

ORIGINAL ARTICLE

A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism

Robert J. Glynn, Sc.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Paul M Ridker, M.D.

ABSTRACT

BACKGROUND

Controversy persists regarding the extent of shared pathways between arterial and venous thrombosis and whether treatments of known efficacy for one disease process have consistent benefits for the other. Observational studies have yielded variable estimates of the effect of statin therapy on the risk of venous thromboembolism, and evidence from randomized trials is lacking.

METHODS

We randomly assigned 17,802 apparently healthy men and women with both low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to receive rosuvastatin, 20 mg per day, or placebo. We followed participants for the first occurrence of pulmonary embolism or deep-vein thrombosis and performed analyses of the data on an intention-to-treat basis.

RESULTS

During a median follow-up period of 1.9 years (maximum, 5.0), symptomatic venous thromboembolism occurred in 94 participants: 34 in the rosuvastatin group and 60 in the placebo group. The rates of venous thromboembolism were 0.18 and 0.32 event per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio with rosuvastatin, 0.57; 95% confidence interval [CI], 0.37 to 0.86; $P=0.007$); the corresponding rates for unprovoked venous thromboembolism (i.e., occurring in the absence of a known malignant condition, trauma, hospitalization, or surgery) were 0.10 and 0.17 (hazard ratio, 0.61; 95% CI, 0.35 to 1.09; $P=0.09$) and for provoked venous thromboembolism (i.e., occurring in patients with cancer or during or shortly after trauma, hospitalization, or surgery), 0.08 and 0.16 (hazard ratio, 0.52; 95% CI, 0.28 to 0.96; $P=0.03$). The rates of pulmonary embolism were 0.09 in the rosuvastatin group and 0.12 in the placebo group (hazard ratio, 0.77; 95% CI, 0.41 to 1.45; $P=0.42$), whereas the rates of deep-vein thrombosis only were 0.09 and 0.20, respectively (hazard ratio, 0.45; 95% CI, 0.25 to 0.79; $P=0.004$). Consistent effects were observed in all the subgroups examined. No significant differences were seen between treatment groups in the rates of bleeding episodes.

CONCLUSIONS

In this trial of apparently healthy persons, rosuvastatin significantly reduced the occurrence of symptomatic venous thromboembolism. (ClinicalTrials.gov number, NCT00239681.)

From the Divisions of Preventive Medicine (R.J.G., E.D., J.G.M., P.M.R.) and Cardiovascular Medicine (P.L., P.M.R.), Brigham and Women's Hospital, Harvard Medical School, Boston; Universidade Federal de São Paulo, São Paulo (F.A.H.F.); McGill University Health Center, Montreal (J.G.); Weill Medical College of Cornell University, New York (A.M.G.); Academic Medical Center, University of Amsterdam, Amsterdam (J.J.P.K.); University of Ulm, Ulm, Germany (W.K.); Hospital Cordoba, Cordoba, Argentina (A.J.L.); Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Herlev, Denmark (B.G.N.); University of Glasgow, Glasgow, Scotland (J.S.); and St. Luke's Episcopal Hospital-Texas Heart Institute, Houston (J.T.W.). Address reprint requests to Dr. Glynn at the Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave., Boston, MA 02215, or at rglynn@rics.bwh.harvard.edu.

This article (10.1056/NEJMoa0900241) was published at NEJM.org on March 29, 2009.

N Engl J Med 2009;360:1851-61.
Copyright © 2009 Massachusetts Medical Society.

VENOUS AND ARTERIAL THROMBOSIS ARE common, serious, and strongly age-related events that often occur together^{1,2} and share some risk factors.³⁻⁷ Controversies persist regarding the nature and extent of their shared pathways and whether treatments of demonstrated efficacy for one condition, including anticoagulant agents, antiplatelet therapy, thrombolytic agents, and statins, have consistent benefits for the primary or secondary prevention of the other.⁸⁻¹⁰

The benefits of statins might accrue not only through their effects on lipid levels but also through their influence on thrombosis and inflammation.¹¹⁻¹³ Two prospective, observational studies showed that substantial and significant reductions in the risk of venous thromboembolism were associated with the use of statins, including a 50% reduction in the risk among statin users in the Heart and Estrogen/Progestin Replacement Study¹⁴ and a 22% reduction among statin users in Ontario, Canada, as calculated on the basis of administrative claims data.¹⁵ Four case-control studies also showed reductions in the risk of venous thrombosis — ranging from 26% to 58% — that were associated with the use of statins.¹⁶⁻¹⁹ However, two additional observational studies, which used computerized databases in the United Kingdom, showed no association between the use of statins and the risk of venous thrombosis.^{20,21} Furthermore, estimation of the potential pleiotropic effects of statins in observational studies is subject to confounding because it is difficult to evaluate the indications for, and barriers to, the initiation of statin therapy, as well as patients' compliance with it.²² In view of these challenges to reliable estimation, evidence from randomized trials is required.²³

Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) examined the question of whether treatment with 20 mg of rosuvastatin daily, as compared with placebo, would reduce the rate of first major cardiovascular events. The occurrence of venous thromboembolism was a protocol-specified secondary end point of the trial.

METHODS

TRIAL DESIGN

JUPITER was a randomized, double-blind, placebo-controlled, multicenter trial that was conducted at 1315 sites in 26 countries. Details of the design

of the study and the findings with respect to the primary end point are presented elsewhere.^{24,25} The trial protocol was designed and written by the study chair and approved by the institutional review board at each participating center. The trial data were analyzed by the academic authors, who vouch for the accuracy and completeness of the data.

