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A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism: the JUPITER Trial

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Abstract

Background—Controversies persist on whether arterial and venous thrombosis share common pathways 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 risk of venous thromboembolism, and randomized evidence is lacking.

Methods—Symptomatic venous thromboembolism was a pre-specified endpoint of Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). We randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg/dL and high-sensitivity C-reactive protein levels of 2.0 mg/L or higher to rosuvastatin, 20 mg/d, or placebo. Intention-to-treat analyses followed participants for the first occurrence of pulmonary embolism or deep vein thrombosis.

Results—During a median follow-up 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 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin 0.57; 95% confidence interval [CI], 0.37 to 0.86; P=0.007), with corresponding rates of 0.10 and 0.17 for unprovoked venous thromboembolism (hazard ratio 0.61; 95% CI, 0.35 to 1.09; P=0.089) and 0.08 and 0.16 for provoked venous thromboembolism (hazard ratio 0.52; 95% CI, 0.28 to 0.96; P=0.033). Corresponding rates of pulmonary embolism were 0.09 and 0.12 (hazard ratio 0.77; 95% CI, 0.41 to 1.45; P=0.42), whereas rates of deep vein thrombosis only were 0.09 and 0.20 (hazard ratio 0.45; 95% CI, 0.25 to 0.79; P=0.004). Consistent effects were observed in all subgroups examined. No differences were seen between treatment groups in rates of bleeding.

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

Venous and arterial thrombosis are strongly age-related, common, and serious events, that often co-occur[1, 2], and share some risk factors[3-7]. Controversies persist on the extent of their shared

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pathways and whether treatments of demonstrated efficacy for one condition, including anticoagulants, antiplatelet therapy, thrombolytics and statins, have consistent benefits for the primary or secondary prevention of the other[8-10].

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 found substantial and significant reductions in the risk of venous thromboembolism associated with statin use, including a 50% reduced hazard among statin users in the Heart and Estrogen/progestin Replacement Study[14], and a 22% reduction among statin users in Ontario, based on administrative claims data[15]. Four case-control studies also found reductions in the risk of venous thrombosis, ranging from a 26% to a 58% decreased risk associated with statin use[16-19]. However, two additional observational studies, based on computerized databases in the United Kingdom, found no association between statin use and risk of venous thrombosis[20, 21]. Further, reliable estimation of the potential pleiotropic effects of statins in observational studies is problematic in light of the substantial challenges arising from confounding by indication and healthy user effects[22]; and the need for randomized evidence has been noted[23].

Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvatatin (JUPITER) tested whether treatment with rosuvastatin, 20 mg daily, as compared with placebo, would decrease 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 conducted at 1315 sites in 26 countries. Details of its design and findings for the primary end point are presented elsewhere[24, 25]. The trial protocol was designed and written by the study chair and approved by the local institutional review board at each participating center. The trial data were analyzed by the academic authors who vouch for their accuracy and completeness.

The trial was financially supported by Astra-Zeneca. 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], the main eligibility criteria were age 50 years or older in men and 60 years or older in women, with no history of cardiovascular disease, and, at the initial screening visit, an 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. Exclusion criteria related to characteristics with known or possible relationships with venous thrombosis included use of lipid-lowering therapy within 6 weeks before screening, current use of post-menopausal 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. 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).

Randomization and follow-up

Potentially eligible subjects who remained willing 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. Between March 14, 2003 and December 15, 2006, the trial randomized 17,802 individuals.

Follow-up visits were scheduled to occur at 13 weeks and then 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 unblinded. Interviews at each follow-up visit assessed outcomes including clinically symptomatic deep vein thrombosis and pulmonary embolism. These visits also assessed initiation of concomitant medications and their indications, with a protocol-specified focus on anticoagulants because statins can potentiate the anticoagulant effect of coumadin. Personnel at each site also contacted their participants mid-way between scheduled visits to identify health changes and address any concerns regarding study participation.

