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Rosuvastatin for Primary Prevention in Older Persons With Elevated C-Reactive Protein and Low to Average Low-Density Lipoprotein Cholesterol Levels: Exploratory Analysis of a Randomized Trial

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Background: Randomized data on statins for primary prevention in older persons are limited, and the relative hazard of cardiovascular disease associated with an elevated cholesterol level weakens with advancing age.

Objective: To assess the efficacy and safety of rosuvastatin in persons 70 years or older.

Design: Secondary analysis of JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), a randomized, double-blind, placebo-controlled trial.

Setting: 1315 sites in 26 countries randomly assigned participants in JUPITER.

Participants: Among the 17 802 participants randomly assigned with low-density lipoprotein (LDL) cholesterol levels less than 3.37 mmol/L (<130 mg/dL) and high-sensitivity C-reactive protein levels of 2.0 mg/L or more without cardiovascular disease, 5695 were 70 years or older.

Intervention: Participants were randomly assigned in a 1:1 ratio to receive 20 mg of rosuvastatin daily or placebo.

Measurements: The primary end point was the occurrence of a first cardiovascular event (myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes).

Results: The 32% of trial participants 70 years or older accrued 49% ($n = 194$) of the 393 confirmed primary end points. The rates of the primary end point in this age group were 1.22 and 1.99 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio, 0.61 [95% CI, 0.46 to 0.82]; $P < 0.001$). Corresponding rates of all-cause mortality in this age group were 1.63 and 2.04 (hazard ratio, 0.80 [CI, 0.62 to 1.04]; $P = 0.090$). Although no significant heterogeneity was found in treatment effects by age, absolute reductions in event rates associated with rosuvastatin were greater in older persons. The relative rate of any serious adverse event among older persons in the rosuvastatin versus placebo group was 1.05 (CI, 0.93 to 1.17).

Limitation: Effect estimates from this exploratory analysis with age cut-point chosen after trial completion should be viewed in the context of the overall trial results.

Conclusion: In apparently healthy older persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin reduces the incidence of major cardiovascular events.

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Statins are underused in high-risk older persons with clear indications (1–3). Moreover, use of statins for primary prevention in older persons without diabetes remains controversial (4) because evidence from randomized trials is limited and the relative hazard associated with an elevated cholesterol level is markedly attenuated by older age (5). The Framingham coronary heart disease risk score reflects this attenuation in its assignment of 6 points to a man and 8 points to a woman aged 40 years with total cholesterol level of 6.48 mmol/L (250 mg/dL), but only 1 and 2 points for men and women, respectively, age 75 years with this level (6). However, absolute risk is critical for treatment decisions, and older age is the dominant risk factor for a first cardiovascular event in persons without diabetes. Thus, at age 75 years, the Framingham risk score assigns 13 points to a man and 16 points to a woman, relative to 0 points for either sex at age 40 years.

Substantial randomized evidence on the efficacy of statins in older persons with diabetes or prevalent vascular disease supports guidelines to treat high-risk persons regardless of age (7–10). However, randomized evidence on statin use in primary prevention among older persons without diabetes is limited. Among the 5804 persons aged 70 to 82 years randomly assigned in the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial (11), pravastatin (40 mg/d) reduced the incidence of important vascular events by 15% (hazard ratio [HR], 0.85 [95% CI, 0.74 to 0.97]; $P = 0.014$), but the observed benefit was somewhat weaker in the 3239 persons without previous vascular disease (HR, 0.94 [CI, 0.77 to 1.15]). The JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) (12) investigators randomly assigned an older population (mean age, 66 years) than those of previous large, primary prevention trials of statins (mean age, 55 to 58 years) (13–

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15). This report focuses on the treatment effects and safety profile among JUPITER participants 70 years or older and compares these findings with results in younger participants.

METHODS

Design

JUPITER was a randomized, double-blind, placebo-controlled trial conducted at 1315 sites in 26 countries. Institutional review boards approved the protocol at each site.

Study Population

The main eligibility criteria were men 50 years or older or women 60 years or older with no history of cardiovascular disease or diabetes, no lipid-lowering therapy within 6 weeks before screening, low-density lipoprotein (LDL) cholesterol levels less than 3.37 mmol/L (<130 mg/dL), and high-sensitivity C-reactive protein levels of 2.0 mg/L or more at screening. Additional eligibility and exclusion criteria, including a willingness to participate for the duration of the trial and provision of written informed consent, are described elsewhere (12). Willing and potentially eligible participants entered a 4-week placebo run-in phase to test their adherence.

Randomization and Follow-up

We randomly assigned participants who remained willing and eligible after the run-in phase in a 1:1 ratio to receive either 20 mg of rosuvastatin daily or a matching placebo. Site investigators randomly assigned their participants through an interactive voice-response system that assigned treatment on the basis of a computer-generated list developed by AstraZeneca (Wilmington, Delaware), stratified by center. From March 2003 to December 2006, we randomly assigned 17 802 participants.

Participants had scheduled follow-up visits at 13 weeks and at 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after randomization. **Figure 1** shows participant accrual and follow-up, by age group.