The trial was initiated by the investigators and was financially supported by AstraZeneca. The sponsor collected the trial data and monitored the study sites but played no role in the conduct of the analyses or drafting of the manuscript.

STUDY POPULATION

As described in detail elsewhere,^{24,25} men 50 years of age or older and women 60 years of age or older were eligible for inclusion in the study if they had no history of cardiovascular disease, and if, at the initial screening visit, they had a low-density lipoprotein (LDL) cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) and a high-sensitivity C-reactive protein level of 2.0 mg per liter or more. Other requirements included a willingness to participate for the duration of the trial, provision of written informed consent, and a triglyceride level of less than 500 mg per deciliter (5.6 mmol per liter). Exclusion criteria that were related to characteristics with known or possible associations with venous thrombosis included the use of lipid-lowering therapy within 6 weeks before screening, current use of postmenopausal hormone-replacement therapy, cancer within 5 years before enrollment (with the exception of basal-cell or squamous-cell carcinoma of the skin), diabetes, and uncontrolled hypertension.

RANDOMIZATION AND FOLLOW-UP

Potentially eligible subjects who remained willing to participate and demonstrated good compliance during a 4-week, placebo run-in phase were randomly assigned in a 1:1 ratio to receive either rosuvastatin, 20 mg daily, or matching placebo. From March 14, 2003, through December 15, 2006, a total of 17,802 persons were randomly assigned to a study group.

Follow-up visits were scheduled to occur at 13 weeks and at 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after randomization. A closeout visit occurred after study termination, at which time participants were informed of their group assignment. At each follow-up visit, participants were interviewed for the assessment of outcomes, in-

cluding clinically symptomatic deep-vein thrombosis and pulmonary embolism. At these visits, the initiation of concomitant medications and their indications were also assessed, with a protocol-specified focus on anticoagulants because statins can potentiate the anticoagulant effect of warfarin. Personnel at each site also contacted their participants midway between scheduled visits to identify any changes in health status and address any concerns regarding participation in the study.

END POINTS

The protocol specified that when a new case of venous thromboembolism was identified, the site investigator would complete a form indicating the source of confirmation of the event, including a venous ultrasonogram or venogram for confirmation of deep-vein thrombosis and an angiogram, computed tomographic scan, or ventilation-perfusion scan for confirmation of pulmonary embolism. Cases of venous thromboembolism included all cases of diagnosed pulmonary embolism or deep-vein thrombosis. We also looked for corroborating evidence in the form of a confirmatory diagnostic test, the initiation of anticoagulation therapy, or death that was considered likely to have been due to a pulmonary embolism.

Deep-vein thrombosis or pulmonary embolism was classified as unprovoked if it occurred in the absence of any recent trauma, hospitalization, or surgery (i.e., occurring within 3 months before the event) and in the absence of a malignant condition that was diagnosed before or up to 3 months after the event. The thrombotic disorder was classified as provoked if it occurred in a patient with cancer or if it occurred during or shortly after trauma, hospitalization, or surgery.

On March 30, 2008, the trial's steering committee accepted the recommendation of the independent data and safety monitoring board to terminate the trial on the basis of convincing evidence of efficacy with respect to the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or confirmed death from cardiovascular causes. Follow-up for the trial's primary and secondary efficacy end points ended on that date. However, follow-up with respect to safety for the prespecified secondary end points (i.e., venous thromboembolism, diabetes, discontinuation of the study medication owing to an adverse event, bone fractures, any death, and death from non-

cardiovascular causes) continued in a blinded manner for each study participant until the date he or she appeared for a formal closeout visit and discontinued the study therapy. The last closeout visit occurred on August 20, 2008.

STATISTICAL ANALYSIS

All analyses of venous thromboembolism were performed on an intention-to-treat basis; only a participant's first diagnosed venous thromboembolism after randomization was included in the analyses. Cox proportional-hazards models were used to estimate hazard ratios and 95% confidence intervals for the comparison of event rates in the two groups. The primary analysis focused on events that occurred on or before March 30, 2008; secondary analyses also included the person-years and events that occurred in the period after March 30, 2008, until a participant's final closeout visit, when the treatment assignment was revealed. Tertiary end points included provoked and unprovoked venous thromboembolism, pulmonary embolism, and deep-vein thrombosis only. Subgroup analyses compared rates of venous thromboembolism between study groups according to the presence or absence of possible or likely determinants of venous thromboembolism.

Because venous thromboembolism commonly occurs around the time of cardiovascular events, additional analyses evaluated whether the apparent effect of rosuvastatin with respect to venous thromboembolism could be secondary to the observed benefit with respect to cardiovascular events. Separate proportional-hazards models were used to estimate the cause-specific hazard of venous thromboembolism and the cause-specific hazard of a primary cardiovascular event, each in analyses that censored follow-up data at the first occurrence of either event. A likelihood-ratio test was used to compare the treatment effect between the two outcomes.⁶ To measure the net clinical benefit of rosuvastatin when the combined effects on venous and arterial thrombosis were considered, we also fitted a proportional-hazards model with the first occurrence of venous thromboembolism or the primary cardiovascular end point as a composite outcome and estimated differences in risk and the number needed to treat²⁶ for absolute measures of treatment efficacy. We repeated these analyses with a composite end point of the first occurrence of venous thromboembolism, cardiovascular disease, or death from any cause.