End Points

The protocol specified that, upon identification of a new case of venous thromboembolism, the site investigator would complete a form indicating the source of confirmation of the event including venous ultrasonogram or venography for deep vein thrombosis, or angiogram or computed tomography scan or ventilation perfusion scan for pulmonary embolism. Consistent with the perspective on all secondary end points, cases with venous thromboembolism included all participants with a diagnosed pulmonary embolism or deep vein thrombosis. An important subgroup included those with corroborating evidence from a confirmatory diagnostic test, initiation of anticoagulation, or death likely due to pulmonary embolism (all but 3 cases). Unprovoked deep vein thrombosis or pulmonary embolism was defined as occurring in the absence of known malignancy (diagnosed either before or up to 3 months after the venous thrombosis), trauma, hospitalization, or surgery within 3 months before the event. Provoked venous thrombosis included events that occurred in patients with cancer or during or shortly after trauma, hospitalization, or surgery.

On March 30, 2008, the trial's steering committee accepted the recommendation of the independent data monitoring board to terminate the trial based on convincing evidence of efficacy for 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, safety follow-up for the pre-specified secondary end points (These were venous thromboembolism, diabetes, study medication cessation due to an adverse event, bone fractures, any death, and non-cardiovascular death.) continued in a blinded manner for each study participant until the date he or she appeared for a formal closeout visit and discontinued 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 and considered only a participant's first diagnosed venous thromboembolism after randomization. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals for the comparison of event rates in the two groups. In addition to the primary focus on events that occurred by March 30, 2008, secondary analyses included the additional person-time and events that occurred until a participant's final closeout visit and unblinding of treatment assignment. Tertiary end points included provoked and unprovoked venous thromboembolism, cases with pulmonary embolism, and cases with deep vein thrombosis only. Subgroup analyses compared rates of venous thromboembolism between treatment 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 on venous thromboembolism could be secondary to the observed benefit on cardiovascular events. Separate proportional hazards models estimated the cause-specific hazard of venous thromboembolism, and the cause-specific hazard of a primary cardiovascular event, each in analyses that censored follow-up at first occurrence of either event. A likelihood ratio test compared the relative treatment effect between the two outcomes[6]. As a measure of the net clinical benefit of rosuvastatin considering combined effects on venous and arterial thrombosis, 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 risk differences and the number needed to treat[26] for absolute measures of treatment efficacy. We also 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

Among the 17,802 randomized participants in JUPITER, 32.0% were initially aged 70 years or older, 38.2% were women, and 25.2% were black or Hispanic (Table 1). In both the rosuvastatin and placebo groups, 37.6% of subjects had a body mass index of 30 kg/m^2 or higher. The median waist circumference was 100 cm in men and 95 cm in women. The metabolic syndrome was present in 41.7% of participants, and 41.3% had a high-sensitivity C-reactive protein level of 5.0 mg/L or higher.

Occurrence of venous thromboembolism

Symptomatic pulmonary embolism or deep vein thrombosis occurred in 94 participants between randomization and March 30, 2008, a median follow-up time of 1.9 years (Table 2). The rates of venous thromboembolism were 0.18 and 0.32 events per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio 0.57; 95% confidence interval [CI] 0.37-0.86; P=0.007) (Table 2). Although cumulative incidence curves did not appear to diverge until about 1 year of treatment (Figure 1), a test for interaction between treatment assignment and continuous follow-up time found no significant violation of the proportional hazards assumption (P=0.14).

Among the 94 cases, 50 were unprovoked whereas 44 occurred in the presence of cancer or recent trauma, hospitalization, or surgery. The observed hazard reductions were similar in analyses restricted to unprovoked events (hazard ratio 0.61; 95% CI: 0.35-1.09; P=0.089) or to provoked events (hazard ratio 0.52; 95% CI: 0.28-0.96; P=0.033) (Table 2 and Figure 1). Half (N=17) of the cases in the rosuvastatin group involved pulmonary embolism, compared with 37% (N=22) of the cases in the placebo group, but these percentages were not different (P=0.21).

Extension of follow-up time through the final closeout visit, when participants learned their treatment assignment, identified an additional 5 cases of venous thromboembolism, to bring 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 revealed similar estimates to those obtained in the primary efficacy analysis.

Analyses that excluded the 3 cases (1 in the rosuvastatin group and 2 in the placebo group) without corroborating evidence from a confirmatory diagnostic test, initiation of anticoagulation, or death likely due to pulmonary embolism, found nearly identical results.

