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Is Lipid Lowering Therapy an Independent Risk Factor for Venous Thromboembolism? A Population-Based Case-Control Study

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Abstract

Introduction—The independent effect of lipid lowering therapy (**LLT**) on venous thromboembolism (**VTE**) risk is uncertain.

Objective—To test statin and non-statin LLT as potential VTE risk factors.

Methods—Using Rochester Epidemiology Project resources, we identified all Olmsted County, MN residents with objectively diagnosed incident VTE (cases) over the 13-year period, 1988–2000 (n=1340), and one to two matched controls (n=1538). We reviewed their complete medical records for baseline characteristics previously identified as independent VTE risk factors, and for statin and non-statin LLT. Using conditional logistic regression, we tested the overall effect of LLT on VTE risk and also separately explored the role of statin versus that of non-statin LLT, adjusting for other baseline characteristics.

Results—Among cases and controls, 74 and 111 received statin LLT, and 32 and 50 received non-statin LLT, respectively. Univariately, and after individually controlling for other potential VTE risk factors (i.e., BMI, trauma/fracture, leg paresis, hospitalization for surgery or medical illness, nursing home residence, active cancer, central venous catheter, varicose veins, prior superficial vein thrombosis, diabetes, congestive heart failure, angina/myocardial infarction, stroke, peripheral vascular disease, smoking, anticoagulation), LLT was associated with decreased odds of VTE (unadjusted OR= 0.73; p= 0.03). When considered separately, statin and non-statin

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Addendum: H.A. Heit and A.A Ashrani conceived the study idea, and developed it in collaboration with other co-authors. All authors contributed to the study design. T.M. Petterson and K.R. Bailey directed the analysis, which was carried out by D.J. Crusan. All authors participated in the interpretation of data. A.A. Ashrani wrote the initial draft. All authors participated in critical revision of the manuscript for intellectual content and approved the final version of the manuscript for publication.

LLT were each associated with moderate, non-significant lower odds of VTE. After adjusting for angina/myocardial infarction, each was significantly associated with decreased odds of VTE (OR= 0.63, p< 0.01 and OR= 0.61, p=0.04, respectively).

Conclusions—LLT is associated with decreased VTE risk after adjusting for known risk factors.

Keywords

Venous thromboembolism; Venous Thrombosis; Pulmonary Embolism; Hydroxymethylglutaryl-CoA Reductase Inhibitors; Hypolipidemic Agents; Epidemiology

Introduction

Hyperlipidemia is a known risk factor for atherosclerotic coronary heart disease (**CHD**) (1). Several studies suggest that hyperlipidemia is associated with an increased risk for VTE (2–4) while other studies dispute this association (5–8). The association of hyperlipidemia and VTE is biologically plausible, as hyperlipidemia has been associated with increased platelet size and platelet activation (9, 10); endothelial dysfunction (11); activation of coagulation factors (3, 12); impaired fibrinolysis (13); and inactivation of tissue factor pathway inhibitor (14). Moreover, there may be an association between atherosclerotic disease and idiopathic VTE (15–17).

Lipid lowering therapy (**LLT**), including 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce the risk of CHD (18–22). Furthermore, there is increasing evidence that, in addition to lowering lipids, statins inhibit vascular endothelial activation and improve endothelial function (23–26); inhibit platelet and coagulation factor activation (27–29, 30); reduce tissue factor expression (31, 32, 33), C-reactive protein and coagulation factor VIII (22, 34); fibrin generation and inflammation (35–37); and enhance fibrinolysis (38, 39).

Data on whether LLT reduces the risk of VTE are conflicting. While several studies reported that statins reduce the risk of incident and recurrent VTE (40–55), others were unable to demonstrate a similar association (56–61), or have shown an increased risk of VTE with fibrates (62, 63). Moreover, individuals with hyperlipidemia and CHD (who are commonly on LLT) have other comorbid conditions, for example, diabetes mellitus, peripheral vascular disease, congestive heart failure, stroke and are frequently hospitalized for surgery or medical illness, both major VTE risk factors. In addition, individuals on LLT may concomitantly be on aspirin, which is effective in secondary prevention of VTE (64, 65). Thus, it is unclear whether the association between statins and VTE risk is independent of other VTE risk factors that might be present concomitantly. To address this gap in knowledge, we performed a population-based case-control study to test the overall effect of LLT on incident VTE risk after controlling for previously identified VTE risk factors. We also explored the effect of statin and non-statin LLT versus no LLT use on VTE risk.

