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Statin Therapy and Levels of Hemostatic Factors in a Healthy Population: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—HMG CoA reductase inhibitors (statins) reduce risk of venous thromboembolism (VTE) in healthy people. Statins reduce levels of inflammation biomarkers, however the mechanism for reduction in VTE risk is unknown. In a large cohort of healthy people, we studied associations of statin use with plasma hemostatic factors related to VTE risk.

Methods—Cross-sectional analyses were performed in the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort study of 6814 healthy men and women age 45–84, free of clinical cardiovascular disease at baseline; 1001 were using statins at baseline. Twenty-three warfarin users were excluded. Age, race, and sex-adjusted mean hemostatic factor levels were compared between statin users and nonusers, and multivariable linear regression models were used to assess associations of statin use with hemostasis factors, adjusted for age, race/ethnicity, education, income, hormone replacement therapy (in women), and major cardiovascular risk factors.

Results—Participants using statins had lower adjusted levels of D-dimer (−9%), C-reactive protein (−21%) and factor VIII (−3%) than non-users ($p<0.05$). Homocysteine and von Willebrand factor were non-significantly lower with statin use. Higher fibrinogen (2%) and PAI-1 (22%)

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Addendum

N. B. Adams: conceived the project, primary responsibility for data analysis planning, drafted manuscript.
P. L. Lutsey: statistical analysis design, performed statistical analysis, wrote sections of paper. A. R. Folsom: conceived research, obtained funding, supervised participant enrollment, designed parent study, contributed to revisions of manuscript.
D. H. Herrington: conceived research, contributed to revisions of the manuscript
C. T. Sibley: contributed to revisions of the manuscript.
N.A. Zakai: conceived research, contributed to revisions of the manuscript
S. Ades: conceived research, contributed to revisions of the manuscript, mentored first author G. L. Burke: chair of study steering committee, obtained funding, supervised participant enrollment, contributed to revisions of the manuscript
M. Cushman: senior author, conceived research, obtained funding, supervised assay work, drafted manuscript.

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levels were observed among statin users than nonusers ($p<0.05$). Further adjustment for LDL and triglyceride levels did not attenuate the observed differences in these factors by statin use.

Conclusions—Findings of lower D-dimer, factor VIII and C-reactive protein levels with statin use suggest hypotheses for mechanisms whereby statins might lower VTE risk. A prospective study or clinical trial linking these biochemical differences to VTE outcomes in statin users and nonusers is warranted.

Keywords

statins; thrombosis; risk factor; blood coagulation; inflammation; fibrinolysis

HMG-CoA reductase inhibitors (statins) are widely used in treatment and prevention of cardiovascular disease. Statins have pleiotropic effects beyond cholesterol synthesis inhibition, which might contribute favorably to clinical outcomes. Most favorable effects of statins are secondary to suppressed synthesis of nonsterol isoprenoids from the mevalonate pathway which decrease isoprenylation of signaling proteins.

Regarding hemostatic function, statins appear to reduce tissue factor, tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) [1–3]. Undas reported that statins enhanced fibrin clot lysis via increased clot permeability, which may contribute to clinical benefits of statins [4]. Other favorable effects include decreased endothelial nitric oxide synthase, decreased production of inflammatory cytokines, and anti-platelet effects [5]. Studies to date regarding hemostatic function have numerous limitations, including small sample size, inclusion of selected populations and sometimes lack of a control group.

Statins reduce the rate of venous thromboembolism (VTE) in healthy people. The JUPITER trial (Justification of the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) demonstrated a 43% reduction in occurrence of symptomatic VTE with rosuvastatin, 20 mg daily, compared to placebo [6]. Several, but not all observational studies support these findings and one study showed a dose response relationship [7–10]. A retrospective cohort of 1795 inpatients reported a dose response, with high dose statin use carrying a lower risk of VTE than standard doses (respective hazard ratios HRs 0.25 and 0.38 compared with no statin use) [11].

Atherosclerosis is associated with increased risk of VTE in some studies [12–17] and statins are anti-atherosclerotic. In a prospective study of changes in carotid intima-media thickness (CIMT) and circulating markers of inflammation, thrombosis, and endothelial activation in coronary patients treated with 20 mg of daily atorvastatin, CIMT regression with atorvastatin correlated with a significant decrease in fibrinogen, interleukin-8, matrix metallopeptidase 9, soluble intercellular cell adhesion molecule 1, E-selectin and von Willebrand factor (vWF) [18]. It is plausible that reduced VTE rates with statins could relate to reduction in atherosclerosis leading to a less procoagulant profile. Whether this may be causal is unknown.