RESULTS

BASELINE CHARACTERISTICS OF THE PARTICIPANTS

Among the 17,802 participants in JUPITER who were randomly assigned to a study group, 32.0% were 70 years of age or older at baseline, 38.2% were women, and 25.2% were black or Hispanic (Table 1). In both the rosuvastatin and placebo groups, 37.6% of the subjects had a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or higher. The median waist circumference was 100 cm in men and 95 cm in women. The metabolic syndrome²⁷ was present in 41.7% of participants, and 41.3% had

a high-sensitivity C-reactive protein level of 5.0 mg per liter or higher. At the time of randomization, 1.4% of the participants in the rosuvastatin group and 1.2% of those in the placebo group were taking anticoagulants.

OCCURRENCE OF VENOUS THROMBOEMBOLISM

Symptomatic pulmonary embolism or deep-vein thrombosis occurred in 94 participants (34 in the rosuvastatin group and 60 in the placebo group) from the time of randomization through March 30, 2008 (median follow-up time, 1.9 years) (Table 2). The rates of venous thromboembolism were 0.18 and 0.32 event per 100 person-years of follow-up

Table 1. Baseline Characteristics of the Trial Participants, According to Study Group.

Characteristic	Rosuvastatin (N = 8901)	Placebo (N = 8901)
Age — no. (%)		
<60 yr	1846 (20.7)	1843 (20.7)
60–69 yr	4177 (46.9)	4241 (47.6)
≥70 yr	2878 (32.3)	2817 (31.6)
Female sex — no. (%)	3426 (38.5)	3375 (37.9)
Race or ethnic group — no. (%)*		
White	6358 (71.4)	6325 (71.1)
Black	1100 (12.4)	1124 (12.6)
Hispanic	1121 (12.6)	1140 (12.8)
Other or unknown	322 (3.6)	312 (3.5)
Body-mass index — no./total no. (%)†		
<25	2040/8873 (23.0)	2033/8883 (22.9)
25 to <30	3495/8873 (39.4)	3514/8883 (39.6)
≥30	3338/8873 (37.6)	3336/8883 (37.6)
Waist circumference — no./total no. (%)		
<100 cm in men and <95 cm in women	4317/8820 (48.9)	4269/8815 (48.4)
≥100 cm in men and ≥95 cm in women	4503/8820 (51.1)	4546/8815 (51.6)
Current smoker — no./total no. (%)	1400/8896 (15.7)	1420/8899 (16.0)
Metabolic syndrome — no./total no. (%)‡	3652/8832 (41.3)	3723/8839 (42.1)
High-sensitivity C-reactive protein ≥5 mg/liter — no. (%)§	3618 (40.6)	3726 (41.9)
LDL cholesterol >100 mg/dl — no./total no. (%)¶	5781/8898 (65.0)	5747/8899 (64.6)
HDL cholesterol <40 mg/dl in men and <50 mg/dl in women — no./total no. (%)¶	2833/8900 (31.8)	2856/8901 (32.1)
Triglycerides ≥150 mg/dl — no./total no. (%)	2900/8900 (32.6)	2936/8901 (33.0)

* Race or ethnic group was self-reported.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The metabolic syndrome was defined according to consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute.²⁷

§ Values for high-sensitivity C-reactive protein are the average of values obtained at two screening visits.

¶ To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

|| To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

in the rosuvastatin and placebo groups, respectively (hazard ratio for the rosuvastatin group, 0.57; 95% confidence interval [CI], 0.37 to 0.86; $P=0.007$) (Table 2). Although cumulative-incidence curves did not appear to diverge until about 1 year after the initiation of treatment (Fig. 1), a test for interaction between treatment assignment and continuous follow-up time showed no significant violation of the proportional-hazards assumption ($P=0.14$).

Among the 94 cases of symptomatic pulmonary embolism or deep-vein thrombosis, 44 occurred in patients with cancer or recent trauma, hospitalization, or surgery (i.e., provoked events), whereas a proximate cause was not identified in 50 cases (i.e., unprovoked events). The observed reductions in risk were similar whether the analyses were restricted to unprovoked events or to provoked events (hazard ratio for unprovoked events in the rosuvastatin group, 0.61; 95% CI, 0.35 to 1.09; $P=0.09$; hazard ratio for provoked events, 0.52; 95% CI, 0.28 to 0.96; $P=0.03$) (Table 2 and Fig. 1). Half (17) of the cases in the rosuvastatin group involved pulmonary embolism, as compared with 37% (22) of the cases in the placebo group, but these percentages did not differ significantly ($P=0.21$).

When the follow-up time was extended through the final closeout visit, at which time participants were informed of their group assignments, an additional 5 cases of venous thromboembolism were identified, bringing the total number of cases to 35 in the rosuvastatin group and 64 in the placebo group (Table 2). Analyses of all cases as well as of components of the outcome produced estimates that were similar to those obtained in the primary efficacy analysis.

Three of the cases (one in the rosuvastatin group and two in the placebo group) did not have corroborating evidence in the form of a confirmatory diagnostic test, initiation of anticoagulation therapy, or death that was likely to have been due to pulmonary embolism. Analyses that excluded these three cases showed nearly identical results. Analyses that were restricted to participants who were not taking anticoagulants at baseline excluded two cases (one in the rosuvastatin group and one in the placebo group) and also yielded nearly the same results.

SUBGROUP ANALYSES

None of the baseline characteristics that were considered in subgroup analyses significantly modified the relationship of rosuvastatin to the risk of

Table 2. Occurrence of Venous Thromboembolism According to Study Group.