JUPITER was designed to continue until accrual of 520 confirmed primary end points, with interim efficacy analyses scheduled to occur on accrual of 195 and 390 confirmed primary end points. The prespecified stopping boundary (based on the O'Brien–Fleming boundaries determined by the Lan–DeMets approach) was exceeded at the first interim analysis. The independent data and safety monitoring board voted to continue the trial for an additional 6 months, at which time the board determined that the criteria specified in its charter for early stopping were exceeded. Its recommendation on 29 March 2008 to stop the trial was accepted the next day by the steering committee. A closeout visit was scheduled after this date, at which time participants learned their group assignment.

Context

Limited data are available on the effectiveness of statins in improving outcomes in older patients.

Contribution

This secondary analysis of JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) showed that nearly half of the 393 first cardiovascular events observed among 17 802 trial participants occurred in the 5695 participants who were 70 years or older (194 events). The absolute reduction in first cardiovascular events associated with rosuvastatin was greater among older than younger participants. Yet, overall mortality did not differ in older patients who received rosuvastatin compared with those who received placebo.

Caution

Randomization was not stratified by age. The study was stopped early, so long-term effects cannot be ascertained.

—The Editors

End Points

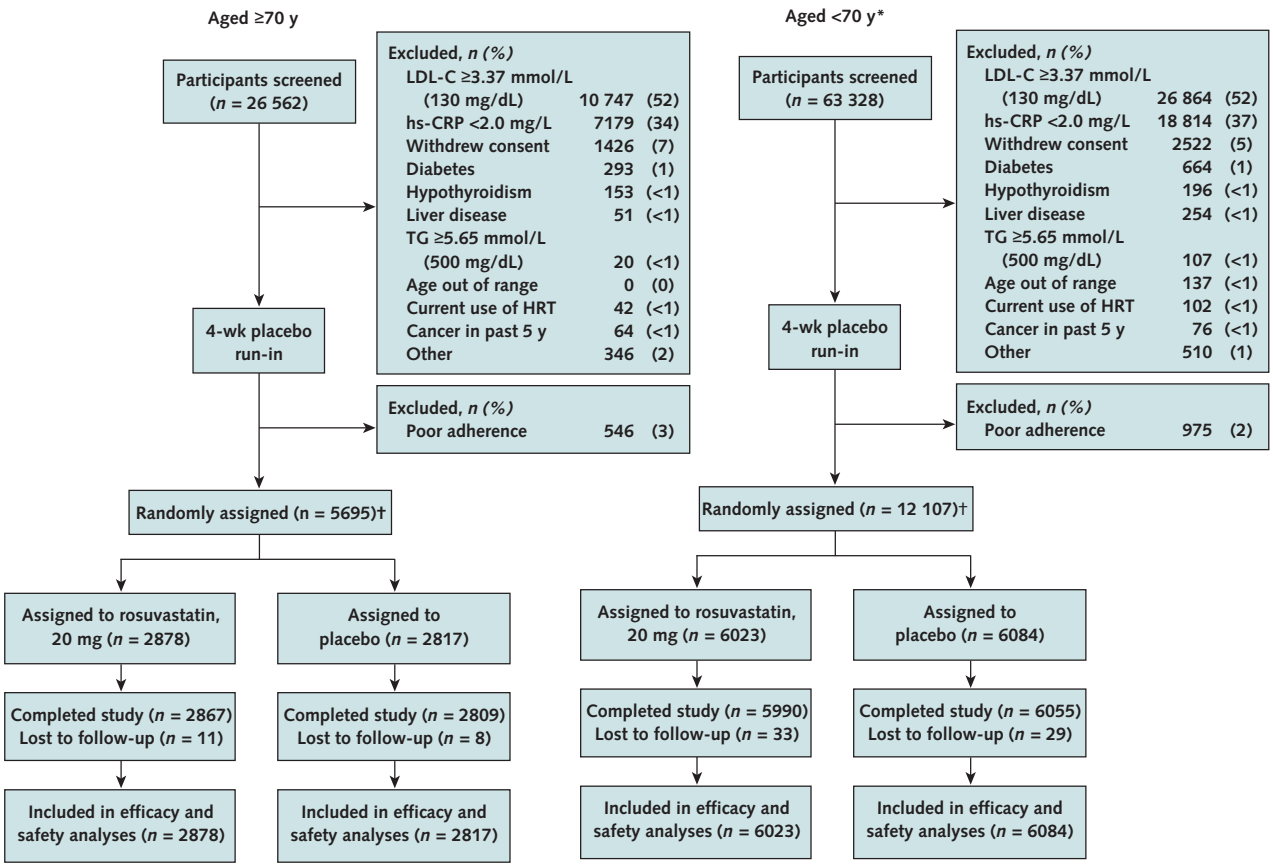
The primary end point was the occurrence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes. Other prespecified end points included the components of the primary end point, death from any cause, venous thromboembolism, and incident diabetes.

An independent end point committee, masked to randomized treatment assignment, adjudicated all reported primary end points that occurred through 30 March 2008. Follow-up for efficacy end points ended on that date. For safety end points, including incident diabetes, blinded treatment and follow-up continued until a participant had a closeout visit and discontinued study therapy. The last closeout visit occurred on 20 August 2008.