Methods

Study Setting and Design

Using the longitudinal and population-based resources of the Rochester Epidemiology Project (**REP**) (66), we identified all Olmsted County, MN residents with incident deep vein thrombosis (**DVT**) and/or pulmonary embolism (**PE**) over the 35-year period, 1966–2000, as previously described (67, 68). Rochester, the County seat, is geographically isolated from other urban centers and home to Mayo Clinic, one of the world's largest private medical centers. Thus, County residents receive medical care from very few providers, primarily Mayo Clinic and another group practice, Olmsted Medical Center, with their affiliated hospitals. Since 1907, every Mayo Clinic patient has been assigned a unique identifier. All information (medical history; clinical assessments; consultations; dismissal summaries; surgical procedures; laboratory, radiology, pathology, and autopsy results; correspondence; and death certificates) from every contact (e.g., office, NH, emergency department, hospital inpatient, hospital outpatient) is contained within a unit medical record. Under auspices of the REP, this records-linkage was expanded to include non-Mayo providers of care to County residents (66). We then performed a case-control study nested within the Olmsted County population. For this study, all Olmsted County residents with a first lifetime objectively-diagnosed DVT or PE during the 13-year period, 1988–2000 were included as cases. We limited the VTE cases to this time frame because the first statin (i.e., lovastatin) was approved by the US Food and Drug Administration in 1987. The REP provides an enumeration of the entire Olmsted County population from which controls can be sampled as described elsewhere (66). Using this system, one to two age- (± one year) and sex-matched Olmsted County residents who had an episode of medical care within ± one year of the case event date and whose medical record number was closest to the case's medical record number were selected as controls as previously described (69–71). Since a patient's medical record number is assigned sequentially and in perpetuity, matching on medical record number assures a similar duration of medical history among cases and matched controls. The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Measurements

Using explicit criteria, trained and experienced nurse abstractors reviewed all medical records (inpatient, outpatient, emergency department, nursing home, autopsy, death certificate, etc.) in the community (72) for cases and controls who provided consent to review of their medical records for research purposes. All records were reviewed from date first seen by a REP healthcare provider until the earliest of death, date of last medical record follow-up or 2000, as previously performed.(67, 69) For cases, data were recorded on the method of diagnosis and type of incident VTE event (DVT, PE or both; chronic thromboembolic pulmonary hypertension). A DVT was categorized as objectively-diagnosed when symptoms or signs of acute DVT were present and the diagnosis was confirmed by computed tomographic or magnetic resonance imaging contrast venography, compression venous duplex ultrasonography, impedance plethysmography or pathology examination of thrombus removed at surgery or autopsy. A PE was categorized as objectively-diagnosed when symptoms and/or signs of acute PE were present and the

diagnosis was confirmed by pulmonary angiography, a ventilation/perfusion lung scan interpreted as high probability for PE, computed tomographic pulmonary angiography, magnetic resonance imaging or pathology examination of thrombus removed at surgery or autopsy. Mayo Clinic pathologists performed all autopsy examinations and completed the death certificates of persons dying within Olmsted County during the study period.