End Point	Rosuvastatin (N=8901)		Placebo (N=8901)		Hazard Ratio (95% CI)	P Value
	no. of patients	no. of events/100 person-yr	no. of patients	no. of events/100 person-yr		
Primary efficacy analysis*						
Venous thromboembolism						
Total	34	0.18	60	0.32	0.57 (0.37–0.86)	0.007
Unprovoked	19	0.10	31	0.17	0.61 (0.35–1.09)	0.09
Provoked	15	0.08	29	0.16	0.52 (0.28–0.96)	0.03
Pulmonary embolism	17	0.09	22	0.12	0.77 (0.41–1.45)	0.42
Deep-vein thrombosis only	17	0.09	38	0.20	0.45 (0.25–0.79)	0.004
Safety analysis†						
Venous thromboembolism						
Total	35	0.18	64	0.33	0.55 (0.36–0.82)	0.003
Unprovoked	20	0.10	34	0.18	0.59 (0.34–1.02)	0.06
Provoked	15	0.08	30	0.16	0.50 (0.27–0.93)	0.02
Pulmonary embolism	17	0.09	24	0.12	0.71 (0.38–1.32)	0.27
Deep-vein thrombosis only	18	0.09	40	0.21	0.45 (0.26–0.78)	0.003

* The primary efficacy analysis was performed on the basis of 94 cases identified by March 30, 2008.

† The safety analysis was performed on the basis of 99 cases that were identified before the study was unblinded.

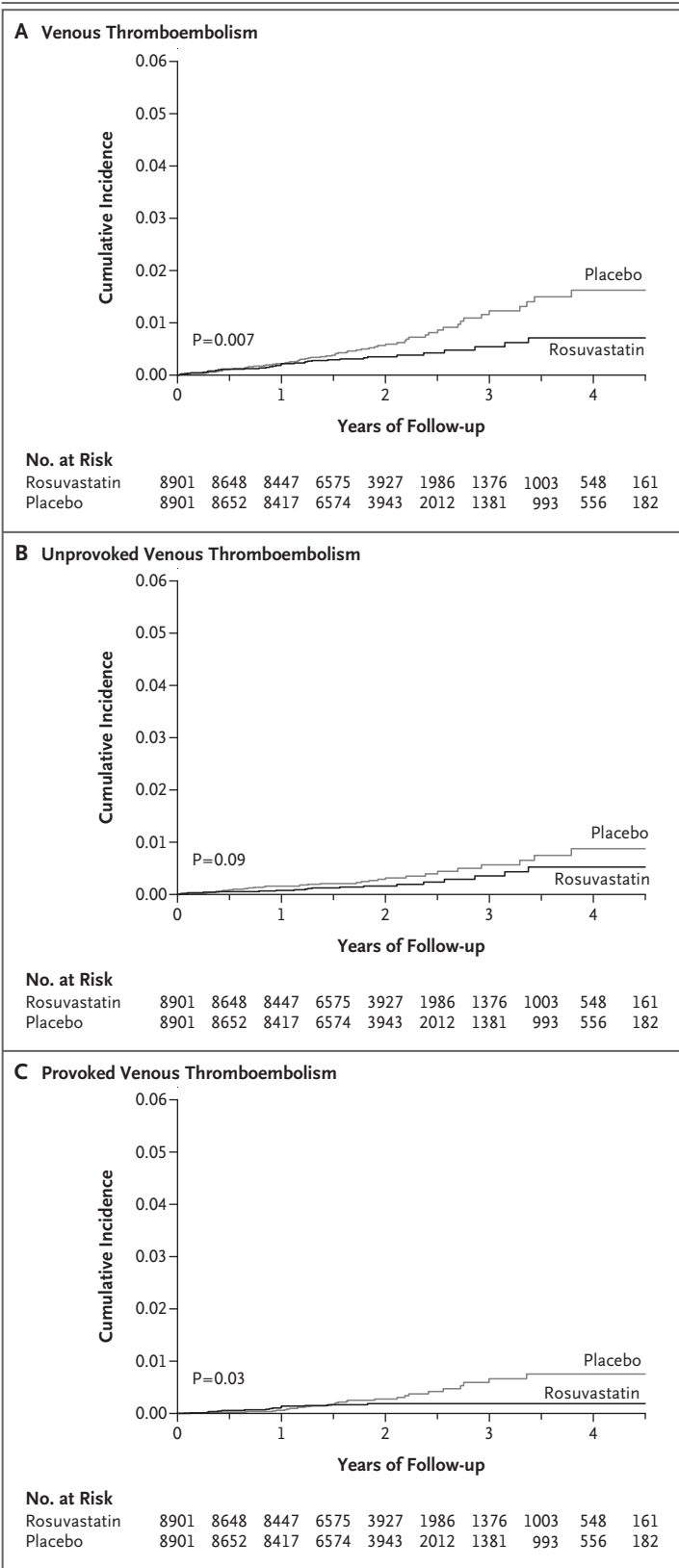


Figure 1. Cumulative Incidence of Venous Thromboembolism in the Rosuvastatin and Placebo Groups.