Subgroup analyses

None of the baseline characteristics considered significantly modified the relationship of rosuvastatin with the hazard of venous thromboembolism (each P-value for interaction > 0.10) (Figure 2). Subgroups with the highest rates of venous thromboembolism in the placebo group included those participants aged 70 years or older, those with a body mass index of 30 kg/m^2 or above, and those with a waist circumference at or above the gender-specific median (≥95 cm in women or ≥100 cm in men). Similar estimated reductions in the hazard of venous thromboembolism were observed in each of these higher risk subgroups, although confidence intervals were wide and effects not individually significant for some comparisons. The rate of venous thromboembolism was also elevated in the placebo group in follow-up time beyond 2 years after randomization, perhaps reflecting the interim development of comorbid conditions that can trigger venous thromboembolism.

Venous thromboembolism and cardiovascular events

Additional analyses sought to identify the independent and possibly incremental effects of rosuvastatin on venous thromboembolism, beyond the benefits previously described for arterial thrombosis[25]. From randomization until March 30, 2008, 173 participants in the rosuvastatin group either had a venous thromboembolism or a primary cardiovascular end point (32 had venous thromboembolism first), and 305 participants in the placebo group had a venous thromboembolism or a primary cardiovascular event (56 had venous thromboembolism first) (Table 3). Few participants had both venous thromboembolism and the primary cardiovascular end point: 6 had venous thromboembolism after a primary cardiovascular event, and 3 had a primary cardiovascular event after venous thromboembolism. The estimated relative hazard of venous thromboembolism as a first event was not different from the estimated relative hazard of 0.56 associated with rosuvastatin for prevention of a primary cardiovascular event (P=0.99). Consideration of the first occurrence of either venous thromboembolism or the primary cardiovascular end point found that rates of this composite end point were 0.93 and 1.66 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% CI: 0.47-0.68; P<0.001).

Net benefits of statin treatment

If venous thromboembolism is combined with the primary cardiovascular end point to consider the first occurrence of either end point, the difference in rates between the placebo and rosuvastatin groups is 0.73 events per 100 person-years (Table 3). This is 24% larger than the rate difference of 0.59 observed for the primary cardiovascular end point alone[25]. The estimated number needed to treat for 4 years to prevent either one venous thromboembolism or one primary cardiovascular end point is 26, and projected to a 5-year treatment period this number is 21. These are reduced from the estimated numbers needed to treat for 4 and 5 years of 31 and 25, respectively, based only on the primary cardiovascular end point[25].

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

Adverse Events

Rates of monitored adverse events and other reported adverse events of interest by treatment group were previously reported[25]. In particular, bleeding was reported as an adverse event in 258 participants assigned to rosuvastatin versus 275 participants assigned to placebo, P=0.45.

Discussion

In this large, randomized trial of initially healthy men and women, 20 mg of rosuvastatin daily was associated with a substantial and statistically significant reduction in the occurrence of venous thromboembolism. The observed effect was comparable in relative magnitude and independent of the benefit seen previously for arterial events. The apparent benefit was also comparable in magnitude for provoked and unprovoked venous thromboembolism, and was of somewhat larger magnitude for the end point of deep vein thrombosis only. 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, costly to treat, and has frequent consequences including venous insufficiency and chronic thromboembolic pulmonary hypertension, so preventive strategies with acceptable costs and side effects are needed. With 94 observed cases, the frequency of venous thromboembolism among the participants in JUPITER was comparable to that of fatal or nonfatal stroke (97 cases) and fatal or nonfatal myocardial infarction (99 cases). This is consistent with population-based estimates that the incidence of venous thromboembolism is similar to that of stroke in Rochester County, Minnesota[28] and that of myocardial infarction in the Brest district of France[29].

In JUPITER, we observed little evidence of increased rates of venous thromboembolism among participants in the placebo group with higher levels of LDL cholesterol or triglycerides, or among those with lower levels of HDL cholesterol. This is consistent with two prospective cohort studies that found no associations of levels of HDL, LDL, total cholesterol or triglycerides with risk of venous thromboembolism[5, 30, 31], but contrasts with the observation of an increased risk of recurrent venous thromboembolism associated with lower levels of HDL cholesterol[32]. Also consistent with the JUPITER data is the lack of association of non-statin lipid-lowering drugs with the occurrence of venous thromboembolism seen in prior studies[15, 17, 18]. Participants in JUPITER with a baseline level of high-sensitivity C-reactive protein at or above 5 mg/L had a somewhat elevated rate of venous thromboembolism. However, prospective observational studies indicate that high-sensitivity C-reactive protein has limited ability to predict future venous thromboembolism after control for body mass index[33, 34]. Statins have several other mechanisms of action that could limit 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 and reducing PAI-1 expression in human endothelial cells[35].

