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The Association of Statin Therapy with the Risk of Recurrent Venous Thrombosis

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Abstract

Background—Meta-analyses of randomized controlled trials suggest that treatment with HMG-CoA reductase inhibitors (statins) lowers the risk of incident venous thrombosis (VT), particularly among those without prevalent clinical cardiovascular disease (CVD). Whether this is true for the prevention of recurrent VT is debated. We used an observational inception cohort to estimate the association of current statin use with the risk of recurrent VT.

Methods and Results—The study setting was a large healthcare organization with detailed medical record and pharmacy information at cohort entry and throughout follow-up. We followed 2,798 subjects 18–89 years of age who experienced a validated incident VT between January 1, 2002 and December 31, 2010, for a first recurrent VT, validated by medical record review. During follow-up, 457 (16%) developed a first recurrent VT. In time-to-event models incorporating time-varying statin use and adjusting for potential confounders, current statin use was associated with a 26% lower risk of recurrent VT: HR=0.74; 95%CI: 0.59–0.94. Among cohort members free of

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Other authors have nothing to disclose.

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CVD (n=2,134), current statin use was also associated with a lower risk (38%) of recurrent VT: HR=0.62; 95%CI: 0.45–0.85. We found similar results when restricting to new users of statins and in subgroups of different statin types and doses.

Conclusions—In a population-based cohort of subjects who had experienced an incident VT, statin use, compared with non-use, was associated with a clinically-relevant lower risk of recurrent VT. These findings suggest a potential secondary benefit of statins among patients who have experienced an incident VT.

Keywords

Venous thrombosis; Recurrence; Hydroxymethylglutaryl-CoA Reductase Inhibitors; Pharmacoepidemiology; Cohort studies

Venous thrombosis (VT) recurs commonly in adults with an incident event within the first year after stopping anticoagulation therapy.¹ While anticoagulation therapy is effective at preventing thrombotic recurrences, the substantial bleeding risk with long-term treatment limits its use to patients with a moderate or high risk of recurrence. The search for alternative treatments that lower the recurrence potential, ideally without increasing the risk of bleeding, is critical to improved clinical management.

Meta-analyzed data from randomized controlled trials suggest that treatment with HMG-CoA reductase inhibitors (statins) may lower the risk of an incident VT by 10%.² In the subgroup of trials that studied individuals without prevalent clinical cardiovascular disease, the data suggest that statins lower this risk by 38%, results driven largely by findings from the JUPITER trial of rosuvastatin, where participants were free of CVD but had elevated levels of high-sensitivity C-reactive protein.^{2,3} Whether this risk reduction also exists for recurrent VT remains unknown, as no data from a randomized clinical trial are available and observational data findings are limited and have not always reached the same conclusions.^{4–7}

Based on the evidence from the primary prevention setting, we hypothesized that statin therapy reduces the risk of a recurrent VT, and that risk-reduction is greatest among those without clinical cardiovascular disease. Using data from a large, population-based cohort of 2,798 adults with a first occurrence of VT, we conducted a medical-record-based, longitudinal study of the association between time-varying current statin use and the risk of recurrent VT.

Methods

Setting and Design

The setting for this population-based study was Group Health Cooperative (GHC), a large integrated health care delivery system in Western Washington State. An inception cohort of all GHC members who had experienced a first VT was created and each individual followed for VT recurrence and comorbidities using GHC medical records and administrative data. The study received GHC institutional review board approval.