For Olmsted County residents meeting our criteria for objectively-diagnosed DVT or PE and matched controls, the study nurses also collected data from the medical record on date of incident event (cases) or index episode of care (controls); patient age at incident event (cases) or index episode of care (controls); gender; patient location at incident event onset (cases) or index episode of care (controls) (four categories, defined as community-dwelling, confined to a hospital, community-dwelling but hospitalized in the previous 92 days, or confined to a nursing home [including chronic rehabilitation facility]); body mass index (**BMI**; kg/m^2); active cancer (recent tumor burden without curative surgery, chemotherapy, or radiotherapy, excluding non-melanoma skin cancer); serious neurologic disease with leg paresis (stroke or other disease affecting the nervous system with associated leg paresis, or acute stroke with leg paresis requiring hospitalization within the previous three months); any surgery requiring general, spinal, or epidural anesthesia; trauma/fracture resulting in hospital admission (major fracture or severe soft tissue injury); varicose veins (varicose veins, or treated varicose veins [injection sclerotherapy or stripping]); central venous catheter or pacemaker wire; pregnancy or postpartum at the time of the incident event; oral contraceptive use; smoking; anticoagulation with heparin (within 12 hours prior to index date) or warfarin (within 3 days prior to index date); and statin and non-statin LLT use. As aspirin use could not be ascertained accurately via medical record review, we collected data on health conditions where aspirin therapy is typically recommended, including diabetes mellitus, congestive heart failure (CHF), angina, and myocardial infarction (MI), ascertained by medical record review; and stroke and peripheral vascular disease (PVD) by ICD-9 codes; and used these as surrogate markers of aspirin use. Hospitalization with or without surgery, nursing home confinement, trauma/fracture, neurological disease with leg paresis, pregnancy or postpartum, oral contraceptive use, hormone therapy and LLT use had to have been documented in the three months prior to the incident VTE event for cases or the index episode of medical care for controls. For subjects to be categorized as having received anticoagulation prophylaxis, they had to receive heparin within 12 hours prior to index date or warfarin within 3 days prior to index date. Smoking status was categorized into “current”, “former”, “ever” and “never” smoker categories, based on the smoking status on the index date. Active cancer had to have been documented in the three months prior to or three months after the incident VTE event for cases or index episode of care for controls. Varicose veins, diabetes mellitus, CHF, angina, MI, stroke, and PVD could be documented any time prior to the incident event/ index date. Body mass index was based on the most recent height and weight measurements prior to the incident VTE event (cases) or index episode of care (controls). If either height or weight was missing, the value was imputed based on case status and 10-year age group (mean value was used). Statin LLT use was defined as any of the following lipid lowering treatments: atorvastatin, cerivastatin, fluvastatin, lovastatin, pravasatatin, simvastatin. Non-statin LLT use was defined as any of the following lipid

lowering treatments: cholestyramine, clofibrate, colesevelam, colestipol, fenofibrate, gemfibrozil, niacin.

Analysis

We evaluated the overall association of LLT use (i.e., either statin or non-statin use) with the odds of VTE, using conditional logistic regression. To assess whether different classes of LLT have an association with the odds of VTE, statin LLT use and non-statin LLT use were compared to no LLT in the same conditional logistic regression model. We next performed bivariate analyses to estimate the association of LLT with the odds of VTE after separately adjusting the above models for each baseline characteristic previously identified as an independent risk factor for VTE, including BMI, trauma/fracture, hospitalization for surgery or medical illness, active cancer, neurological disease with leg paresis, nursing home confinement, central venous catheter/ pacemaker wire, varicose veins, superficial thrombophlebitis, oral contraceptives, pregnancy/ post-partum phase, hormone replacement therapy, warfarin anticoagulation, heparin anticoagulation and smoking (69). As aspirin has been demonstrated to be effective in secondary VTE prevention (64, 65), we also performed bivariate analyses to estimate the association of LLT with the odds of VTE after adjusting health conditions like diabetes mellitus, CHF, angina, MI, stroke and PVD where aspirin therapy is typically recommended, as a surrogate marker for aspirin use. We also estimated the association of LLT with the odds of VTE in a multivariable model, adjusting for patient age and all of the above VTE risk factors.

Results

Over the 13-year period, 1988–2000, 1417 residents of Olmsted County developed a first lifetime VTE. Of these, 1340 (94.6%) incident VTE events were objectively-diagnosed. The distribution of VTE events by event type was 768 (57.3%) DVT alone, 567 (42.3%) PE with or without DVT, and 5 (0.4%) chronic thromboembolic pulmonary hypertension; 134 of 1340 (10%) VTE events were diagnosed at autopsy (128 of which were PE). The mean ± standard deviation (**SD**) age of the cases and matched controls (n=1538) was 65.0 ± 19.0 and 64.6 ± 18.8 years, respectively. Fifty five percent of cases and controls were females.

Among all cases and controls, 74 (5.5%) and 111 (7.2%) received statin LLT, and 32 (2.4%) and 50 (3.3%) received non-statin LLT, respectively (Table 1). Seven (0.5%) cases and ten (0.7%) controls were on both statin and non-statin LLT. The prevalence of VTE risk factors among VTE cases and controls is shown in Table 1.