Limitations of our study include its restriction to initially healthy participants, limited long-term follow-up, and the need to elaborate the potential mechanisms of action of statins on the occurrence of venous thromboembolism. Main strengths of our study include its prospective, double-blind treatment assignment and end point ascertainment, and its pre-specification of venous thromboembolism as a trial end point. Our study also does not allow for evaluation of the relationship of dose of statin with risk of venous thromboembolism. Some observational evidence suggests a possibly greater benefit with higher doses[16], but confounding and small study size were limitations. While JUPITER focused on symptomatic venous thromboembolism, asymptomatic venous thromboembolism is common and consequential[36], 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 evidence on statin use in high risk individuals, such as those with a prior venous thrombosis, is needed.

In conclusion, in this randomized trial of apparently 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 risk of arterial thrombosis. Widening the treatment target to a consideration of venous thromboembolism and death in addition to arterial thrombosis increases the estimated benefits associated with statin use.

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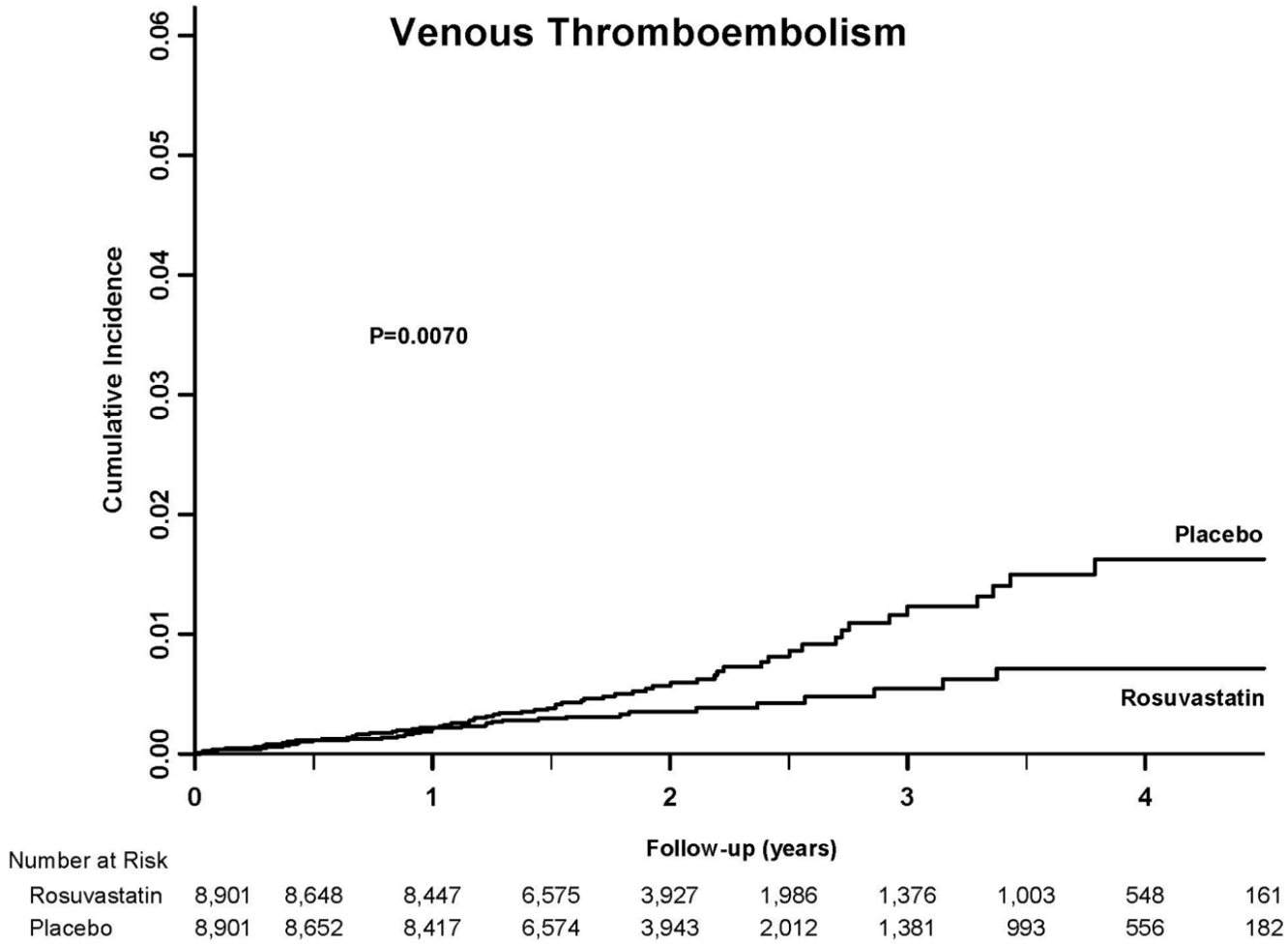