Statistical Analysis

We chose the cut-point at age 70 years for this report after trial completion but before conducting these analyses because previous primary prevention trials included few persons in this age group and use of statins for primary prevention in older persons is controversial. Analyses of the primary, prespecified secondary and safety outcomes followed the intention-to-treat principle and used Cox proportional hazards models to estimate treatment effects separately by age group. We evaluated the possible heterogeneity in the treatment effect by age by using a likelihood ratio test of an age-group-by-treatment interaction in a model fitted to the entire population. Because the competing risk for death is an important consideration in the treatment of older persons, we considered composite end points, including either death or other end points. We

Figure 1. **Study flow diagram.**



HRT = hormone replacement therapy; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.
* Includes 12 persons for whom age is unknown.
† Randomization was not stratified by age.

based the evaluation of the proportional hazards assumption on a likelihood ratio test of the interaction between treatment and study time. Alternative analyses stratified on geographic region yielded similar effect estimates.

We also evaluated absolute treatment effects as the difference between the incidence rate of an outcome in the placebo group minus the incidence rate in the rosuvastatin group separately by age group. We based estimates of the number of patients needed to treat to prevent 1 event on the difference between Kaplan–Meier estimates of cumulative risk at 4 years (16).

Role of the Funding Source

The study chair designed and wrote the trial protocol. AstraZeneca financially supported the trial, collected the data, and monitored the sites but remained blinded to treatment status throughout the trial and played no role in the analyses or drafting of the primary study results (12, 17, 18) or this manuscript, or in the decision to submit the manuscript for publication.

RESULTS

Participants in JUPITER who were 70 years or older at randomization had a somewhat different profile of other cardiovascular risk factors, relative to participants aged 50 to 69 years at randomization (**Table 1**). Higher percentages of older participants were women or had hypertension, and lower percentages were obese or smoked cigarettes, relative to younger participants.

Achieved levels of lipids and high-sensitivity C-reactive protein during follow-up were similar in older (aged ≥70 years) and younger participants. Specifically, among the 89% of participants with blood samples at 12 months, the median LDL cholesterol levels in the rosuvastatin group (1.40 mmol/L [54 mg/dL] and 1.43 mmol/L [55 mg/dL] in older and younger participants, respectively) were half those in each age group that received placebo. The median high-sensitivity C-reactive protein levels (2.3 and 2.2 mg/L in older and younger participants, respectively) were 36% to 37% lower in the rosuvastatin versus placebo group, separately in each age group.

In both age groups combined (12), rosuvastatin was associated with a 44% reduction in the hazard of the primary end point (HR, 0.56 [CI, 0.46 to 0.69]; $P < 0.001$). The 32% of trial participants who were 70 years or older accrued 49% ($n = 194$) of the 393 confirmed primary cardiovascular end points in JUPITER (**Table 2**). For the primary composite cardiovascular end point, as well as for most of its components, relative treatment effects were slightly attenuated in older participants, but substantial treatment benefits were still seen and no significant interactions between age and treatment effect for any outcome ($P > 0.10$ for each) were found. For the primary end point, as well as for composites that included total mortality, a treatment benefit emerged shortly after treatment initiation in both older and younger participants, and no violation of the proportional hazards assumption was seen in either age group (**Figure 2**).

The absolute reduction in the incidence of the primary end point associated with rosuvastatin was 48% larger (0.77 vs. 0.52 events per 100 person-years) among participants 70 years or older relative to those younger than 70 years. For composite end points that included any death, larger differences in absolute treatment effects were seen between age groups. The estimated number of older persons who needed treatment for 4 years to prevent 1 primary end point was 24 (CI, 15 to 57) compared with 36 (CI, 23 to 77) in the younger age group; for the composite, including the primary end point, any death, or venous thromboembolism, similar estimates were 17 (CI, 12 to 33) for older persons versus 27 (CI, 17 to 57) for younger persons.

Similar hazard reductions were seen in both older men and women, and no significant heterogeneity was observed across subgroups among older participants (**Figure 3**). A clear treatment benefit was observed among higher-risk older subgroups, including those with Framingham risk scores greater than 10% and those with hypertension.

Older participants assigned to placebo had higher rates of any serious adverse event, as well as of most specific adverse events, compared with younger participants (**Table 3**). Among older participants, rates of muscle weakness, stiffness or pain, renal disorder, bleeding events, gastrointestinal disorder, hepatic disorder, and incident diabetes were higher in the rosuvastatin group, but none of these associations was statistically significant ($P > 0.10$ for each).