Panel A shows the incidence of any venous thromboembolism, Panel B the incidence of unprovoked venous thromboembolism (i.e., occurring in the absence of a known malignant condition, trauma, hospitalization, or surgery), and Panel C the incidence of provoked venous thromboembolism (i.e., occurring in patients with cancer or during or shortly after trauma, hospitalization, or surgery). The P values were calculated on the basis of a likelihood-ratio test of the effect of rosuvastatin, with the use of a proportional-hazards model.

venous thromboembolism ($P > 0.10$ for each interaction) (Fig. 2). Subgroups with the highest rates of venous thromboembolism in the placebo group included participants who were 70 years of age or older, those who had a body-mass index of 30 or higher, and those who had a waist circumference at or above the sex-specific median (95 cm in women and 100 cm in men). Similar estimated reductions in the risk of venous thromboembolism were observed in each of these higher-risk subgroups, although the confidence intervals were wide and the effects were not significant for some comparisons. The rate of venous thromboembolism was also elevated in the placebo group for a follow-up time of more than 2 years after randomization, perhaps reflecting the interim development of coexisting conditions that can trigger venous thromboembolism. With respect to baseline lipid levels, rates of venous thromboembolism in the placebo group and the observed effects of rosuvastatin were similar between participants with LDL cholesterol levels of 100 mg per deciliter (2.6 mmol per liter) or lower and those with LDL cholesterol levels above this level; between men with high-density lipoprotein (HDL) cholesterol levels below 40 mg per deciliter (1.0 mmol per liter) or women with levels below 50 mg per liter (1.3 mmol per liter) and men or women with HDL cholesterol levels at or above these levels; and between participants with triglyceride levels below 150 mg per deciliter (1.7 mmol per liter) and those with triglyceride levels at or above this level.

VENOUS THROMBOEMBOLISM AND CARDIOVASCULAR EVENTS

In additional analyses, we sought to identify the independent and possibly incremental effects of rosuvastatin on venous thromboembolism, beyond the benefits previously described with respect to

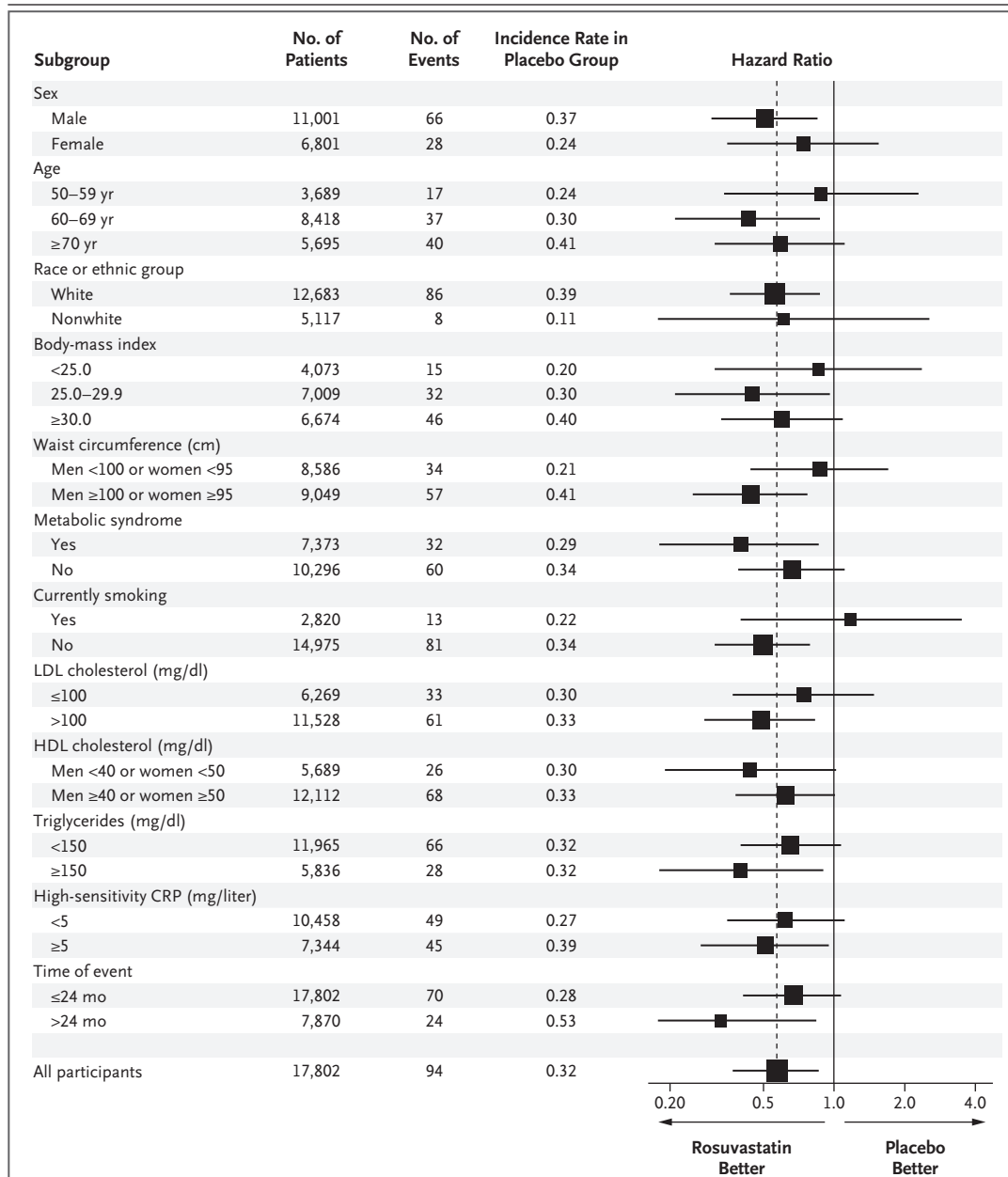


Figure 2. Effects of Rosuvastatin on the Risk of Venous Thromboembolism, According to Baseline Characteristics of the Study Participants.