In an unadjusted conditional logistic model comparing any LLT use versus no LLT use, LLT use was associated with decreased odds of VTE [odds ratio (**OR**) =0.73; 95% confidence interval (**CI**): 0.55, 0.96; p-value=0.03] (Table 2). In bivariate analyses comparing LLT use to no LLT and individually controlling for each of the previously-identified VTE risk factors, LLT remained similarly associated with lower odds of VTE (Table 2). The odds of VTE were lower after adjusting for hospitalization (OR=0.61; 95% CI: 0.44, 0.86; p-value=0.01). However, after controlling for active cancer, the decreased odds of VTE were not as robust (OR=0.77; 95% CI: 0.57, 1.04; p-value=0.09). Of note, there was a tendency for lower use of LLT in the active cancer group. Of the 333 cases and

49 controls who had active cancer, 17 (5.1%) cancer cases and 3 (6.1%) cancer controls were on LLT. In contrast, 82 (8.1%) of the 1007 non-cancer cases were on LLT; and 148 (9.9%) of the 1489 non-cancer controls were on LLT. Furthermore, bivariate analyses comparing LLT use to no LLT and individually controlling for health conditions like diabetes mellitus, CHF, angina, MI, stroke and PVD where aspirin therapy is typically recommended, LLT remained similarly associated with lower odds of VTE (Table 2). The odds of VTE were lower after adjusting for angina/MI (OR=0.59; 95% CI: 0.44, 0.79; p-value <0.01).

In a multivariable analysis, after adjusting for BMI, trauma/fracture, hospitalization for surgery or medical illness, active cancer, leg paresis, central venous catheter/ pacemaker wire, varicose veins, nursing home confinement, prior superficial thrombosis, oral contraceptive, pregnancy/postpartum, hormone therapy, heparin therapy, warfarin therapy, smoking, diabetes mellitus, CHF, angina, MI, stroke and PVD, LLT use remained associated with a decreased odds of VTE (OR=0.67; 95% CI: 0.43, 1.04) with borderline statistical significance (p=0.08) (Table 2).

We also separately assessed type of LLT (i.e., statin and non-statin) in the same conditional logistic model for an association with VTE. Compared to no LLT use, both statin and non-statin LLT were associated with a moderate but non-significantly lower odds of VTE (unadjusted OR=0.78; p=0.12, and OR=0.72; p=0.16, respectively; Table 3). Similar reductions in the odds of VTE were noted with statin and non-statin LLT after individually adjusting for previously described VTE risk factors and possible aspirin use. When adjusted for hospitalization with or without surgery, statin LLT was significantly associated with reduced odds of VTE (OR= 0.60; p= 0.01); the lower odds of VTE with non-statin LLT use was equal quantitatively, but was not statistically significant (OR= 0.65; p=0.13; Table 3). When adjusted for angina/MI, both statin and non-statin LLT were significantly associated with reduced odds of VTE (OR= 0.63; p= 0.005 and OR=0.61; p=0.04, respectively; Table 3). In multivariable analysis, after adjusting for all previously identified VTE risk factors, statin LLT use was marginally significantly associated with a reduced odds of VTE (OR=0.66; p=0.1); the association with non-statin LLT use was, again, equal quantitatively, but not statistically significant (OR=0.71; p-value=0.36) (Table 3). When statin LLT use was compared to no statin use (i.e., non-statin LLT use or no LLT use combined; data not shown), the results were very similar to those obtained when comparing statin LLT use to no LLT (Table 3), or when comparing any LLT use to no LLT (Table 2).

Discussion

In this study, we found that LLT is associated with reduced odds of VTE. We noted that the VTE risk reductions were very similar for both statin and non-statin LLT, although the association between statin LLT and VTE risk reduction was statistically stronger than that for non-statin LLT. This finding may be attributable to low power to detect such an association, as fewer individuals were on non-statin LLT. We also noted that after controlling for other known risk factors for VTE, with the exception of active cancer and prior superficial vein thrombosis, LLT use was still significantly associated with reduced VTE risk. In particular, adjusting for hospitalization with or without surgery and angina/MI

strengthened the association between LLT use and reduced VTE risk. Furthermore, even after adjusting for BMI and diabetes mellitus which are indirectly associated with hyperlipidemia, LLT use was still significantly associated with reduced VTE risk. LLT use remained significantly associated with reduced VTE risk after adjusting for heparin therapy, warfarin therapy and health conditions where aspirin is typically recommended (e.g., diabetes mellitus, CHF, angina, MI, stroke and PVD). The less robust association of LLT use with decreased VTE risk in individuals after controlling for active cancer may be explained by the lower use of LLT in subjects with active cancer.

