0.1	12	0.1	0.99	10	0.1	0.75	0.93
Colon cancer**	28	0.2	10	0.1	0.47	6	0.1	0.04	0.30
Psychiatric disorders	619	3.6	307	3.8	0.67	296	3.2	0.15	0.23
Insomnia††	205	1.1	104	1.2	0.79	118	1.2	0.40	0.52
Depression‡‡	217	1.2	103	1.2	0.83	83	0.9	0.005	0.01
Anxiety§§	158	0.9	66	0.8	0.29	65	0.7	0.09	0.54
Anger‖ ‖	4	0.02	0	0	—	1	0.01	—	—
Diabetes mellitus	209	1.2	105	1.2	0.025	151	1.6	0.06	0.70
Hepatobiliary disorders	177	1.0	71	0.8	0.35	108	1.1	0.43	0.27

*A 90-year-old man with laboratory-confirmed influenza lay on the floor overnight and developed rhabdomyolysis after the study ended, but before his final visit. †Peripheral neuropathy includes preferred terms neuropathy peripheral, polyneuropathy, demyelinating polyneuropathy, myelopathy, neuromyopathy, and peripheral sensory neuropathy. ‡Memory impairment includes preferred terms memory impairment, dementia, dementia Alzheimer's type, and cognitive disorder. §Proteinuria includes preferred terms proteinuria, microalbuminuria, and nephrotic syndrome. ‖Renal failure includes preferred terms renal failure, renal failure chronic, renal failure acute, renal impairment, azotemia, anuria, oliguria, nephritis, glomerulonephritis, and nephropathy. ¶Prostate cancer includes preferred terms prostate cancer, prostate cancer recurrent, and prostate cancer metastatic. #Breast cancer includes preferred terms breast cancer and breast cancer metastatic. **Colon cancer includes preferred terms colon cancer, colon cancer metastatic, colon cancer stage I, rectal cancer, rectosigmoid cancer, colon cancer stage III, and colorectal cancer. ††Insomnia includes preferred terms insomnia and initial insomnia. ‡‡Depression includes preferred terms depression, depressed mood, major depression, suicidal ideation, completed suicide, suicide attempt, depression suicidal, and depressive symptom. §§Anxiety includes preferred terms anxiety, nervousness, and generalized anxiety disorder. ‖ ‖Anger includes preferred terms anger, aggression, and intermittent explosive disorder.

LDL-C = low-density lipoprotein cholesterol.

LDL-C <50 mg/dl. With regard to adverse events, myalgia and diabetes mellitus were somewhat more common among participants attaining LDL-C <50 mg/dl, but these rates were not significantly different from rates among patients not attaining LDL-C <50 mg/dl. Rates of other adverse events, including muscle weakness, myopathy, neuropsychiatric events, renal dysfunction, hemorrhagic stroke, and cancer, were not higher among patients allocated to rosuvastatin than among participants allocated to placebo, regardless of attained LDL-C level.

A major strength of this analysis is its large sample size; the number of JUPITER study participants with LDL-C <50 mg/dl is greater than the entire active treatment group of many controlled statin trials (2). Other strengths include the diversity of the cohort, placebo-controlled design, independent endpoint adjudication, and systematic adverse event ascertainment. Adverse events were reported by clinic physicians blinded to treatment assignment and on-treatment LDL-C, but were not adjudicated. The major limitation of this analysis is that classification into the 2 rosuvastatin groups is made on the basis of a nonrandomized outcome (attainment of LDL-C <50 mg/dl); hence, comparisons of these 2 groups to placebo or to each other is subject to potential confounding bias from factors correlated with LDL-C lowering. Because adherence to study medication would directly affect LDL-C categori-

Table 4 ALT or CK Elevation, Proteinuria, or Hematuria at Any Follow-Up Visit by Treatment Assignment and Attained LDL-C