Table 1. **Baseline Characteristics of Trial Participants**

Characteristic	Aged 70 to 97 y		Aged 50 to 69 y	
	Rosuvastatin Group ($n = 2878$)	Placebo Group ($n = 2817$)	Rosuvastatin Group ($n = 6023$)	Placebo Group ($n = 6084$)
Median age (interquartile range), *y*	74 (72–77)	74 (72–78)	63 (58–66)	63 (58–66)
Women, *n (%)*	1485 (51.6)	1446 (51.3)	1941 (32.2)	1929 (31.7)
Race or ethnicity, *n (%)*				
White	2030 (70.6)	1953 (69.3)	4328 (71.9)	4372 (71.9)
Black	382 (13.3)	372 (13.2)	718 (11.9)	752 (12.4)
Hispanic	383 (13.3)	420 (14.9)	738 (12.3)	720 (11.8)
Other or unknown	82 (2.8)	72 (2.6)	239 (4.0)	240 (3.9)
Geographic region, *n (%)*				
United States or Canada	1009 (35.1)	1040 (36.9)	1998 (33.2)	1994 (32.8)
Central or South America	465 (16.2)	468 (16.6))	842 (14.0)	831 (13.7)
Europe	970 (33.7)	889 (31.6)	2291 (38.0)	2365 (38.9)
South Africa	416 (14.5)	398 (14.1)	839 (13.9)	844 (13.9)
Israel	18 (0.6)	22 (0.8)	53 (0.9)	50 (0.8)
Body mass index, *n (%)*				
<25 kg/m^2	748 (26.1)	752 (26.8)	1292 (21.5)	1281 (21.1)
25 to <30 kg/m^2	1184 (41.3)	1175 (41.8)	2311 (38.5)	2339 (38.5)
≥30 kg/m^2	938 (32.7)	884 (31.5)	2400 (40.0)	2452 (40.4)
Hypertension, *n (%)*	1883 (65.5)	1849 (65.7)	3196 (53.1)	3280 (53.9)
Current smoker, *n (%)*	232 (8.1)	245 (8.7)	1168 (19.4)	1175 (19.3)
The metabolic syndrome, *n (%)**	1152 (40.4)	1105 (39.5)	2500 (41.8)	2618 (43.4)
Framingham risk score >10, *n (%)*	1984 (69.1)	1948 (69.3)	2458 (40.9)	2505 (41.2)
hs-CRP level ≥5.0 mg/L, *n (%)*	1204 (41.8)	1211 (43.0)	2414 (40.1)	2515 (41.3)
LDL cholesterol level >2.59 mmol/L (>100 mg/dL), *n (%)*	1894 (65.8)	1831 (65.0)	3887 (64.6)	3916 (64.4)
HDL cholesterol level <1.04 mmol/L (<40 mg/dL) in men or <1.30 mmol/L (<50 mg/dL) in women, *n (%)*	864 (30.0)	845 (30.0)	1969 (32.7)	2011 (33.1)
Triglyceride level ≥1.70 mmol/L (≥150 mg/dL), *n (%)*	811 (28.2)	809 (28.7)	2089 (34.7)	2127 (35.0)
Fasting glucose level ≥5.55 mmol/L (≥100 mg/dL), *n (%)*	881 (30.6)	842 (29.9)	1874 (31.1)	1972 (32.4)

HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = high-density lipoprotein.
* The metabolic syndrome was defined according to consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute (19).

Table 2. **Relative and Absolute Treatment Effects, by Age**

Treatment Effect	Rosuvastatin Group		Placebo Group		Hazard Ratio (95% CI)†	*P* Value	Rate Difference (95% CI)†
	Patients, *n*	Rate*	Patients, *n*	Rate*			
Aged 70–97 y‡							
Primary end point	75	1.22	119	1.99	0.61 (0.46 to 0.82)	<0.001	0.77 (0.32 to 1.22)
MI	17	0.27	30	0.50	0.55 (0.31 to 1.00)	0.046	0.22 (0.00 to 0.44)
Stroke	22	0.35	39	0.64	0.55 (0.33 to 0.93)	0.023	0.29 (0.04 to 0.54)
Revascularization or hospitalization for unstable angina	30	0.48	57	0.95	0.51 (0.33 to 0.80)	0.003	0.46 (0.16 to 0.76)
Cardiovascular death	21	0.34	25	0.41	0.83 (0.47 to 1.48)	0.53	0.07 (−0.14 to 0.29)
Any death	108	1.63	133	2.04	0.80 (0.62 to 1.04)	0.090	0.40 (−0.06 to 0.87)
VTE	15	0.24	25	0.41	0.59 (0.31 to 1.11)	0.096	0.17 (−0.003 to 0.37)
MI, stroke, or any death	131	2.11	183	3.04	0.70 (0.56 to 0.87)	0.001	0.93 (0.35 to 1.50)
Primary end point or death or VTE	165	2.69	233	3.91	0.69 (0.56 to 0.84)	<0.001	1.23 (0.58 to 1.88)
Aged 50–69 y‡							
Primary end point	67	0.54	132	1.06	0.51 (0.38 to 0.69)	<0.001	0.52 (0.29 to 0.74)
MI	14	0.11	38	0.30	0.37 (0.20 to 0.69)	<0.001	0.19 (0.08 to 0.30)
Stroke	11	0.09	25	0.20	0.45 (0.22 to 0.91)	0.020	0.11 (0.02 to 0.20)
Revascularization or hospitalization for unstable angina	46	0.37	86	0.69	0.54 (0.38 to 0.77)	<0.001	0.32 (0.14 to 0.50)
Cardiovascular death	14	0.11	18	0.14	0.79 (0.39 to 1.58)	0.50	0.03 (−0.06 to 0.12)
Any death	90	0.68	114	0.86	0.80 (0.60 to 1.04)	0.10	0.18 (−0.04 to 0.39)
VTE	19	0.15	35	0.28	0.55 (0.31 to 0.96)	0.031	0.13 (0.01 to 0.24)
MI, stroke, or any death	108	0.87	170	1.35	0.64 (0.50 to 0.81)	<0.001	0.49 (0.22 to 0.75)
Primary end point or death or VTE	155	1.25	250	2.00	0.62 (0.51 to 0.76)	<0.001	0.75 (0.44 to 1.07)