Hazard ratios for the rosuvastatin group as compared with the placebo group are shown, with the size of each black square proportionate to the number of participants in the subgroup in whom venous thromboembolism developed; the horizontal lines indicate 95% confidence intervals. The dashed vertical line indicates the overall hazard ratio for the entire trial cohort. The incidence rate in the placebo group is the number of events per 100 person-years of follow-up. Not shown are P values for tests of interaction between rosuvastatin and subgroup variables, each of which was nonsignificant ($P>0.10$). For each subgroup, the number of patients for whom data were available is shown. Data were missing for some participants in some subgroups. The metabolic syndrome was defined according to consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute.²⁷ To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. The body-mass index is the weight in kilograms divided by the square of the height in meters. CRP denotes C-reactive protein, HDL high-density lipoprotein, and LDL low-density lipoprotein.

arterial thrombosis.²⁵ From the time of randomization through March 30, 2008, a total of 173 participants in the rosuvastatin group had either venous thromboembolism or a primary cardiovascular end point (32 had venous thromboembolism as the first event), and 305 participants in the placebo group had either venous thromboembolism or a primary cardiovascular event (56 had venous thromboembolism as the first event) (Table 3). A few participants had both venous thromboembolism and the primary cardiovascular end point: six had venous thromboembolism after a primary cardiovascular event, and three had a primary cardiovascular event after venous thromboembolism. The estimated relative hazard of venous thromboembolism as a first event did not differ significantly from the estimated relative hazard of 0.56 associated with rosuvastatin for the prevention of a primary cardiovascular event ($P=0.99$). For the composite end point of the first occurrence of either venous thromboembolism or the primary cardiovascular end point, the rates were 0.93 and 1.66 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio with rosuvastatin, 0.56; 95% CI, 0.47 to 0.68; $P<0.001$).

NET BENEFITS OF STATIN TREATMENT

When we considered the composite end point of the first occurrence of either venous thromboembolism or the primary cardiovascular end point,

the difference in rates between the placebo and rosuvastatin groups was 0.73 event per 100 person-years (Table 3). This difference is 24% larger than the difference in rates of 0.59 event per 100 person-years that was observed for the primary cardiovascular end point alone.²⁵ The estimated number needed to treat for 4 years to prevent either one episode of venous thromboembolism or one primary cardiovascular end point is 26, and the projected number needed to treat for 5 years is 21. These numbers are smaller than the estimated numbers needed to treat for 4 years and for 5 years to prevent the primary cardiovascular end point only (31 and 25, respectively).²⁵

Among the 94 participants in whom venous thromboembolism developed, 21 died by March 30, 2008 (14 in the placebo group). Altogether, 320 participants in the rosuvastatin group had a first cardiovascular event or venous thromboembolism or died, as compared with 483 participants in the placebo group (hazard ratio 0.66; 95% CI, 0.57 to 0.76; $P<0.001$). When this composite end point was considered, the number of patients needed to treat for 4 years to prevent one event was estimated to be 23, and the number needed to treat for 5 years was projected to be 18.

ADVERSE EVENTS

Rates of monitored adverse events and other reported adverse events of interest in the two study groups were reported previously.²⁵ In particular,

Table 3. Occurrence of Venous Thromboembolism, Cardiovascular Disease, and Death According to Study Group.*

End Point	Rosuvastatin (N=8901)		Placebo (N=8901)		Hazard Ratio (95% CI)	P Value
	no. of patients	no. of events/100 person-yr	no. of patients	no. of events/100 person-yr		
Venous thromboembolism with no prior cardiovascular event	32	0.17	56	0.30	0.57 (0.37–0.88)	0.009
Cardiovascular event with no prior venous thromboembolism	141	0.76	249	1.35	0.56 (0.46–0.69)	<0.001
Venous thromboembolism after cardiovascular event	2	0.61	4	0.65	0.98 (0.18–5.34)	0.98
First cardiovascular event or venous thromboembolism	173	0.93	305	1.66	0.56 (0.47–0.68)	<0.001
Death after venous thromboembolism	7	18.24	14	20.38	0.88 (0.35–2.18)	0.78
First cardiovascular event, venous thromboembolism, or death	320	1.73	483	2.62	0.66 (0.57–0.76)	<0.001

* Cardiovascular event refers to the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

bleeding was reported as an adverse event in 258 participants assigned to rosuvastatin and 275 participants assigned to placebo ($P=0.45$).

DISCUSSION

In this substudy from a large, randomized trial of initially healthy men and women, treatment with 20 mg of rosuvastatin daily was associated with a significant reduction in the occurrence of venous thromboembolism. The observed treatment effect was similar to, and independent of, the previously observed effect for arterial events. The apparent benefit was also similar whether venous thromboembolism was provoked or unprovoked. The benefit was somewhat larger for the end point of deep-vein thrombosis only than for the end point of pulmonary embolism. Consistent effects were seen across subgroups, with a notable benefit observed in the high-risk subgroups of older participants and those with elevated waist circumference.

Venous thromboembolism is common, difficult to diagnose, and costly to treat, and it frequently results in venous insufficiency and chronic thromboembolic pulmonary hypertension; preventive strategies that have acceptable costs and side effects are therefore needed. The frequency of venous thromboembolism among the participants in JUPITER — 94 observed cases — was similar to that of fatal or nonfatal stroke (97 cases) and of fatal or nonfatal myocardial infarction (99 cases).²⁵ This finding is consistent with population-based estimates from Rochester County, Minnesota,²⁸ which showed that the incidence of venous thromboembolism was similar to that of stroke, and from the Brest region of France,²⁹ which showed that the incidence of venous thromboembolism was similar to that of myocardial infarction.