Participants

Study participants were GHC members, men 30 to 89 years of age and women 18 to 89 years of age, who experienced an incident VT event, either a deep vein thrombosis (DVT) or pulmonary embolism (PE), between January 1, 2002, and December 31, 2010.⁸ Incident VT was identified using International Classification of Disease (*ICD*) 9 diagnostic codes for inpatient and emergency room visits, the *ICD-10* diagnostic code for fatal PE events, and GHC pharmacy records for the use of low molecular weight heparin in the outpatient setting. Trained abstractors reviewed the medical record of each potential case to verify the diagnosis of VT. Participants were eligible if the incident VT event was diagnosed by an imaging modality, if the event was a fatal PE, or if the event was diagnosed by a physician based on the presence of symptoms in the absence of imaging. Ninety-eight percent of eligible VT cases had positive diagnostic imaging test results. Incident events were categorized by location of the thrombus and by whether the event was idiopathic or was secondary to a known thrombosis risk factor, including prevalent cancer at the time of the event or in the 2 years prior; inpatient surgery, hospitalization, or fracture in the 30 days prior to event; or current use of oral estrogen hormone therapy or oral contraceptives. Among 2,843 incident events, we excluded women who were pregnant in the year prior to the event (n=23) and participants who died on the day of the incident event (n=19) or who had no additional follow-up after the incident event (n=3) leaving 2,798 for analyses.

Data collection

Data collection was conducted by trained medical abstractors using GHC medical records and administrative files from the time preceding the incident VT to the end of follow-up (as late as December 2014) or death. GHC medical records contain files for all hospitalizations, physician notes for ambulatory care visits, diagnostic test reports, prescriptions, and laboratory results.

Recurrent VT—A recurrent VT was defined as a thrombus at a new location at any time after the incident event or as an extension of an existing thrombosis at a previous location at least 14 days after the incident event. The adjudication of recurrent events was based on evaluating evidence from multiple sources that included follow-up imaging, initiation of anticoagulant treatment, and physician and patient reports. All events needed to have sufficient evidence in the medical record to validate a VT diagnosis. A physician needed to provide a diagnosis that was supported by some level of clinical evidence for the event to qualify as eligible; symptoms alone were not sufficient evidence for a validated diagnosis in this study. Events were classified by thrombus location and as idiopathic versus secondary. Abstractors were unaware of study hypotheses.

Medications

Statins: Statin use was based on prescription fills at GHC pharmacies, where 86% of study members reported filling most (>90%) or all of their prescriptions. The type of statin prescribed was determined primarily by which agent was the GHC preferred agent, which changed from simvastatin to lovastatin during the study. Less than 18% of person-time on statins represented use of other statins. For each prescription, a run-out date was determined

using the fill date and days-supply, assuming 80% compliance with prescribing instructions plus a 30-day extension to best approximate use based on filling patterns we observed at GHC. Throughout follow-up, participants were categorized as current statin users, recent stoppers, or non-users. Recent stopping of statin therapy was defined as the time interval 2 years after the last calculated run-out date; after 2 years, non-use status was assigned. Dose was estimated using pill content, the number of pills dispensed, and the days of supply of the prescription. Standardized daily doses were calculated based on simvastatin equivalents: low (<20 mg), medium (20 to <40 mg), and high (≥ 40 mg).⁹

Other therapies: Information on anticoagulation and aspirin use, which included treatment start and stop dates, was collected from the medical record by abstractors. Current use of estrogens was based on GHC prescription fills assuming 80% compliance for hormone replacement therapy and 100% compliance for oral contraceptives.

Covariates—Behavioral and clinical information from the medical record and telephone interview was collected at baseline (at the time of the incident VT event) and through follow-up (medical record review only). This included information on smoking, weight and height, cholesterol and lipid levels and their treatment, and clinical cardiovascular disease (CVD) defined as a history of myocardial infarction, unstable angina, angina pectoris, cardiac revascularization procedure, ischemic and hemorrhagic stroke, peripheral vascular disease, and carotid endarterectomy. We also collected information on cancer diagnoses and treatments for new neoplasms, recurrences, and metastases. Hospitalization, surgery, and fracture dates were collected from GHC administrative records. Time-varying indicator variables were set to one on the date of hospitalization, surgery, or fracture and reset to zero 30 days thereafter. Race was based on information recorded in the medical record but was augmented by self-report for those participating in a telephone interview. Missing data were limited and restricted to BMI and race (<2%). Multiple imputation was performed using chained equations with the Gaussian normal regression imputation method to impute missing BMI values and multinomial logistic regression to impute missing values for race in Stata version 13.0 statistical software (Stata Corporation, College Station, Texas).^{10,11}