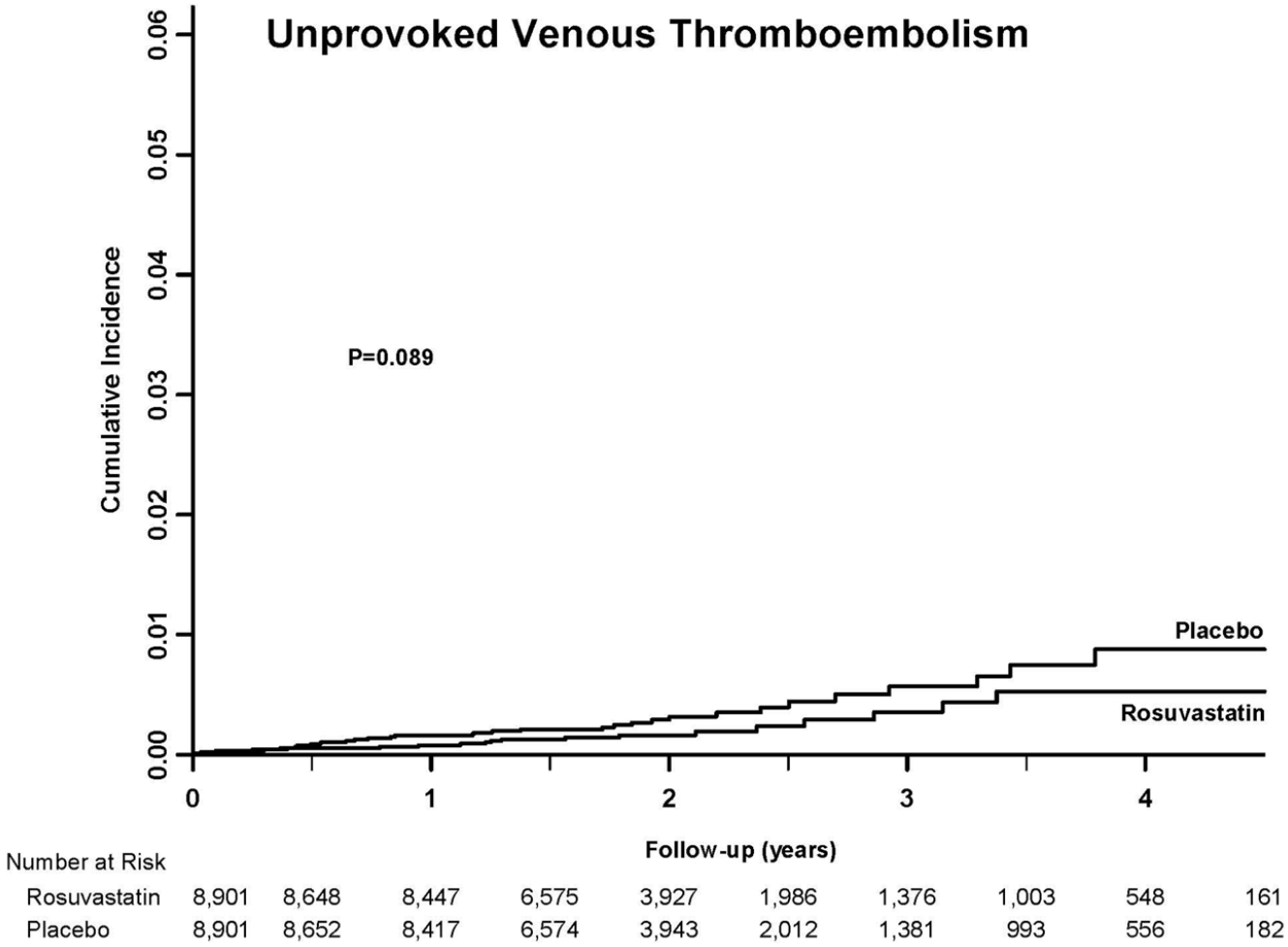