In JUPITER, we observed little evidence of increased rates of venous thromboembolism among participants in the placebo group who had levels of LDL cholesterol or triglycerides that exceeded the specified cutoff points or among those who had levels of HDL cholesterol that were lower than the specified cutoff points. This finding is consistent with the results of two prospective cohort studies that showed no association of levels of HDL, LDL, or total cholesterol or of triglycerides with the risk of venous thromboembolism,^{5,30,31} but contrasts with the observation in another study that an increased risk of recurrent venous thromboembolism was associated with low levels

of HDL cholesterol.³² In addition, the observation in previous studies^{15,17,18} that there was no association between nonstatin lipid-lowering drugs and the occurrence of venous thromboembolism is consistent with the JUPITER data. Among participants in JUPITER who had a baseline level of high-sensitivity C-reactive protein of 5 mg per liter or higher, the rate of venous thromboembolism was somewhat elevated. However, prospective observational studies indicate that measurement of high-sensitivity C-reactive protein has limited value in predicting the occurrence of venous thromboembolism, after adjustment for the body-mass index.^{33,34} Statins have several other mechanisms of action that could limit the occurrence of venous thromboembolism. Statins inhibit isoprenylation of signaling proteins, with several potential antithrombotic consequences, such as reduced tissue factor expression and thrombin generation, attenuated fibrinogen cleavage, and activation of factors V and VII.^{11,12,34} Statins also augment the activity of the transcription factor Kruppel-like factor 2 (KLF-2), promoting thrombomodulin expression on endothelial cells, thereby enhancing the activity of the protein C anticoagulant pathway.³⁵

The main strengths of our study include the prospective, double-blind treatment assignment and end-point ascertainment and prespecification of venous thromboembolism as an end point. The limitations of our study include its restriction to initially healthy participants and the limited long-term follow-up. In addition, we did not elaborate the potential mechanisms of action of statins with respect to the prevention of venous thromboembolism. Our study also does not allow for an evaluation of the relationship between the dose of the statin and the risk of venous thromboembolism. Data from an observational study suggest that there may be a greater benefit with higher doses,¹⁶ but the evidence is limited by confounding and by the small size of the study. JUPITER focused on symptomatic venous thromboembolism, but asymptomatic venous thromboembolism is common and consequential³⁶; thus, the magnitude of the absolute risk may have been underestimated. Overall, validation of our results and further elucidation of the potential mechanisms will be important to confirm our findings. In particular, randomized data on statin use in high-risk persons, such as those with previous venous thrombosis, is needed.

In conclusion, in this randomized trial of ap-

parently healthy men and women, rosuvastatin was associated with a significant reduction in the risk of venous thromboembolism. This risk reduction appears to be an independent benefit of statin use, beyond the reduction in the risk of arterial thrombosis. Widening the goal of treatment to include prevention of venous thromboembolism and death, in addition to arterial thrombosis, increases the estimated benefit of statin use.

Supported primarily by AstraZeneca and also by a grant from the National Institute on Aging (AG031061).

Dr. Glynn reports receiving grant support from AstraZeneca; Dr. Fonseca, receiving consulting and lecture fees from AstraZeneca, Pfizer, and Merck-Schering-Plough; Dr. Genest, receiving lecture fees from AstraZeneca, Merck-Schering-Plough, and GlaxoSmithKline and consulting fees from AstraZeneca and Merck-Schering-Plough; Dr. Gotto, receiving consulting fees from Dupont, Novartis, Aegerion, Arisaph, Kowa, Merck-Schering-Plough, Genentech, and Martek, and receiving publication royalties; Dr. Kastelein, receiving research support from AstraZeneca, Pfizer, Roche, Novartis, Merck-Schering-Plough, Isis, Genzyme, and Sanofi-Aventis, lecture fees from AstraZeneca, GlaxoSmithKline, Pfizer, Novartis, Merck-Schering-Plough, Roche, Isis, Genzyme, and Boehringer Ingelheim, and consulting fees

from AstraZeneca, Abbott, Pfizer, Isis, Genzyme, Roche, Novartis, Merck-Schering-Plough, Eli Lilly, and Sanofi-Aventis; Dr. Koenig, receiving research support from Anthera, Siemens, AstraZeneca, and GlaxoSmithKline, lecture fees from AstraZeneca, Pfizer, Novartis, GlaxoSmithKline, diaDexus, Roche, and Boehringer Ingelheim, and consulting fees from GlaxoSmithKline, Medlogix, Anthera, and Roche; Dr. Libby, receiving lecture and consulting fees from AstraZeneca; Dr. Lorenzatti, receiving consulting fees from Abbott, AstraZeneca, Novartis, and Takeda and lecture fees from Abbott, AstraZeneca, and Merck-Schering-Plough; Dr. Nordestgaard, receiving lecture fees from AstraZeneca, Abbott, Sanofi-Aventis, Pfizer, Boehringer Ingelheim, and Merck-Schering-Plough and consulting fees from AstraZeneca and BG Medicine; Dr. Shepherd, receiving lecture fees from AstraZeneca and Pfizer and consulting fees from AstraZeneca, Pfizer, Merck-Schering-Plough and Oxford Biosciences; and Dr. Ridker, receiving grant support from AstraZeneca, Novartis, Roche, and Sanofi-Aventis, having a collaborative grant with Amgen, which provides genotyping for his research, receiving consulting fees, lecture fees, or both from AstraZeneca, Novartis, Merck-Schering-Plough, Sanofi-Aventis, Isis, Siemens, and Vascular Biogenics, and being listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease. These patents have been licensed to several entities, including AstraZeneca and Siemens. No other potential conflict of interest relevant to this article was reported.