Statistical Analyses

We used Cox proportional hazards regression models to estimate the association between current or recent statin use and the risk of VT recurrence. A categorical statin use variable (current user, non-user, recent-stopper [within past 2 years]) was used because of concerns that recent-stoppers had risks unlike non-users and current users. Time zero was the date of the incident VT diagnosis, and participants were followed until their first recurrent VT. Participants were censored at pregnancy, death, and at the end of follow-up, whichever came first. We estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association between current statin use and risk of VT recurrence while adjusting for the following *a priori* selected covariates: age (linear), sex, BMI (linear), race (white, black, and other), the status of the incident event as idiopathic or secondary, and time-varying measures of current anticoagulation use, current aspirin use, smoking status (never, former, and current), prevalent CVD, recent cancer (diagnosis or treatment within the last 2 years), recent fracture

status, and recent hospitalization status. Evidence for departure from the proportional hazards assumption was evaluated using Schoenfeld residuals;¹² none was found.

Primary analyses were conducted: (1) among all cohort members; and (2) among those without CVD at the time of the incident event, with censoring at the time of development of CVD. We conducted several sensitivity analyses: (1) to test our compliance assumption, we assumed 100% compliance with statin prescribing instructions instead of 80%; (2) to approximate a new-user design, we excluded from analyses those who had used statins before or at the time of their incident event;¹³ (3) to approximate an intention-to-treat analysis among new users, we also performed analysis that did not reclassify initiators as stoppers when pharmacy fills indicated no more statin prescriptions were being filled, and (4) to evaluate recurrent VT risk after the end of anticoagulation use, we restricted person-time at risk to that after the end of anticoagulation treatment.

Secondary analyses were conducted comparing specific statin drugs (lovastatin, simvastatin, and other statin) and, among statin users, different daily doses (low, medium, and high). We also examined the association in those with prior CVD, including those with CVD at baseline and allowing participants to enter these analyses at the time of CVD diagnosis during follow-up. As exploratory analyses, we evaluated associations in subgroups based on use of time-varying anticoagulation and time-varying aspirin, sex, median age (<67 years versus ≥67 years), obesity (BMI <30 compared with BMI ≥30), and idiopathic versus secondary status of the incident event. We tested for statistical evidence of interaction between current anticoagulation use and current statin use using the likelihood ratio test.

Results

The cohort consisted of 2,798 participants with incident VT events (53% PEs) that occurred between January 1, 2002 and December 31, 2010. The average age of the cohort at baseline was 65.8 years and 55% were female (Table 1). Among the incident events, 204 (7.3%) died within 30 days of the incident event, 146 of which were among those with PE.

Hyperlipidemia and prevalent CVD were each present in 24% of the cohort. At baseline, 23% were treated with lipid-lowering medications that were almost exclusively statins: 61% low dose, 30% medium dose, and 9% high dose. Characteristics of users by baseline CVD prevalence and statin use are presented in Table 2. Among those without CVD, statin users were on average older with a higher BMI and were more likely to be male and to have diabetes.

Average follow-up was 3.4 years and ranged from 0 to 11 years. During follow-up, 27% of the baseline users of statins stopped therapy without restarting whereas 21% of the non-users at baseline initiated statin therapy before the end of follow-up. Overall, 38% of the cohort used statins at some point during follow-up. Among the 2,134 (76%) without CVD at baseline, 151 (7%) developed CVD during follow-up.

During follow-up, 457 (16%) cohort members had a first recurrent VT event, 96% of which were documented by imaging. Among the events, 253 (55%) were at a new site, 180 (39%)

included a PE, 279 (61%) were idiopathic, and 76 (16.6%) occurred among those using anticoagulation therapy.