	Placebo (n = 8,150)		Rosuvastatin: No LDL-C <50 mg/dl (n = 4,000)			Rosuvastatin: LDL-C <50 mg/dl (n = 4,154)			p Value vs. No LDL-C <50 mg/dl
	n	Rate	n	Rate	p Value vs. Placebo	n	Rate	p Value vs. Placebo	
ALT >3 × ULN	84	0.5	56	0.7	0.06	66	0.7	0.007	0.78
CK >10 × ULN	1	0.005	1	0.01	0.45	1	0.01	0.84	1.00
≥2+ proteinuria	387	2.2	210	2.5	0.01	251	2.6	0.13	0.29
≥2+ hematuria	531	3.0	295	3.6	0.008	346	3.7	0.003	0.56
eGFR change, ml/min/1.73 m^2, mean (SD)	−9.0 (13.5)		−9.1 (14.1)		0.004	−7.9 (13.1)		0.04	0.50

Alanine aminotransferase (ALT) was measured and urine protein and blood assessed by dipstick at baseline, at 3 and 6 months after randomization, semiannually thereafter, and at the final visit. Creatine kinase (CK) was measured at baseline and final visits, and at clinic physician discretion for muscle symptoms. Rates are per 100 person-years. The p values are adjusted for age, sex, baseline LDL-C, HDL-C, hsCRP, smoking status, systolic blood pressure, impaired fasting glucose status, body mass index, and family history. In addition, p values for change in estimated glomerular filtration rate (eGFR) [baseline to final visit] are adjusted for baseline eGFR.

NC = not calculated; ULN = upper limit of normal; other abbreviations as in Table 1.

zation, the impact of adherence bias is difficult to assess. However, some reassurance is gained in that the effects were not meaningfully affected by adjustment for several factors potentially correlated with LDL-C lowering. An additional limitation is the early trial stoppage for benefit, which truncated rosuvastatin exposure at a median of 2 years, although approximately 1,000 participants were treated for up to 5 years. The JUPITER cohort included only middle-aged and older adults with average or low LDL-C and hsCRP ≥2 mg/dl, which may limit the extent to which results are applicable to the broader population.

Baseline characteristics differ slightly from prior JUPITER trial reports (17,18), as this analysis excluded 1,498 participants with no post-randomization lipoprotein measurement. Numbers of adverse events also differ due to the Medical Dictionary for Regulatory Activities preferred terms specified for each adverse event and the exclusion of non–treatment-emergent adverse events. However, analyses performed using alternative adverse event definitions revealed virtually identical outcomes.

Both favorable and unfavorable consequences have been attributed to attainment of very low LDL-C (5,6,8,9). The JUPITER study adds to existing trial data, reinforcing the graded relationship between on-treatment LDL-C and cardiovascular event reduction, and expanding the range over which LDL-C lowering confers cardiovascular risk reduction (Fig. 5) (7,21–23). Consistent with prior reports

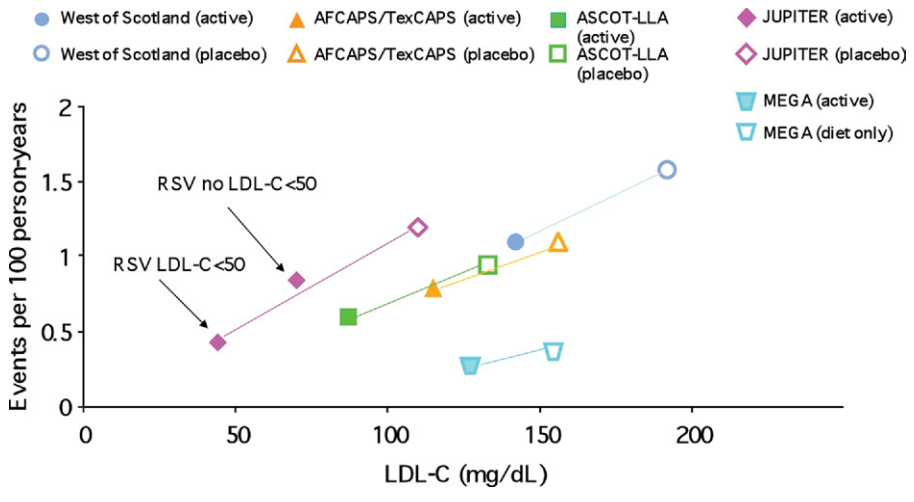

Figure 5 Relation of Major Cardiovascular Event Rate to LDL-C at 1 Year in Primary Prevention Trials