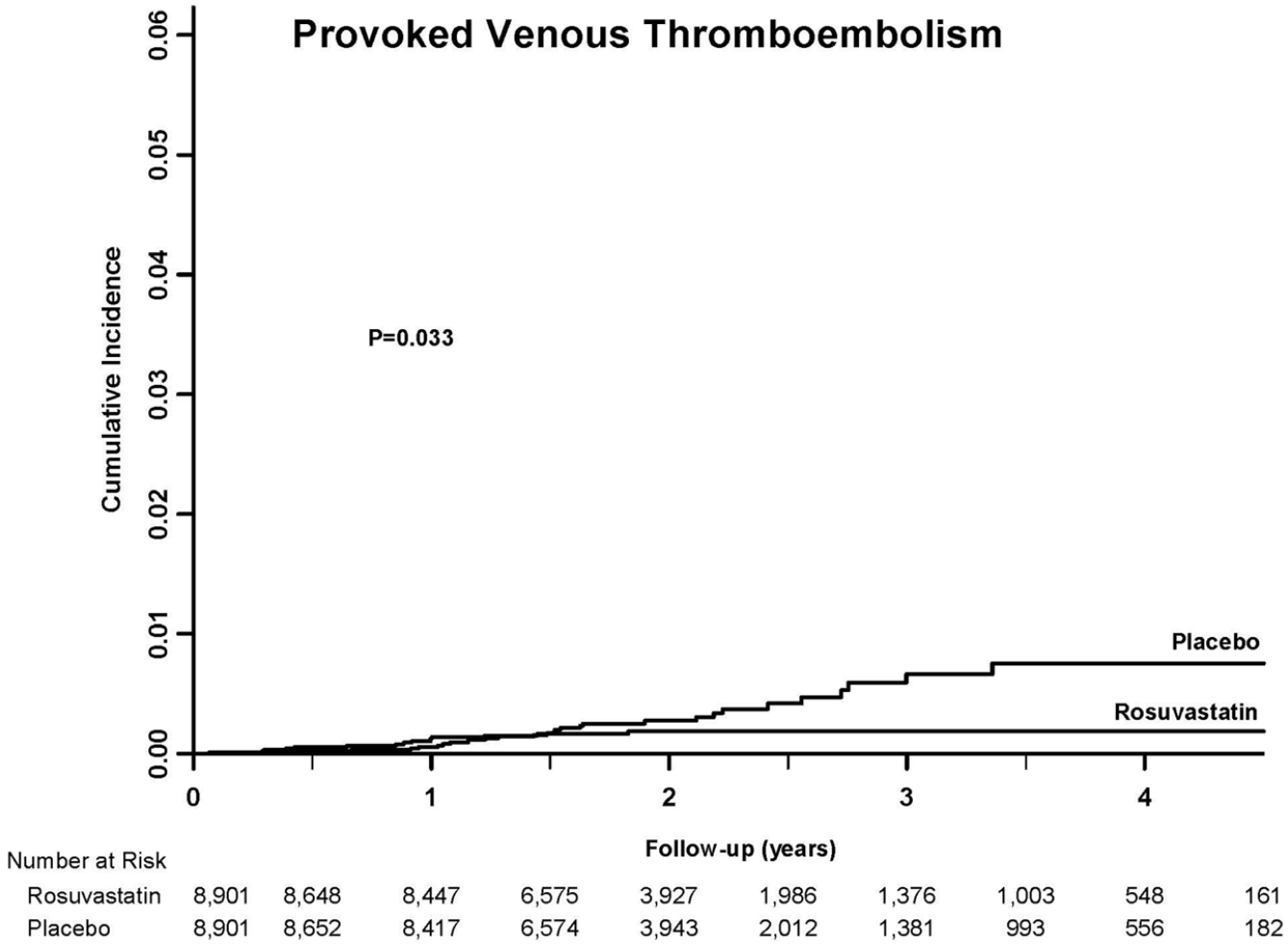

Figure 1.