Here we studied the association of statin use with biomarkers of vascular risk in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort in order to generate hypotheses of why statins reduce VTE rates. MESA provided a unique opportunity to conduct a cross sectional study on associations of statin use with hemostatic biomarkers in a large population-based study of healthy individuals, including 1,001 statin users and 5,786 nonusers, and allowed for control for many important confounders.

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Methods

Study Population

The MESA is a population based prospective epidemiologic cohort of 6,814 Caucasian, African-American, Hispanic and Chinese men and women aged 45–84, who were free of cardiovascular diseases or active cancer at baseline. Participants were recruited from six United States centers. The primary objective is to determine factors related to the progression of subclinical cardiovascular disease. Participants provided a complete medical history and had anthropometric and laboratory measurements collected during a baseline visit in July 2000–August 2002. Institutional Review Boards at each center approved the study and all participants gave written informed consent. VTE events were not captured. Details regarding MESA recruitment, objectives, and design have been published [19].

Definitions

Self-reported participant characteristics included race-ethnicity (Caucasian, African American, Hispanic or Chinese), annual income (≤$20,000, $20,000–49,000 or ≥$50,000) and education (high school or less, some college or Bachelor's degree or higher). Diabetes was defined as using insulin or oral agents or fasting glucose ≥126 mg/dL. Smoking was defined as having smoked within the last 30 days. Hypertension was defined using measured blood pressure ≥140/90 mmHg or current treatment for hypertension. The dosages and frequency of medications were determined by self-report and review of pharmacy containers for all medications used during the 2 weeks before the baseline visit. In the current analyses, the frequency of medication use was as reported by the participant, not the prescribed frequency.

Laboratory Measurements

All assays were measured in two central laboratories. D-dimer, fibrinogen, factor VIII (FVIII), homocysteine and C-reactive protein (CRP) were measured in the entire cohort at baseline. PAI-1 and vWF were measured in a 1000 person random sample (150 were statin users). Characteristics of the 1000 person random sample did not differ from entire cohort.

D-dimer and vWF were measured by immunoturbidometry (Liatest D-DI; Diagnostica Stago, Parsippany, NJ) on the Sta-R analyzer (Diagnostica Stago, Parsippany, NJ) with analytical coefficients of variation (CVs) of 8 and 4.5%, respectively. Fibrinogen antigen and CRP were measured by immunonephelometry using the BNII nephelometer (N Antiserum to Human Fibrinogen, N High Sensitivity CRP, Dade Behring Inc., Deerfield, IL) with CVs of 2.6% and 2.1–5.7%, respectively. Factor VIII coagulant activity was measured as the clotting time of a sample in factor VIII-deficient plasma in the presence of activators utilizing the Sta-R analyzer (STA-Deficient VIII), with a CV of 10%. PAI-1 was measured by in-house immunoassay sensitive to free PAI-1 (both latent and active) but not PAI-1 in complex with tPA with a CV of 3.5% [20]. Total homocysteine was measured by fluorescence polarization immunoassay (IMx Homocysteine Assay, Axis Biochemicals ASA, Oslo, Norway) using the IMx Analyzer (Abbott Diagnostics, Abbott Park, IL). The CV range was 3.8–5.1%. Triglycerides were measured using Triglyceride GB reagent (Roche Diagnostics, Indianapolis, IN) on the Roche COBAS FARA centrifugal analyzer with a CV of 4.0%. HDL-cholesterol was measured using the cholesterol oxidase method (Roche Diagnostics) after precipitation of the non-HDL-cholesterol with magnesium/dextran with a CV of 2.9%. LDL-cholesterol was calculated using the Friedewald formula.

Statistical Analysis

We excluded 23 warfarin users and 4 participants with missing data, leaving an analytic sample of 6,787. P values <0.05 denoted statistical significance.

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Means and frequencies of age, race/ethnicity, education, household income, use of hormone replacement therapy, major cardiovascular risk factors and hemostatic factors were compared between statin users and nonusers using Student's t-test for continuous variables and Chi-square analysis for categorical variables. Distributions of biomarkers were visually assessed and log transformed if there was a non-normal distribution (D-dimer, homocysteine, CRP and PAI-1). Geometric means were reported for transformed biomarkers to enhance interpretability.