The rate of recurrence was 5.2 (95% CI: 4.7–5.9) per 100 person-years among non-users of statins and was 3.9 (95% CI: 3.3–4.7) per 100 person-years among current statin users (Table 3). Among all cohort members, in adjusted models, current use of statin therapy was associated with a lower risk of recurrent VT: HR = 0.74 (95% CI: 0.59–0.94). In sensitivity analyses, when exposure was defined by 100% compliance, the evidence for association was similar: HR = 0.74 (95% CI: 0.59–0.94). Restricting the cohort to the subset of new users of statin therapy (n=1,948) resulted in a similar relative risk estimate: HR = 0.62 (95% CI: 0.41–0.93). The estimate from the intention-to-treat analysis was similar to the estimate from the primary analysis: HR = 0.69 (95% CI: 0.48–0.94). Results were similar in analyses that restricted person-time at risk to be after the end of anticoagulation treatment: HR = 0.76 (95% CI: 0.59–0.98). Recent stopping was not associated with a risk of recurrent VT: HR = 0.89 (95% CI: 0.61–1.3).

Among cohort members free of prior CVD, current use of statin therapy was associated with a 38% lower risk of recurrent VT: HR = 0.62 (95% CI: 0.45–0.85) (Table 3). Among cohort members with prior CVD, there was no evidence that current statin use was associated with VT recurrence: HR = 1.1 (95% CI: 0.70–1.7). There was no strong statistical evidence, however, of multiplicative interaction whereby CVD modified the association between statins and VT recurrence (p-value = 0.43).

Relative risk estimates were similar for current use of the different statin drugs in the full cohort and in the cohort without prior CVD (Table 3). Among current statin users, relative to medium daily dose, neither low dose (HR: 0.85; 95% CI: 0.52–1.4) nor high dose (HR: 1.0; 95% CI: 0.66–1.6) was associated with risk of recurrent VT. We did not detect statistical interaction by current use of statins with current use of anticoagulation therapy (p-value for interaction = 0.13), with current use of aspirin (p-value for interaction = 0.32), and with anticoagulation and/or aspirin (p-value for interaction = 0.42), see Supplemental Table S1–3. When analyses were conducted in subgroups defined by combinations of key covariates, sex, age, obesity, and idiopathic VT status, we did not detect differences in the HR association with statin use (Figures 1a and 1b).

Discussion

In a population-based cohort of subjects with a history of VT, statin use, compared with non-use, was associated with a 26% and a 38% lower risk of recurrent VT in the full cohort and among those without a history of CVD, respectively. The risk among recent statin stoppers was not different from non-users. Sensitivity analyses indicated our findings were similar when assuming a compliance of 100% or among new users of statins. Relative risks were similar for the 2 main statins used (simvastatin and lovastatin) and did not differ by statin dose. Relative risk estimates were also similar for participants with idiopathic incident VT, among whom the clinical challenge of defining the best duration of anticoagulation is greatest.

A major limitation to the interpretation of the results is the potential for confounding because statin use was not randomized. Use was determined by participants and their GHC physicians. Indications for treatment likely included hyperlipidemia, CVD, or diabetes; given the lack of prior evidence, it is unlikely treatment was initiated as prophylaxis for VT recurrence. We adjusted for potential confounding factors using high-quality information collected by medical record review. However, as with any observational study, confounding by unmeasured characteristics associated with statin use and with a lower risk of VT recurrence could be present and could bias our relative risk estimates away from the null. This situation was likely the case for 2 non-cardiovascular outcomes, where observational studies had suggested protective associations with statins yet subsequent clinical trials demonstrated none.^{14,15} We were also concerned that those who discontinued treatment might have done so for reasons associated with thrombotic risk. Hence we categorized recent stoppers separately from current users and non-users; recent discontinuation of statin therapy, however, was not associated with VT recurrence. Strengths of our study include the population-based design, the nearly complete data on filled prescriptions to determine time-varying statin exposure, a full review of the medical record that includes review of provider notes to identify and validate recurrent VT events and potential confounding factors, and the analytic ability to separate current from past users of statins and to stratify by baseline CVD status, which provides estimates comparable to the statin randomized trials and incident VT outcomes. We also provide new information on potential effect modification of anti-coagulation and aspirin therapy on the statin-VT recurrence association. Although this is not the first publication of an observational study to address the statin-VT recurrence association, our approach addresses misclassification and confounding bias to a level not achievable by previously published studies, which relied on administrative data. Given that confounding is arguably the largest threat to internal validity in an observational study, the results presented here provide a more robust level of scientific evidence.