Panel A. Cumulative incidence of venous thromboembolism by treatment group in JUPITER. The P-value is based on a likelihood ratio test of the effect of rosuvastatin in a proportional hazards model.

Panel B. Cumulative incidence of unprovoked venous thromboembolism by treatment group in JUPITER. The P-value is based on a likelihood ratio test of the effect of rosuvastatin in a proportional hazards model.

Panel C. Cumulative incidence of provoked venous thromboembolism by treatment group in JUPITER. The P-value is based on a likelihood ratio test of the effect of rosuvastatin in a proportional hazards model.

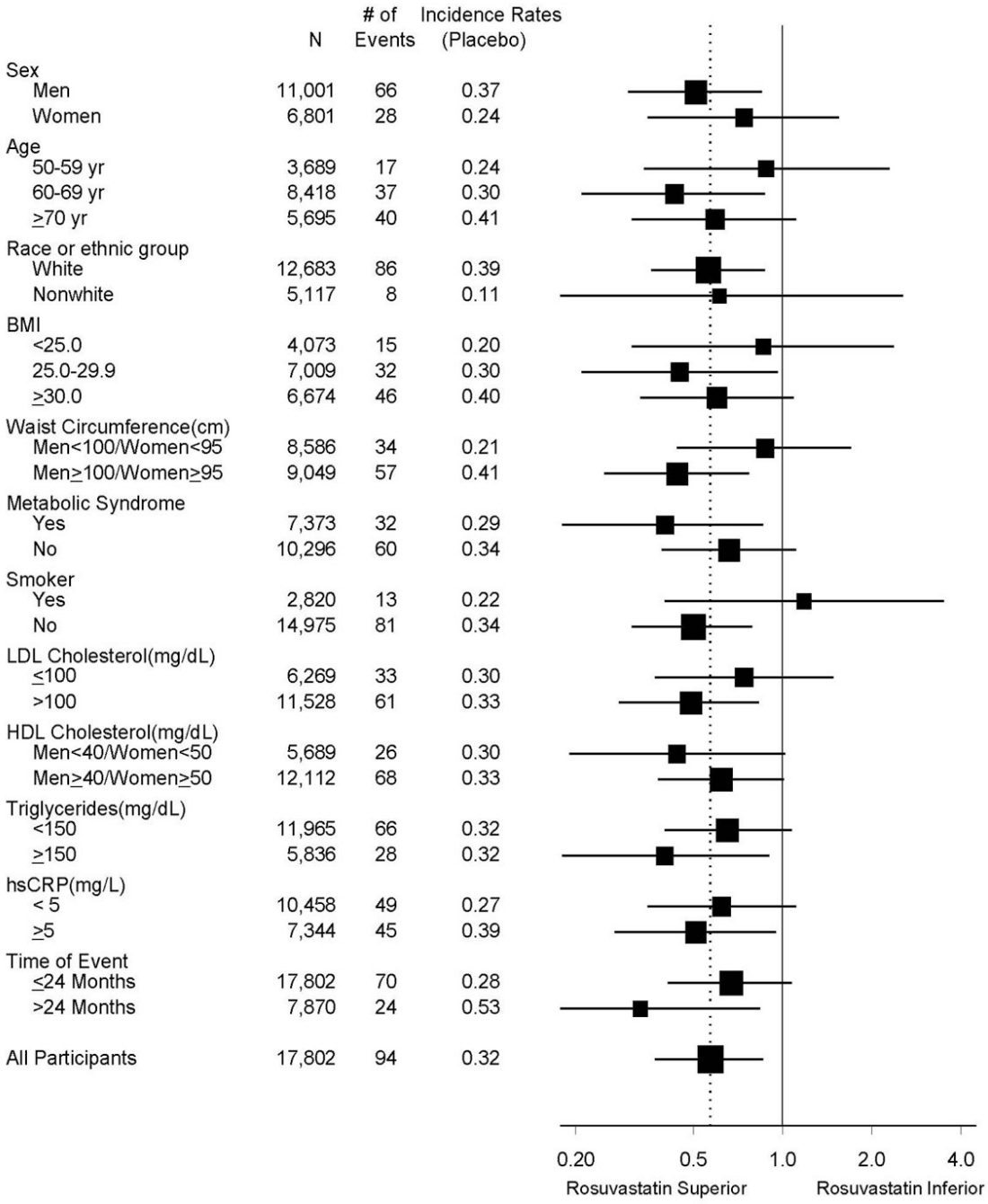

Figure 2.