Multivariable linear regression models were used to assess the independence of relationships between statin use and hemostatic factors, and to adjust for confounding by indication for statin use. Potential confounders were added to three different models to control for their effects. The first model adjusted for demographic characteristics: age, sex, race/ethnicity, education level and income. Given that statins are used primarily by participants who have risk factors for cardiovascular disease, model 2 included model 1 covariates plus cardiovascular risk factors (smoking status, alcohol use, body mass index, diabetes, hypertension, and regular aspirin use) and hormone replacement therapy in women (coded as men, women not using hormones, and women using hormones). To assess whether the association of statins with lipid levels and subclinical atherosclerosis might mediate hemostatic factor level differences by statin use, model 3 controlled for model 2 covariates plus triglycerides, LDL cholesterol, insulin levels, and carotid intimal-medial thickness z-score [21]. Finally, in model 4 CRP was added to model 2 covariates to assess mediation by inflammation status.

We classified statin drug and dose into potency categories based on ability to lower total cholesterol. Low, medium and high potency were defined as less than 20%, 20–29% and ≥30% reduction in cholesterol, respectively, based on a Cochrane review [22]. Analysis of covariance was used to compute crude and adjusted mean hemostatic factor levels by statin potency category using models 1 and 2 described above. To test for linear trend in means, we entered the potency categories into a model as a continuous variable.

Results

Table 1 shows participant characteristics by statin use. There were 1,001 using statins, with 489 using atorvastatin, 287 simvastatin, 129 pravastatin and <45 participants each using fluvastatin, lovastatin and cerivastatin. Statin users were more likely than nonusers to be older, have diabetes, hypertension, and be on regular aspirin but had similar distributions of sex, race, education level and income. Unadjusted levels of D-dimer, fibrinogen, factor VIII, and vWF were higher in statin users, while CRP, total and LDL cholesterol were lower. Homocysteine and PAI-1 did not differ by statin use.

Adjusting for age, sex, race, education level, and household income (Table 2, model 1), statin users had 5.7% lower D-dimer than non-users (95% CI −11.1, 0%). This difference was larger after adjustment for cardiovascular risk factors (−9.0%, 95% CI −14.4, −3.3%) (model 2). Results were not altered after further adjustment for LDL, triglycerides, insulin levels and carotid intima-media thickness z-score (model 3). Factor VIII was lower in statin users in models 2 and 3 (−3.5%, 95% CI −6.4, −0.6%). CRP was substantially lower in statin users in models 1, 2 and 3 (−14.3%, −21.1%, −21.2%, respectively). Homocysteine and vWF did not differ significantly by statin use, although there was a trend toward lower levels of both in statin users. Across all models fibrinogen and PAI-1 were higher among statin users, with fibrinogen 3.4% higher (95% CI 1.9, 4.8%) and PAI-1 20.7% higher (95% CI 2.6, 42.0%) in model 3 (Table 2). Addition of CRP to model 2 covariates revealed mild attenuation of the association of D-dimer with statin use, and the association of factor VIII was attenuated to the null (model 4, table 2).

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Among statin users, 232 participants were using low potency, 579 medium potency and 190 high potency (Table 3). Only CRP was lower with increasing statin potency. While not statistically significant, there was a trend toward lower vWF and PAI-1 with greater statin potency.

Discussion

The main findings of this cross-sectional study were that statin use was associated with lower D-dimer and factor VIII, higher fibrinogen and PAI-1 and non-statistically significant lower homocysteine and vWF. We confirmed the well described dose-dependent lowering of CRP with statin use [23] and found that differences in CRP partly explained associations of statin use with factor VIII, vWF and D-dimer, but not other factors. Lipid levels did not mediate the differences in hemostatic factor associations with statin treatment. Differences in carotid intima-media thickness did not explain the observed associations, suggesting that the associations are not due to subclinical atherosclerosis regression causing lower hemostatic activation. Higher statin potency was associated only with lower CRP.