Based on meta-analyzed results from randomized trials of statins for the outcome of incident VT, we hypothesized that the association of statin use with recurrent VT would be strongest among those without prevalent CVD, which was observed: HR = 0.62 (95% CI: 0.41–0.94) in the randomized trials and HR = 0.62 (95% CI: 0.45–0.85) in this study.² The stratum of participants with prevalent CVD was small and full-cohort results were driven primarily by the no-prior-CVD stratum. Although we had sufficient statistical power for association testing among those without CVD to detect a 38% reduction in risk, we may have lacked sufficient power to detect a difference in the level of association between those with and those without prior CVD. We found no evidence that larger doses of statin conferred greater protection from recurrent VT, similar to what was reported from the randomized clinical trials meta-analysis where incident VT was the outcome.² We also did not observe large differences in relative-risks based on the type of statin used, similar to what was observed in the randomized trials meta-analysis.²

Findings from Previous Studies

No experimental evidence is available to relate current statin use to the risk of recurrent VT, and relative risk estimates for the association of statin use with incident VT from experimental data range from HR = 0.89 (95% CI: 0.78–1.01) for all trials to HR = 0.62

(95% CI: 0.41–0.94) for trials in adults without CVD.² Four observational studies using 3 data sources have been published addressing the relationship between statin use and VT recurrence risk. No association was reported by French investigators in a hospital-based inception cohort that included 432 incident idiopathic events with 60 recurrences: HR = 1.02 (95% CI: 0.36–2.91) for time-varying statin use compared with non-use.⁴ Using administrative data and restricting incident and recurrent events to those hospitalized with a PE, investigators reported a lower risk associated with any use of statins after the incident event according to Dutch national pharmacy claim files in 3,093 patients: HR = 0.50 (95% CI: 0.36–0.70).⁵ Two studies analyzed national hospital and pharmacy administrative data from Denmark and reached similar conclusions: time-varying exposure to statins was associated with a 28% reduction in risk and higher-potency statin therapy was associated with lower risk.^{6,7}

Biologic Plausibility

There is evidence that statins reduce pro-inflammatory cytokines and pro-coagulation hemostatic factors, leading to improved endothelial function and lower thrombotic risk.^{16–26} In a recent systematic review, authors conclude that anti-thrombotic properties of statins are likely inflammation-mediated through interleukins 6 and 8, C-reactive protein, and monocyte chemotactic protein 1.²⁷ This pro-inflammatory pathway is consistent with our observations that only current use of statins is associated with a reduction of the risk of VT recurrence. It is not clear, however, why this pathway would only be relevant to those without prior CVD. The point estimate for the absolute rate of recurrence appeared lower in those with CVD (4.7 events per 100 person-years) than without (5.3 events per 100 person-years) and might suggest that some interventional factor, such as aspirin use, is lowering baseline risk. We adjust for aspirin use in our models. We also modeled an interaction between statin use and aspirin use and did not detect effect modification in the full cohort. Our data on aspirin use are limited, however, so it is possible that incomplete adjustment or stratification for aspirin use confounds the observed association of statins with VT recurrence in the CVD stratum. It could also be that statins and aspirin share similar therapeutic pathways to VT recurrence and so that the addition of statins to aspirin therapy would not provide additional protection from recurrent VT. Lastly, the different statin-recurrent VT associations for people with prevalent CVD and for those without prevalent CVD could be due to chance, which is supported by the lack of statistical evidence of interaction with prevalent CVD status.