Effects of rosuvastatin on the occurrence of venous thromboembolism according to baseline characteristics. The relative hazards for rosuvastatin as compared with placebo are shown, with the size of each black square proportionate to the number of participants who developed venous thromboembolism in the subgroup; the horizontal lines indicate 95% confidence intervals. The dashed vertical line indicates the overall relative hazard for the complete 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 indicators of subgroup categories, each of which was non-significant (P>0.10). 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].

Table 1

Baseline Characteristics of the Trial Participants, According to Study Group

Characteristic	Rosuvastatin (N=8901)	Placebo (N=8901)
Age, yr- no. (%)		
< 60	1846 (20.7)	1843 (20.7)
60-69	4177 (46.9)	4241 (47.6)
≥ 70	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 (kg/m^2)†		
<25	2040 (23.0)	2033 (22.9)
25-<30	3495 (39.4)	3514 (39.6)
≥30	3338 (37.6)	3336 (37.6)
Waist circumference (cm)†		
Men<100, women<95	4317 (49.0)	4269 (48.4)
Men≥100, women≥95	4503 (51.0)	4546 (51.6)
Current smoker – no. (%)†	1400 (15.7)	1420 (16.0)
Metabolic syndrome – no. (%)‡	3652 (41.4)	3723 (42.1)
High sensitivity C-reactive protein ≥ 5 mg/l – no. (%)‖	3618 (40.6)	3726 (41.0)
LDL cholesterol > 100 mg/dl – no. (%)†	5781 (65.0)	5747 (64.6)
HDL cholesterol (mg/dl) men<40, women<50 – no. (%)*	2833 (31.8)	2856 (32.1)
Triglycerides ≥ 150 mg/dl – no. (%)†	2900 (32.6)	2936 (33.0)

*Race or ethnic group was self-reported

†Data were missing for some subjects for body mass index, waist circumference, smoking, metabolic syndrome, LDL and HDL cholesterol and triglycerides

‡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 C-reactive protein for a participant were the average of values obtained at two screening visits

Table 2

Occurrence of Venous Thromboembolism by Study Group

End point	Rosuvastatin (N=8901)		Placebo (N=8901)		Hazard ratio (95% CI)	P Value
	No. of patients	Rate per 100 person-yr	No. of patients	Rate per 100 person-yr		
Primary efficacy analysis, 94 cases by March 30, 2008						
All cases of VTE*	34	0.18	60	0.32	0.57 (0.37-0.86)	0.007
Unprovoked VTE*	19	0.10	31	0.17	0.61 (0.35-1.09)	0.089
Provoked VTE*	15	0.08	29	0.16	0.52 (0.28-0.96)	0.033
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, 99 cases before unblinding						
All cases of VTE*	35	0.18	64	0.33	0.55 (0.36-0.82)	0.003
Unprovoked VTE*	20	0.10	34	0.18	0.59 (0.34-1.02)	0.055
Provoked VTE*	15	0.08	30	0.16	0.50 (0.27-0.93)	0.024
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

*VTE denotes venous thromboembolism

Table 3

Occurrence of Venous Thromboembolism, Cardiovascular Disease and Death by Study Group

End point	Rosuvastatin (N=8901)		Placebo (N=8901)		Hazard ratio (95% CI)	P Value
	No. of patients	Rate per 100 person-yr	No. of patients	Rate per 100 person-yr		
VTE with no prior CVD*	32	0.17	56	0.30	0.57 (0.37-0.88)	0.009
CVD with no prior VTE*	141	0.76	249	1.35	0.56 (0.46-0.69)	<0.001
VTE after CVD*	2	0.61	4	0.65	0.98 (0.18-5.34)	0.98
First CVD or VTE*	173	0.93	305	1.66	0.56 (0.47-0.68)	<0.001
Death after VTE*	7	18.2	14	20.3	0.88 (0.35-2.18)	0.78
First CVD, VTE or Death*	320	1.73	483	2.62	0.66 (0.57-0.76)	<0.001

*VTE denotes venous thromboembolism, whereas CVD denotes the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.