REFERENCES

- Prandoni P, Bilora F, Marchiori A, et al. An association between atherosclerosis and venous thrombosis. *N Engl J Med* 2003;348:1435-41.
- Sørensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalization due to acute arterial cardiovascular events: a 20-year cohort study. *Lancet* 2007;370:1773-9.
- Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. *JAMA* 1997;277:642-5.
- Hansson P-O, Eriksson H, Welin L, Svärdsudd K, Wilhelmsen L. Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: "The Study of Men Born in 1913." *Arch Intern Med* 1999;159:1886-90.
- Tsai AW, Cushman M, Rosamond W, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med* 2002;162:1182-9.
- Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *Am J Epidemiol* 2005;162:975-82.
- Ageno W, Beccattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation* 2008;117:93-102.
- Lowe GDO. Arterial disease and venous thrombosis: are they related, and if so, what should we do about it? *J Thromb Haemost* 2006;4:1882-5.
- Agnelli G, Becattini C. Venous thromboembolism and atherosclerosis: common denominators or different diseases? *J Thromb Haemost* 2006;4:1886-90.
- Glynn RJ, Ridker PM, Goldhaber SZ, Buring JE. Effect of low-dose aspirin on the occurrence of venous thromboembolism: a randomized trial. *Ann Intern Med* 2007;147:525-33.
- Undas A, Brummel-Ziedins KE, Mann KG. Statins and blood coagulation. *Arterioscler Thromb Vasc Biol* 2005;25:287-94.
- Kaba NK, Francis CW, Moss AJ, et al. Effects of lipids and lipid-lowering therapy on hemostatic factors in patients with myocardial infarction. *J Thromb Haemost* 2004;2:718-25.
- Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001;286:64-70.
- Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the Heart and Estrogen/Progestin Replacement Study. *Ann Intern Med* 2000;132:689-96.
- Ray JG, Mamdani M, Tsuyuki RT, Anderson DR, Yeo EL, Laupacis A. Use of statins and the subsequent development of deep vein thrombosis. *Arch Intern Med* 2001;161:1405-10.
- Doggen CJM, Lemaitre RN, Smith NL, Heckbert SR, Psaty BM. HMG CoA reductase inhibitors and the risk of venous thrombosis among postmenopausal women. *J Thromb Haemost* 2004;2:700-1.
- Lacut K, Oger E, Le Gal G, et al. Statins but not fibrates are associated with a reduced risk of venous thromboembolism: a hospital-based case-control study. *Fundam Clin Pharmacol* 2004;18:477-82.
- Ramcharan AS, van Stralen KJ, Snoep JD, Mantel-Teeuwisse AK, Rosendaal FR, Doggen CJM. HMG-CoA-reductase inhibitors, other lipid lowering medication, antiplatelet therapy, and the risk of venous thrombosis. *J Thromb Haemost* 2009;7:514-20.
- Sørensen HT, Horvath-Puho E, Søgaard KK, et al. Arterial cardiovascular events, statins, low dose aspirin and subsequent risk of venous thromboembolism: a population-based case-control study. *J Thromb Haemost* 2009;7:521-8.
- Yang CC, Jick SS, Jick H. Statins and the risk of idiopathic venous thromboembolism. *Br J Clin Pharmacol* 2002;53:101-5.
- Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. *Br J Clin Pharmacol* 2008;67:99-109.
- Glynn RJ, Schneeweiss S, Wang PS, Levin R, Avorn J. Selective prescribing led to overestimation of the benefits of lipid-lowering drugs. *J Clin Epidemiol* 2006;59:819-28.

23. Ray JG. Do we care if statins prevent venous thromboembolism? *J Thromb Haemost* 2004;2:695-6.
24. Ridker PM, Fonseca FAH, Genest J, et al. Baseline characteristics of participants in the JUPITER trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Am J Cardiol* 2007;100:1659-64.
25. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-207.
26. 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.
27. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: executive summary. *Circulation* 2005;112:2735-52.
28. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;158:585-93.
29. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. *Thromb Haemost* 2000;83:657-60.
30. Everett BM, Glynn RJ, Buring JE, Ridker PM. Lipid biomarkers, hormone therapy, and risk of venous thromboembolism in women. *J Thromb Haemost* 2009 January 24 (Epub ahead of print).
31. Chamberlain AM, Folsom AR, Heckbert SR, Rosamond WD, Cushman M. High-density lipoprotein cholesterol and venous thromboembolism in the Longitudinal Investigation of Thromboembolism Etiology (LITE). *Blood* 2008;112:2675-80.
32. Eichinger S, Pecheniuk NM, Hron G, et al. High-density lipoprotein and the risk of recurrent venous thromboembolism. *Circulation* 2007;115:1609-14.
33. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973-9. [Erratum, *N Engl J Med* 1997;337:356.]
34. Tsai AW, Cushman M, Rosamond WD, et al. Coagulation factors, inflammation markers, and venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE). *Am J Med* 2002;113:636-42.
35. Sen-Banerjee S, Mir S, Lin Z, et al. Kruppel-like factor 2 as a novel mediator of statin effects in endothelial cells. *Circulation* 2005;112:720-6.
36. Vaitkus PT, Leizorovicz A, Cohen AT, Turpie AGG, Olsson C-G, Goldhaber SZ. Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients. *Thromb Haemost* 2005;93:76-9.

Copyright © 2009 Massachusetts Medical Society.

COLLECTIONS OF ARTICLES ON THE JOURNAL'S WEB SITE

The *Journal's* Web site (NEJM.org) sorts published articles into more than 50 distinct clinical collections, which can be used as convenient entry points to clinical content. In each collection, articles are cited in reverse chronological order, with the most recent first.