MI = myocardial infarction; VTE = venous thromboembolism.
* Rates are per 100 person-years.
† Hazard ratios compare hazards in the rosuvastatin group with those in the placebo group; rate differences are rates in the placebo group minus those in the rosuvastatin group with 95% CIs based on the normal approximation to the Poisson distribution.
‡ Median follow-up, 2.0 y; maximum follow-up, 5.0 y.

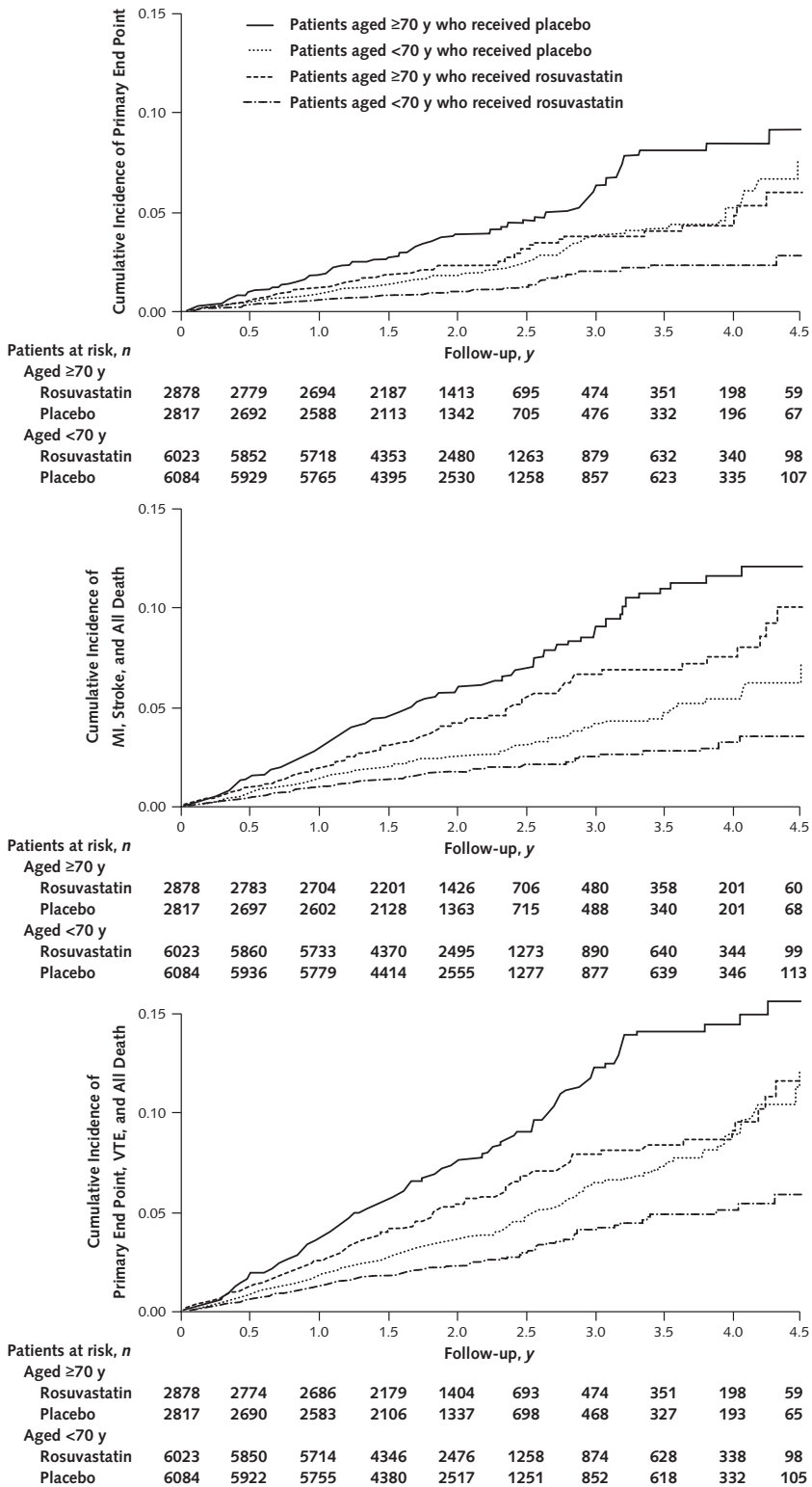
DISCUSSION

Among the 5695 randomly assigned participants in JUPITER who were 70 years or older, rosuvastatin substantially reduced the incidence of major cardiovascular events. In these older persons, clear benefits over time emerged shortly after treatment initiation and appeared in analyses of broader end points (including total mortality), in separate analyses of myocardial infarction and stroke, among older men and women separately, and in high-risk subgroups. The observed relative treatment effects in older persons were consistent with those seen in younger participants, but absolute event rates and treatment benefits were greater in older persons.