There are no reports that statin therapy is associated with an increased risk of bleeding, a reasonable expectation if statins have anticoagulant properties.²⁸ A recent, large meta-analysis of incident VT, however, has identified genetic predictors in new biologic pathways leading to risk that are not in the well-characterized coagulation and fibrinolysis pathways.²⁹

Clinical Significance

The prevention of recurrent VT is one of the most important clinical challenges of VT management. Treatment options to prevent recurrent VT are limited by non-compliance and risk of bleeding associated with anticoagulation treatments. Statin therapy may be a good candidate for preventive therapy, since these drugs are well tolerated, have a demonstrated

safety record, are relatively inexpensive, and have no known bleeding risks. The magnitude of the association found in our study is similar to the estimated effect of aspirin on recurrent VT, and appears clinically relevant.³⁰ Interventional data are only available from studies addressing the prevention of an incident VT event, but our study findings demonstrate that a randomized trial of statins for the prevention of recurrent VT is warranted.

Conclusions

Our study provides new information on a well-characterized inception cohort with high quality pharmacy data and event ascertainment to inform a potential causal association between current statin use and VT recurrence. In a population-based cohort of individuals with incident VT, current use of statins was associated with a lower risk of recurrent VT. These findings suggest that the secondary benefits of statins may extend to reducing risk of VT recurrence in those who have experienced a first VT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Essentials

- A lowered risk of recurrent venous thrombosis (VT) with statin treatment is controversial.
- Among observational inception cohort of 2,798 adults with incident VT, 457 had recurrent VT.
- Time-to-event models with time-varying statin use and adjustment for potential confounders.
- Compared to non-use, current statin use was associated with 26% lower risk of recurrent VT.

Figure 1.

a. Subgroup analyses of the current statin use and recurrent VT association

HR = Hazards ratio; CI: confidence interval; P-value: p-value for interaction of current statin use by subgroup characteristic.

b. Subgroup analyses of the current statin use and recurrent VT association among those without prevalent cardiovascular disease

HR = Hazards ratio; CI: confidence interval; P-value: p-value for interaction of current statin use by subgroup characteristic.

Table 1

Characteristics of the cohort

Characteristics	All (n = 2798)	Women (n = 1552)	Men (n = 1246)
<i>Subject characteristics at baseline</i>			
Mean age, years (SD)	65.8 (14.8)	65.9 (16.3)	65.6 (12.7)
Mean BMI, kg/m ² (SD)	30.2 (7.7)	30.4 (8.5)	29.9 (6.7)
Current smoker, %	8.9	8.9	9.0
Hyperlipidemia ¹ , %	24.3	20.3	29.4
Prevalent CVD, %	23.7	21.1	27.1
Cancer ² , %	23.3	23.6	22.9
Recent hospitalization, <30 days	23.3	24.6	21.7
Oral estrogen hormone therapy, %	5.9	10.6	0.0
Baseline lipid-lowering treatment			
Statin, %	22.1	19.5	25.4
Simvastatin, %	42.8	43.7	42.0
Lovastatin, %	48.5	49.0	48.0
Other statin, %	8.7	7.3	10.1
Non-statin, %	1.3	0.8	1.8
<i>Event characteristics</i>			
Incident VT event			
PE, %	52.9	54.5	50.9
Idiopathic ³ , %	50.9	43.9	59.6
Death within 30 days ⁴ , %	7.3	7.6	6.9
Anticoagulation treatment ⁵	96.7	96.9	96.4

SD = standard deviation; GHC = Group Health Cooperative; BMI = body mass index; CVD = cardiovascular disease including a history of myocardial infarction, unstable angina, angina pectoris, cardiac revascularization procedure, ischemic and hemorrhagic stroke, peripheral vascular disease, and carotid endarterectomy; VT = venous thrombosis; PE = pulmonary embolism

¹Defined as hyperlipidemic if taking a lipid-lowering medication at index and with a physician diagnosis of hyperlipidemia.

²Defined as cancer diagnosis or treatment in the 2 years prior to index.

³Defined as no cancer at event or in the 2 years prior; no inpatient surgery, hospitalization or fracture in the 30 days prior to event; not pregnant at the time of the event or in the 1 year prior; not currently using oral estrogen hormone therapy; not currently using oral contraceptives.

⁴Defined as death in <31 days following an incident VT.

⁵Defined as treatment prevalent at the time of incident VT event or started within 30 days.