Placebo groups are indicated by **open symbols**, and statin groups by **solid symbols**. Clinical events for West of Scotland **(blue circles)** and ASCOT-LLA **(green squares)**, myocardial infarction (MI)/coronary heart disease (CHD) death; AFCAPS/TexCAPs **(orange triangles)**, fatal and nonfatal MI, unstable angina, sudden death; MEGA **(blue baskets)**, fatal and nonfatal MI, angina, cardiac and sudden death, revascularization; JUPITER **(purple diamonds)**, MI, stroke, cardiovascular death, arterial revascularization, unstable angina. Rosuvastatin (RSV)-treated participants without low-density lipoprotein cholesterol (LDL-C) <50 mg/dl (median 69 mg/dl) and with LDL-C <50 mg/dl (median 44 mg/dl) are plotted separately. (Data are from references 7, 19, 22–24.) AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese.

(2,5), LDL-C level at 1 year predicts subsequent cardiovascular events in a multivariable adjusted model ($p = 0.002$). Lower targets for LDL-C remain controversial, will need to be evaluated in prospective settings, and may not be achievable among patients with very elevated LDL-C. Nonetheless, the JUPITER trial data provide reassurance regarding the safety of treating with rosuvastatin at very low levels of LDL-C.

Safety findings among patients attaining LDL-C <50 mg/dl were consistent with the established safety profile of rosuvastatin (24). Elevation of ALT and dipstick proteinuria and hematuria were more frequent with rosuvastatin than with placebo, but within the rosuvastatin group, were not more frequent among subjects attaining LDL-C <50 mg/dl. Proteinuria with statins is attributable to 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibition in proximal renal tubular cells, leading to reduced protein reabsorption (25). Thus, concordance between proteinuria and extent of LDL-C reduction with rosuvastatin might have been expected, but was not observed. The higher frequency of diabetes mellitus reported as an adverse event is consistent with the 0.08% greater increase in glycosylated hemoglobin observed with rosuvastatin in the JUPITER trial (18). The mechanisms underlying the higher rates of observed hematuria and reported diabetes mellitus are not known.

Several other adverse consequences of either low cholesterol or statin therapy have been proposed. Hemorrhagic stroke has been reported in association with low cholesterol (26–27); in the JUPITER trial, although the number of hemorrhagic strokes was small, we found no increase in hemorrhagic stroke with rosuvastatin, even among patients with LDL-C <50 mg/dl. Cataract formation has been linked to statins in canine studies (28), but no such relationship has been confirmed in humans (29–31). We found no increase in cataracts with rosuvastatin or with attainment of LDL-C <50 mg/dl. Peripheral neuropathy has been attributed to statin-mediated axonal degeneration (10,11,32), but was no more frequent with rosuvastatin or with attainment of LDL-C <50 mg/dl in the JUPITER trial. Depression, anxiety, aggression, fatigue, cognitive impairment, and insomnia have been ascribed to statins through a variety of proposed mechanisms, including localized low cholesterol levels in the brain, transient hypoperfusion, impairment of blood-brain barrier function, and mitochondria-mediated effects (9,13,33). In the JUPITER study, rates of psychiatric adverse events were similar in the placebo and rosuvastatin groups, and in subjects with and without LDL-C <50 mg/dl.

Cancer was more frequent with statin treatment in several early placebo-controlled trials, although numbers of cases were small (34,35). This issue has persisted despite meta-analyses demonstrating no increase in cancer risk (36–38). In the JUPITER study, rates of cancer were no different with rosuvastatin than with placebo, and no higher among subjects attaining LDL-C <50 mg/dl. Cancer was a leading cause of death in the JUPITER study, and fewer cancer deaths were seen with rosuvastatin than with placebo ($p = 0.02$) (18).

The cardiovascular prevention community has searched for a threshold or a percent reduction below which further LDL-C lowering no longer reduces cardiovascular events (2). Our analysis suggests that this threshold, if it exists, may be <50 mg/dl (Fig. 5) or >50% LDL-C reduction. In prior analyses from this cohort, we have similarly found greater clinical benefits among subjects who attain hsCRP levels <2 mg/l, an effect largely unrelated to LDL-C reduction (17). Among adults without prevalent cardiovascular disease or diabetes, rosuvastatin was well tolerated during the term of exposure in the JUPITER trial, and participants attaining LDL-C <50 mg/dl with rosuvastatin experienced fewer cardiovascular events and lower all-cause mortality.

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