JUPITER differed from previous primary prevention trials of statins in its enrollment of an older population, inclusion of stroke in the primary end point, and enrollment of persons with normal LDL cholesterol levels but elevated high-sensitivity C-reactive protein levels. Because age is the dominant risk factor for a first cardiovascular event in nondiabetic persons, the lower age limit and absence of an upper age limit contributed to enrollment of a population that incurred many cardiovascular events. Prevention of stroke is an important treatment target for statin therapy (20), and stroke contributes an increasing proportion of total cardiovascular events with increasing age. Enrollment of persons with elevated high-sensitivity C-reactive protein levels contributed further to the identification of a population at increased risk for both coronary heart disease and stroke (21, 22), who were found to benefit from statin therapy despite normal LDL cholesterol levels.

Meta-analysis of observational studies found that a 1-mmol/L (39-mg/dL) lower total cholesterol level was associated with a 56% reduction (CI, 52% to 58%) in the hazard of death from ischemic heart disease at ages 40 to 49 years, but a 17% reduction (CI, 15% to 19%) at ages 70 to 89 years (5). For stroke, a slightly reduced risk associated with lower total cholesterol levels at ages 40 to 69 years did not persist on control for blood pressure, and persons aged 70 to 89 years had no reduction in the hazard of stroke associated with lower cholesterol levels. The apparently attenuated associations of total cholesterol levels with cardiovascular events in older persons may be partly due to confounding by age-related comorbid conditions (23). Nonetheless, the weakened association of total cholesterol levels with cardiovascular risk in older persons and the limited randomized evidence on statin therapy for primary prevention directed by lipid levels in older persons

Figure 2. **Cumulative incidence of the primary and other composite end points, by time, treatment, and age group.**

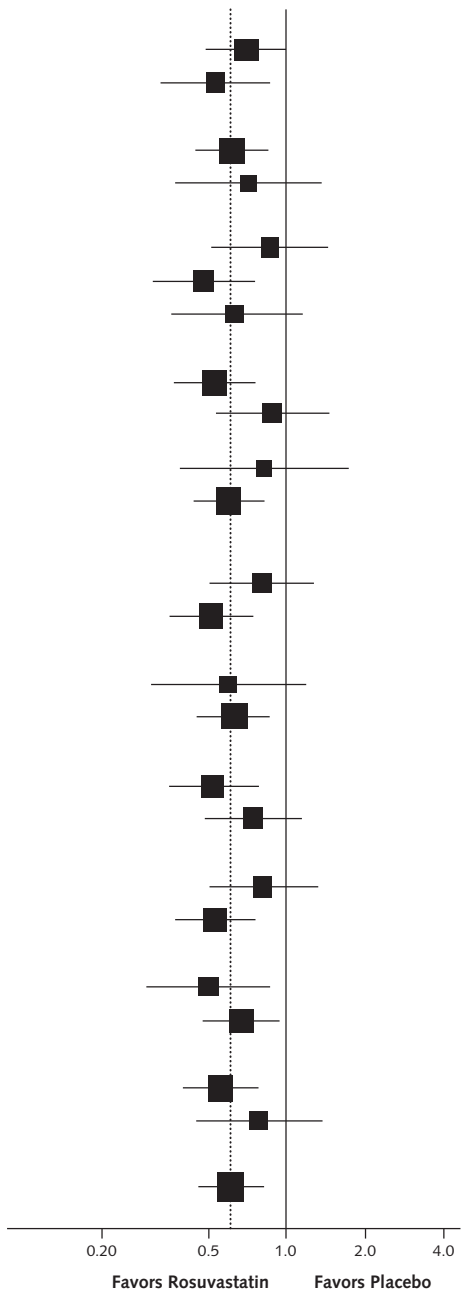


MI = myocardial infarction; VTE = venous thromboembolism.

Top. Cumulative incidence of the primary end point (MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes). **Middle**. Cumulative incidence of the composite end point, including MI, stroke, or any death. **Bottom**. Cumulative incidence of the composite end point, including the primary end point (MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes), VTE, or any death.

Figure 3. **Forest plot of the effect of rosuvastatin on the primary end point within subgroups of trial participants 70 years or older.**

Aged ≥70 y	Participants, *n*	Events, *n*	Incidence Rates	
			Rosuvastatin	Placebo
Sex				
Male	2764	122	1.66	2.46
Female	2931	72	0.79	1.54
Race				
White	3983	156	1.28	2.16
Black, Hispanic, other	1711	38	1.01	1.51
BMI				
<25.0 kg/m^2	1500	59	1.71	2.04
25.0–29.9 kg/m^2	2359	86	1.10	2.32
≥30.0 kg/m^2	1822	48	0.94	1.52
Hypertension				
Yes	3732	132	1.16	2.24
No	1960	62	1.32	1.55
Smoking status				
Smoker	477	27	2.49	3.08
Nonsmoker	5215	167	1.11	1.89
The metabolic syndrome				
Yes	2257	74	1.37	1.73
No	3397	119	1.10	2.17
Framingham risk score				
≤10%	1753	35	0.67	1.15
>10%	3932	159	1.47	2.39
hs-CRP level				
<5 mg/L	3280	108	1.05	2.01
≥5 mg/L	2415	86	1.46	1.97
LDL-C level				
≤100 mg/dL	1969	68	1.48	1.85
>100 mg/dL	3725	126	1.09	2.07
HDL-C level				
<40 mg/dL (men)/<50 mg/dL (women)	1709	57	1.08	2.15
≥40 mg/dL (men)/≥50 mg/dL (women)	3985	137	1.28	1.93
Triglyceride level				
<150 mg/dL	4074	143	1.19	2.14
≥150 mg/dL	1620	51	1.28	1.62
All participants	5695	194	1.22	1.99