The reduced odds of VTE observed with LLT is biologically plausible, as hyperlipidemia has been associated with increased platelet activation (9, 10); endothelial dysfunction (11); activation of coagulation factors (3, 12); impaired fibrinolysis (13); and inactivation of tissue factor pathway inhibitor (14). Thus, lowering of lipids with statin and non-statin LLT use could theoretically reduce risk of VTE. As the number of cases and controls using different classes of non-statin LLT were small individually (Table 1), we elected to pool the different classes of non-statin LLT to evaluate their potential lipid lowering effects on the risk of VTE. Furthermore, statins have been demonstrated to inhibit vascular endothelial activation and improve endothelial function (23–26); inhibit platelet and coagulation factor activation (27–30); reduce tissue factor expression (31–33), C-reactive protein and coagulation factor VIII (22, 34); fibrin generation and inflammation (35–37); and enhance fibrinolysis (38, 39).

Available data on the association of LLT with VTE are conflicting, with some studies reporting an association of statins with reduced VTE risk (40–52) while others found no association or even an increased risk.(56–59, 61) For example, a clinical trial that randomized apparently healthy individuals with elevated C-reactive protein levels (median age 66 years) to rosuvastatin or placebo (JUPITER trial) found VTE incidence was reduced from 0.32 to 0.18 per 100-person years with rosuvastatin [hazard ratio (**HR**):0.57 (95% CI: 0.37, 0.86)] (47), while another clinical trial that randomized older individuals (median age 75 years) to pravastatin or placebo (PROSPER trial) found no association between pravastatin and VTE (HR= 1.42; 95% CI: 0.80, 2.52).(59) In nested case-control studies, statins were either not associated with idiopathic VTE (56) or were associated with reduced VTE (46, 48) and DVT risk.(45) In cohort studies, statins were variously associated with a decreased risk of DVT,(42) an increased risk of VTE,(57) or not associated with VTE.(58) In several meta-analyses, statins appeared to reduce VTE risk.(49–51) In contrast, in a meta-analysis of published and unpublished randomized statin clinical trials with primary end-points other than VTE, statins had minimal or no VTE protective effects (OR 0.89; 95% CI: 0.78–1.01, p = 0.08), and there was no doseresponse relationship in VTE risk reduction between higher dose statin therapy to standard dose statin therapy (OR 0.98; 95% CI: 0.80–1.20, p = 0.87).(61) Potential reasons for these conflicting results include selected and differing study populations and lipid-lowering drugs, diagnostic uncertainty or misclassification, differing study endpoints and inadequate control for VTE risk factors.

Our study has several important strengths. Due to the unique features of the REP, our study avoids referral bias and other potential distortions of including a too healthy population. We believe that this cohort better reflects “real world” clinical practice in contrast to a highly selected population participating in clinical trials. All VTE cases met strict criteria for

objectively-confirmed acute DVT and/or PE, and we confirmed that controls did not have VTE, based on direct review of their source documents (i.e., imaging, surgical and autopsy reports) rather than depending on administrative codes. We included the entire spectrum of VTE disease occurring in the community, including persons with rapidly fatal and chronic care facility (e.g., nursing home) events who did not reach the hospital. We insured a comparable control group by performing a population-based study where both cases and controls were residents from the same community with similar lifetime access to medical care. The use of LLT within three months prior to the index date was confirmed by reviewing the medical records. We adjusted for all potential VTE risk factors when testing for association between LLT use and VTE.

Our study also has important limitations. The age-, sex- and racial-distribution of Olmsted County is similar to that for Minnesota, the upper mid-west, and the U.S. white population; however, residents of Olmsted County exhibit higher median income and education level compared to these geographic regions.(66, 73, 74) While no single geographic area is representative of all others, the under-representation of minorities may compromise the generalizability of our findings to different racial and ethnic groups. While we required that all risk factors be documented in the medical record prior to the onset of the VTE event, actual use of LLT or aspirin could not be reliably ascertained from the medical records, although we adjusted for medical conditions where aspirin is commonly recommended. We did not ascertain the efficacy of LLT therapy on the lipid profile to address whether the lower VTE risk with LLT use was predominantly due to its lipid lowering properties. We cannot exclude that the observed statistical association between LLT use and lower VTE risk could be due to unmeasured confounding variables (e.g., behavioral and socio-economic factors). Finally, our sample size was too small to test the effect of different types and doses of LLT on VTE risk.