Our data suggest potential mechanisms for lower VTE incidence in statin users. All studied biomarkers are implicated in etiology of in VTE. D-dimer, a global marker of hemostatic activation is not causal as it is a byproduct of coagulation activation, but it is a strong risk factor for first and recurrent thrombosis [24–27]. To assess whether observed differences in biomarkers by statin use here might be mediators of statin effects on thrombosis, we review here the differences in levels of the studied factors among those with and without VTE in some landmark studies. In the current study, factor VIII was 3.7% lower with statin use (2.5% lower accounting for CRP). The Longitudinal Investigation of Thromboembolism Etiology (LITE) assessed baseline biomarker levels and 8 year risk of venous thromboembolism in nearly 20,000 participants free of VTE at baseline [28]. Mean baseline factor VIII was 151% in those who developed VTE and 129% in those who did not, a difference of 14.6%. In a case control study of 301 patients with first episode of venous thrombosis and 301 controls, those with VTE had a mean FVIII concentration 9% or 17% higher than controls, depending on blood group [29]. We observed a 21% lower CRP in statin users than non-users. In the LITE study baseline CRP was 3.2 mg/L in those who went on to develop VTE and 2.3 mg/L in those who did not, a 39% difference [28]. Similarly, in LITE mean baseline D-dimer was 155 ng/mL in those with subsequent VTE, compared to 112 ng/mL in those without VTE, a 38% difference [25]. In the Leiden Thrombophilia Study mean D-dimer was 102 ng/mL in deep vein thrombosis cases and 75 ng/mL in controls, a 36% difference [24]. In the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial of patients with previous unprovoked venous thrombosis, baseline D-dimer was 460 ng/mL in those who later had recurrent VTE and 350 ng/mL in those who did not, a 31% difference [27]. We observed a 9% lower D-dimer with statin use (Table 2, model 3). Taken in aggregate with the literature, the findings suggest a hypothesis that statin-related difference in D-dimer and CRP, but less so factor VIII, might relate to a reduced incidence of VTE.

Prior studies of statin use and hemostatic factors included selected populations smaller than the current study and reported conflicting findings. Van Dee Ree et al, studied 217 patients with diabetes who had dyslipidemia and elevated hemostatic factors (FVIIa, VWF, PAI-1, fibrinogen and D-dimer). Patients were randomized to receive atorvastatin 10 or 80 mg daily or placebo, and dose dependent reductions of D-dimer and PAI-1, but not other factors, were observed [30]. Smaller statin trials, often without control groups, failed to show consistent reductions in hemostatic factor levels. Trifiletti et al assessed atorvastatin 20 mg daily in 32 hypercholesterolemic patients at 6 and 12 months of therapy. PAI-1 and prothrombin fragment 1 + 2 were significantly reduced but D-dimer, t-PA and fibrinogen were unaffected

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[31]. Bolaman et al studied 44 patients with hypercholesterolemia treated with atorvastatin 10 mg daily for 6 months. Fibrinogen increased while D-dimer, protein C and S, vWF, antithrombin and others were unchanged. Similarly [32], Dangas et al reported lowering of PAI-1 and plasminogen with no significant change in D-dimer, prothrombin fragment 1 + 2, vWF, CRP and other hemostatic factors in 93 patients with high LDL cholesterol with pravastatin 20 or 40 mg daily for 6 months [33]. Our study is larger than all of the above studies, so had better power, and it had a control group, which some studies did not have.

We observed higher PAI-1 and fibrinogen among statin users compared to nonusers. Elevated fibrinogen and PAI-1 are not consistently related to VTE risk [34–36]. The significance of this finding as it relates to VTE risk, and the difference from other research described above, especially in relation to PAI-1, is unknown and requires further study. It is also not clear why statins might have disparate influence on inflammation-sensitive markers.

In agreement with published findings for CRP [36], there was no impact of LDL level on associations of statin use with biomarkers in this study. Further, other than for CRP, statin potency was not associated with biomarker levels. Large randomized controlled trials would be needed to document effects of statin potency on hemostatic factor levels, and this would provide further evidence to support a hypothesis that statin use lowers VTE risk through alterations in hemostatic factors.