HRs with 95% CIs are plotted. Incidence rates are per 100 person-years. To convert cholestrol and triglyceride values to mmol/L, multiply by 0.0259 and 0.0113, respectively. BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol.

raise questions about how lipid levels should be used to inform treatment decisions in older persons. Relative treatment benefits seem to be independent of baseline lipid levels (24), many older persons are at substantial risk despite apparently normal lipid levels, and JUPITER findings indicate that these persons receive a benefit regardless of their lipid levels if high-sensitivity C-reactive protein are elevated.

JUPITER provides new information on the effects of statins in older persons that can inform evaluations of the

Table 3. **Monitored Adverse Events and Other Events of Interest, by Age and Treatment Group**

Monitored Adverse Event	Aged 70 to 97 y					Aged 50 to 69 y				
	Rosuvastatin Group		Placebo Group		Hazard Ratio (95% CI)†	Rosuvastatin Group		Placebo Group		Hazard Ratio (95% CI)†
	Patients, *n*	Rate*	Patients, *n*	Rate*		Patients, *n*	Rate*	Patients, *n*	Rate*	
Any serious adverse event	622	10.93	584	10.45	1.05 (0.93–1.17)	730	6.07	793	6.51	0.93 (0.84–1.03)
Muscle weakness, stiffness, or pain	494	8.92	467	8.50	1.04 (0.92–1.19)	927	8.14	908	7.85	1.04 (0.94–1.13)
Myopathy	4	0.06	3	0.05	1.31 (0.29–5.84)	6	0.05	6	0.05	1.01 (0.33–3.14)
Rhabdomyolysis	1		0			0		0		
Newly diagnosed cancer	144	2.30	155	2.54	0.91 (0.73–1.14)	154	1.21	159	1.23	0.98 (0.79–1.22)
Death from cancer	18	0.27	31	0.48	0.58 (0.32–1.03)	17	0.13	27	0.20	0.63 (0.35–1.16)
Gastrointestinal disorder	665	12.41	621	11.71	1.06 (0.95–1.18)	1088	9.72	1090	9.54	1.02 (0.94–1.11)
Renal disorder	222	3.63	191	3.17	1.14 (0.94–1.39)	313	2.51	289	2.28	1.10 (0.94–1.29)
Bleeding event	127	2.04	106	1.73	1.18 (0.91–1.53)	131	1.03	169	1.32	0.78 (0.62–0.98)
Hepatic disorder	61	0.96	59	0.95	1.01 (0.71–1.45)	155	1.22	127	0.99	1.24 (0.98–1.57)
Newly diagnosed diabetes	82	1.30	64	1.03	1.25 (0.90–1.74)	188	1.48	152	1.18	1.26 (1.02–1.56)

* Rates are per 100 person-years.
† Hazard ratios compare hazards in the rosuvastatin group with those in the placebo group.

effect of alternative prescribing strategies. Several authors have noted the limitations arising from the need to project previous treatment recommendations for healthy older persons from the available randomized evidence in younger persons, from older persons with diabetes or prevalent cardiovascular disease, or from the observational data on cholesterol levels and risk for cardiovascular disease (4, 25, 26). For example, in their comparison of alternative treatment strategies, Pletcher and coworkers (26) assumed, in their base-case scenario, that the relative treatment benefit associated with a given LDL cholesterol reduction is much less in an older person than in a younger person. Their sensitivity analyses, under the assumption supported by JUPITER data that relative treatment benefits are unchanged across age groups, found a preference for strategies more focused on treating older persons. JUPITER also points to the need to include stroke prevention in evaluations of cost-effectiveness, both because of its high personal and financial impact as well as its increased percentage of total cardiovascular events with age. Thus, evaluations restricted to coronary events can undervalue treatment in older persons.

Comorbidity and proximity to death are barriers to preventive care in older persons. Physicians reasonably hesitate to initiate a therapy if they expect that a patient will not live long enough to benefit. Data from JUPITER indicate that a treatment benefit emerges shortly after initiation, absolute risk is high, and the absolute risk reduction is greater in older versus younger persons. Consideration of composite end points including total mortality provides a treatment evaluation that accounts for the competing risks for death. Adding total mortality to the end point indicates that fewer patients need treatment to prevent 1 event.

These exploratory analyses need to be interpreted in light of the overall trial results, but they confirm that the overall treatment effect was reliably seen in older participants. Early stopping of the trial limited the information on the long-term effects of treatment, although cumulative risks between treatment groups continued to diverge up to 4 years of follow-up, and reliable estimates of effects were seen even in subgroups of older participants. Stopping early on the basis of a principled and conservative monitoring plan yields a valid estimate of treatment effects (27) and meets ethical requirements to inform participants when equipoise no longer holds and let society know when better treatments are available (28, 29).