Table 2

Characteristics by statin use and CVD status at baseline

Characteristics	No Prior CVD		Prior CVD	
	No Statin (n=1850)	Statin (n=284)	No Statin (n=329)	Statin (n=335)
Mean age, years (SD)	62.5 (15.6)	68.7 (10.6)	73.7 (11.2)	73.3 (9.7)
Male, %	41.6	48.9	48.3	53.1
Mean BMI, kg/m ² (SD)	30.3 (8.2)	31.2 (7.2)	28.8 (6.7)	29.9 (6.5)
Current smoker, %	8.9	6.0	10.9	9.3
Diabetes, %	5.7	34.5	21.9	26.3
Total cholesterol, mean (SD)	211.9 (34.8)	191.9 (48.0)	206.0 (49.4)	179.2 (40.1)
Hyperlipidemia ^I , %	3.4	87.3	19.5	91.3
Aspirin, %	20.6	35.6	43.5	53.7
Cancer, %	24.3	26.4	21.3	16.7
Recent Hospitalization, %	20.0	24.3	29.2	35.0
Oral estrogen hormone therapy, %	6.3	5.3	6.4	3.6
Idiopathic event, %	51.0	50.7	50.2	51.0
Initiated statin during follow-up, %	18.1	0.0	35.6	0.0
Stopped statin during follow-up, %	6.7	28.2	10.3	25.4

SD = standard deviation; BMI = body mass index, CVD = cardiovascular disease including a history of myocardial infarction, unstable angina, angina pectoris, cardiac revascularization procedure, ischemic and hemorrhagic stroke, peripheral vascular disease, and carotid endarterectomy

^I Defined as hyperlipidemic if taking a lipid-lowering medication at index and with a physician diagnosis of hyperlipidemia.

Table 3
Association of lipid-lowering treatment with recurrent VT among the full cohort and by CVD status

	Non-users of statins	Recent stoppers of statins	Current users of statins			
			Any statin	Simvastatin	Lowastatin	Other statin
Full Cohort						
Person-years	5967.3	561.9	2844.1	1671.5	750.4	422.1
Events	313	32	112	62	34	16
Rate/100-PYs	5.2 (4.7–5.9)	5.7 (4.0–8.1)	3.9 (3.3–4.7)	3.7 (2.9–4.8)	4.5 (3.2–6.3)	3.8 (2.3–6.2)
Adjusted HR * (95% CI)	1.0 (reference)	0.89 (0.61–1.3)	0.74 (0.59–0.94)	0.76 (0.57–1.0)	0.71 (0.49–1.0)	0.79 (0.47–1.3)
P-value	-	0.540	0.013	0.055	0.063	0.367
Cohort without Prior CVD						
Person-years	5305.3	318.2	1449.3	930.3	378.7	140.3
Events	282	19	49	30	14	5
Rate/100-pys	5.3 (4.7–6.0)	6.0 (3.8–9.4)	3.4 (2.6–4.5)	3.2 (2.3–4.6)	3.7 (2.2–6.2)	3.6 (1.5–8.6)
Adjusted HR * (95% CI)	1.0 (reference)	1.00 (0.62–1.6)	0.62 (0.45–0.85)	0.62 (0.42–0.92)	0.55 (0.32–0.94)	0.92 (0.38–2.2)
P-value	-	0.990	0.003	0.017	0.031	0.851
Cohort with Prior CVD						
Person-years	660.4	247.5	1392.5	-	-	-
Events	31	13	63	-	-	-
Rate/100-pys	4.7 (3.3–6.7)	5.3 (3.0–9.0)	4.5 (3.5–5.8)	-	-	-
Adjusted HR * (95% CI)	1.00 (reference)	0.99 (0.52–2.0)	1.1 (0.70–1.7)	-	-	-
P-value	-	0.966	0.704	-	-	-

CVD = Cardiovascular disease; PY = person years; HR = hazard ratio; CI = confidence interval.

* Adjusted for age, sex, race, BMI, idiopathic incident event, and time-dependent cancers, smoking status, CVD, anticoagulation therapy, aspirin use, hospitalization, and fracture.