Limitations of this cross-sectional analysis require discussion. We cannot make conclusions regarding causality. Although we adjusted for confounders, our models may not have fully addressed indication bias; statins are prescribed to patients with cardiovascular disease risk factors, many of which are associated with adverse hemostatic factors. Thus, our estimates of the differences in biomarkers by statin use are likely underestimates. However, if we neglected to control for a missing covariate of importance, the direction of such bias would be unpredictable. While a cross sectional study may not allow full confidence in the findings, prior similarly designed cross sectional studies of drug effects on hemostasis have provided very accurate results when compared to prospective trials, increasing the confidence in our findings [37–39]. We performed many statistical tests and because of the hypothesis-forming nature of the work did not adjust for multiple testing. Therefore, some findings may be due to chance and results require confirmation. The analysis of statin potency and hemostatic factor levels may have been limited by power in that there were relatively few people receiving low and high potency statins. It is also possible that confounding by indication, with higher risk participants being on more dose intense statins and incomplete control for this risk, led to null results. Additionally, power was limited for analysis of vWF and PAI-1, which were only measured in 1000 participants. In the primary analysis we combined all statin users into one exposed group. Atorvastatin users comprised nearly half of the statin users and lovastatin, cerivastatin or fluvastatin use was rare. Rosuvastatin, studied in JUPITER, was not represented. It is possible that different statin drugs have different effects on hemostatic factors. Finally, there was no follow up for venous thrombosis in this cohort so we are unable to study whether the biomarker differences we observed impact thrombosis incidence.

Strengths of this study include large cohort of statin users and non-users representing four ethnic groups that are geographically dispersed. The use of a central laboratory and standardized data collection methods further strengthens this study. The large quantity of data collected allowed adjustment for known confounders that may potentially alter the association of hemostatic factor levels and statin use, such as sex, age, race, medications, cardiovascular disease, diabetes and postmenopausal estrogen use.

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Findings of lower D-dimer, factor VIII and CRP levels with statin use suggest mechanisms whereby statins might lower VTE risk. A prospective study or trial linking these biomarker changes with statin use to VTE outcomes is warranted.

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Table 1

Characteristics of participants by statin use, MESA, 2000–2002

	Statin Use (n=1001)	No statin use (n=5786)	P
Age, mean years (SD)	65.9 (8.7)	61.5 (10.3)	< 0.001
Male, n (%)	468 (46.7)	2727 (47.1)	0.82
Race/ethnicity, n (%)			<0.001
Caucasian	431 (43.1)	2177 (37.6)	
African American	289 (28.9)	1598 (27.6)	
Hispanic	178 (17.8)	1311 (22.7)	
Chinese	103 (10.3)	700 (12.1)	
Education, n (%)			0.38
High school or less	167 (16.7)	1051 (18.2)	
Some College	484 (48.4)	2674 (46.7)	
Bachelor's degree or higher	349 (34.9)	2040 (35.4)	
Income, n (%) (272 missing income data)			0.64
≤ $20,000	240 (25.0)	1312 (23.6)	
$20,000–49,000	347 (36.1)	2033 (36.6)	
≥ $50,000	373 (38.8)	2210 (40)	
Hormone replacement use, n (%)	157 (15.7)	870 (15.0)	0.87
Diabetes, n (%)	222 (22.2)	631 (10.9)	<0.001
Hypertension, n (%)	636 (63.5)	2406 (41.6)	<0.001
Current smoker, n (%)	98 (9.8)	789 (13.6)	0.001
Alcohol, current use, n (%)	555 (55.7)	3179 (55.4)	0.84
BMI, mean kg m^2 (SD)	28.9 (5.2)	28.2 (5.5)	<0.001
LDL cholesterol, mean mg/dl (SD)	104 (28)	120 (31)	<0.001
HDL cholesterol, mean mg/dl (SD)	50 (14)	51 (15)	0.71
Triglycerides, mean, mg/dl (SD)	139 (85)	130 (89)	0.005
Regular Aspirin use, n (%)	340 (35.6)	958 (17.3)	<0.001
Common carotid intimal-medial thickness, mean mm, (SD)	0.92 (0.20)	0.86 (0.19)	<0.001
Internal carotid intimal-medial thickness, mean mm (SD)	1.27 (0.67)	1.04 (0.58)	<0.001
Hemostatic factors			
CRP **, mean mg/L	1.70	1.95	
ln CRP	0.53 (1.10)	0.67 (1.17)	0.001
D-dimer **, mean ug/ml	0.24	0.22	
ln D-dimer	−1.42 (0.94)	−1.51 (0.92)	0.008
Fibrinogen antigen, mean mg/dl, (SD)	360 (75)	344 (73)	<0.001
Factor VIII, mean % (SD)	168 (67)	163 (67)	0.025
Homocysteine **, mean umol/L	9.1	8.8	
ln Homocysteine	2.21 (0.30)	2.18 (0.30)	<0.001
von Willebrand factor, mean, %, (SD)	141 (59)	138 (56)	0.60
Plasminogen activator inhibitor-1 **, mean ng/ml	22	17	
ln plasminogen activator inhibitor-1	3.09 (0.86)	2.87 (0.91)	0.02