Overall, among persons aged 70 years or older in this randomized trial, rosuvastatin was associated with a significant reduction in the rate of a first major cardiovascular event. Because older participants had much higher event rates, absolute treatment benefits were greater in this age group.

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References

1. **DeWilde S, Carey IM, Bremner SA, Richards N, Hilton SR, Cook DG.** Evolution of statin prescribing 1994-2001: a case of agism but not of sexism? Heart. 2003;89:417-21. [PMID: 12639870]

2. **Ko DT, Mamdani M, Alter DA.** Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. JAMA. 2004;291:1864-70. [PMID: 15100205]

3. **Setoguchi S, Glynn RJ, Avorn J, Levin R, Winkelmayer WC.** Ten-year trends of cardiovascular drug use after myocardial infarction among community-dwelling persons > or = 65 years of age. Am J Cardiol. 2007;100:1061-7. [PMID: 17884362]

4. **Abramson J, Wright JM.** Are lipid-lowering guidelines evidence-based? Lancet. 2007;369:168-9. [PMID: 17240267]

5. **Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, et al; Prospective Studies Collaboration.** Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370:1829-39. [PMID: 18061058]

6. **National Cholesterol Education Program.** ATP III Guidelines At-A-Glance Quick Desk Reference. NIH publication no. 01-3305. Bethesda, MD: U.S. Department of Health and Human Services; 2001. Accessed at www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf on 3 March 2010.

7. **Lewis SJ, Moye LA, Sacks FM, Johnstone DE, Timmis G, Mitchell J, et al.** Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. Ann Intern Med. 1998;129:681-9. [PMID: 9841599]

8. **Hunt D, Young P, Simes J, Hague W, Mann S, Owensby D, et al.** Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: Results from the LIPID trial. Ann Intern Med. 2001;134:931-40. [PMID: 11352694]

9. **Wenger NK, Lewis SJ, Herrington DM, Bittner V, Welty FK; Treating to New Targets Study Steering Committee and Investigators.** Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. Ann Intern Med. 2007;147:1-9. [PMID: 17606955]

10. **Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al; Cholesterol Treatment Trialists' (CTT) Collaborators.** Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371:117-25. [PMID: 18191683]

11. **Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al; PROSPER study group.** PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623-30. [PMID: 12457784]

12. **Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al; JUPITER Study Group.** Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195-207. [PMID: 18997196]

13. **Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al.** Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333:1301-7. [PMID: 7566020]

14. **Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al.** Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279:1615-22. [PMID: 9613910]

15. **Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, et al; MEGA Study Group.** Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368:1155-63. [PMID: 17011942]

16. **Altman DG, Andersen PK.** Calculating the number needed to treat for trials where the outcome is time to an event. BMJ. 1999;319:1492-5. [PMID: 10582940]

17. **Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al; JUPITER Trial Study Group.** Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009;373:1175-82. [PMID: 19329177]

18. **Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al.** A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med. 2009;360:1851-61. [PMID: 19329822]

19. **Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al; American Heart Association.** Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735-52. [PMID: 16157765]

20. **Amarenco P, Labreuche J, Lavallée P, Touboul PJ.** Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke. 2004;35:2902-9. [PMID: 15514180]

21. **Ridker PM, Rifai N, Rose L, Buring JE, Cook NR.** Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002;347:1557-65. [PMID: 12432042]

22. **Everett BM, Kurth T, Buring JE, Ridker PM.** The relative strength of C-reactive protein and lipid levels as determinants of ischemic stroke compared with coronary heart disease in women. J Am Coll Cardiol. 2006;48:2235-42. [PMID: 17161253]

23. **Corti MC, Guralnik JM, Salive ME, Harris T, Ferrucci L, Glynn RJ, et al.** Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. Ann Intern Med. 1997;126:753-60. [PMID: 9148647]

24. **Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al; Cholesterol Treatment Trialists' (CTT) Collaborators.** Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267-78. [PMID: 16214597]

25. **McAlister FA, van Diepen S, Padwal RS, Johnson JA, Majumdar SR.** How evidence-based are the recommendations in evidence-based guidelines? PLoS Med. 2007;4:e250. [PMID: 17683197]

26. **Pletcher MJ, Lazar L, Bibbins-Domingo K, Moran A, Rodondi N, Coxson P, et al.** Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern Med. 2009;150:243-54. [PMID: 19221376]

27. **Freidlin B, Korn EL.** Stopping clinical trials early for benefit: impact on estimation. Clin Trials. 2009;6:119-25. [PMID: 19342463]

28. **Korn EL, Freidlin B, Mooney M.** Stopping or reporting early for positive results in randomized clinical trials: the National Cancer Institute Cooperative Group experience from 1990 to 2005. J Clin Oncol. 2009;27:1712-21. [PMID: 19237631]

29. **Sargent D.** Early stopping for benefit in National Cancer Institute-sponsored randomized Phase III trials: the system is working [Editorial]. J Clin Oncol. 2009;27:1543-4. [PMID: 19237627]

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