** Geometric means

ln=natural log

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Table 2

Adjusted mean hemostatic factor levels by statin use, MESA, 2000–2002

Factor	Statin users	Nonusers	% Difference (95% CI)	P value
D-dimer *,ug/ml				
Model 1 †	0.21	0.22	−5.7 (0.0, −11.1)	0.05
Model 2	0.21	0.23	−9.0 (−3.3, −14.4)	0.002
Model 3	0.20	0.22	−9.2 (−3.4, −14.8)	0.003
Model 4	0.20	0.23	−7.4 (−1.7, −12.8)	0.01
Fibrinogen, mg/dl				
Model 1	356	345	3.4 (2.0, 4.8)	<0.0001
Model 2	353	345	2.3 (0.9, 3.7)	0.002
Model 3	356	344	3.4 (1.9, 4.8)	<0.0001
Model 4	356	345	3.4 (2.1, 4.7)	<0.0001
Factor VIII, %				
Model 1	164	163	0.2 (−2.6, 2.9)	0.90
Model 2	159	164	−3.0 (−5.9, −0.2)	0.04
Model 3	158	164	−3.5 (−6.4, −0.6)	0.02
Model 4	160	164	−2.5 (−5.3, 0.3)	0.08
Homocysteine *, umol/L				
Model 1	8.79	8.85	−0.6 (−2.5, 1.3)	0.54
Model 2	8.76	8.87	−1.2 (−3.2, 0.7)	0.22
Model 3	8.73	8.87	−1.5 (−3.5, 0.5)	0.14
Model 4	8.76	8.87	−1.2 (−3.1, 0.8)	0.24
CRP *, mg/L				
Model 1	1.67	1.94	−14.3 (−7.5, −20.6)	<0.0001
Model 2	1.55	1.97	−21.1 (−15.2, −26.7)	<0.0001
Model 3	1.54	1.96	−21.2 (−15.1, −26.9)	<0.0001
vWF, %				
Model 1	138	141	−1.7 (−9.2, 5.8)	0.66
Model 2	136	141	−3.5 (−11.3, 4.4)	0.39
Model 3	134	140	−4.3 (−12.4, 3.8)	0.29
PAI-1 *, mg/ml				
Model 1	22.9	17.9	28.1 (7.0, 53.4)	0.007
Model 2	21.9	18.0	21.7 (2.7, 44.3)	0.02
Model 3	21.4	17.7	20.7 (2.6, 42.0)	0.02
Model 4	21.8	18.0	21.1 (2.0, 43.8)	0.03

* Geometric means reported

† Model 1 = adjusted for age, sex, education, individual income, race

Model 2 = model 1 + adjustment for smoking status, current alcohol use, BMI, diabetes status, HTN status, ASA, and sex/HRT use among women (in lieu of a dichotomous sex variable)

Model 3 = model 2 + LDL, triglycerides, insulin, carotid intimal-medial thickness z-score

Model 4 = Model 2 + CRP

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Table 3

Adjusted mean hemostatic factor levels by statin potency, MESA, 2000–2002

		Statin Potency			
		Low	**Medium**	**High**	**p-trend**
	N	**232**	**579**	**190**	
D-Dimer *, ug/ml	Model 1†	0.26	0.23	0.25	0.38
	Model 2	0.26	0.22	0.25	0.40
Fibrinogen, mg/dL	Model 1	366	357	363	0.56
	Model 2	365	356	363	0.60
Factor VIII, %	Model 1	164	170	166	0.61
	Model 2	163	169	163	0.88
Homocysteine *, umol/L	Model 1	9.20	9.05	9.10	0.66
	Model 2	9.28	9.08	9.14	0.56
CRP *, mg/L	Model 1	2.06	1.60	1.65	0.02
	Model 2	2.04	1.62	1.63	0.02
	N (MESA 1,000)	**23**	**74**	**20**	
vWF, %	Model 1	161	139	132	0.12
	Model 2	160	140	140	0.27
PAI-1 *, ng/ml	Model 1	36.8	19.0	23.9	0.10
	Model 2	36.8	19.4	25.4	0.12

* Geometric means reported

† Model covariates as in Table 2.