In conclusion, LLT is associated with reduced VTE risk after adjusting for previously-identified VTE risk factors.

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Highlights

- Lipid lowering therapy (LLT) is associated with decreased odds of VTE.
- This association persisted even after controlling for other VTE risk factors.
- Both statin and non-statin LLT had similar but non-significant lower odds of VTE.

TABLE 1

Baseline Characteristics of Venous Thromboembolism Cases and Controls

Baseline Characteristic	Cases (n=1340)	Controls (n=1538)
Statin lipid lowering therapy alone, *n (%)*	67 (5.0)	101 (6.6)
Lovastatin, n (%)	25 (37.3)	35 (34.7)
Simvastatin, n (%)	21 (31.3)	33 (32.7)
Atorvastatin, n (%)	11 (16.4)	17 (16.8)
Pravasatatin, n (%)	7 (10.4)	12 (11.9)
Fluvastatin, n (%)	4 (6.0)	5 (5.0)
Non-statin lipid lowering therapy alone, *n (%)*	25 (1.9)	40 (2.6)
Niacin, n (%)	11 (44.0)	19 (47.5)
Gemfibrozil, n (%)	10 (40.0)	16 (40.0)
Cholestyramine, n (%)	4 (16.0)	7 (17.5)
Cholestipol, n (%)	1 (4.0)	0 (0.0)
Both statin and non-statin therapy, *n (%)*	7 (0.5)	10 (0.7)
Age, *mean ± SD*	65.0 (19.0)	64.6 (18.8)
Female, n (%)	744 (55.5)	850 (55.3)
Body mass index (BMI, kg/m^2), *mean ± SD*	27.9 ± 7.0	26.7 ± 5.3
Trauma / fracture, *n (%)*	171 (12.8)	40 (2.6)
Hospitalized +/− surgery†, n (%)	613 (45.7)	138 (9.0)
Active cancer, *n (%)*	333 (24.9)	49 (3.2)
Neurological disease *n (%)*	93 (6.9)	13 (0.8)
Pacemaker/vascular catheterization *n (%)*	240 (17.9)	51 (3.3)
Varicose veins, *n (%)*	365 (27.2)	354 (23.0)
Nursing home confinement§ *n (%)*	170 (12.7)	104 (6.8)
Prior Superficial Thrombosis, n (%)	203 (15.1)	84 (5.5)
Oral Contraceptives (Females Only), n (%)	61 (8.2)	41 (4.8)
Females, Age 18–45, n (%)	54 (43.2)	38 (26.8)
Females, Age 46+, n (%)	5 (0.8)	2 (0.3)
Pregnancy/Postpartum (Females Only), n (%)	25 (3.4)	10 (1.2)
Females, Age 18–45, n (%)	25 (20.0)	10 (7.0)
Estrogen/Progesterone/Oral Contraceptives*, n (%)	227 (16.9)	176 (11.4)
Females, Age 18–45, n (%)	65 (52.0)	46 (32.4)
Females, Age 46+, n (%)	138 (22.7)	126 (18.2)
Pulmonary Hypertension, n (%)	57 (4.3)	23 (1.5)
Diabetes, n (%)	168 (12.5)	142 (9.2)
CHF, n (%)	243 (18.1)	152 (9.9)
PFO, n (%)	24 (1.8)	22 (1.4)
Angina/MI, n (%)	338 (25.2)	289 (18.8)
Congenital Heart Disease, n (%)	9 (0.7)	1 (0.1)
Cardiomyopathy, n (%)	29 (2.2)	24 (1.6)

Baseline Characteristic	Cases (n=1340)	Controls (n=1538)
Valvular Heart Disease, n (%)	165 (12.3)	137 (8.9)
Stroke, n (%)	239 (17.8)	184 (12.0)
Peripheral Vascular Disease, n (%)	166 (12.4)	144 (9.4)
Ever Smoker, n (%)	699 (52.2)	759 (49.3)
Current Smoker, n (%)	177 (13.2)	209 (13.6)
Former Smoker, n (%)	522 (39.0)	550 (35.8)
Never Smoker, n (%)	641 (47.8)	779 (50.7)
Warfarin, n (%)	44 (3.3)	43 (2.8)
Heparin, n (%)	53 (4.0)	6 (0.4)

† In hospital or within 92 days of previous hospitalization compared to no hospitalization in the past 92 days. Includes patients hospitalized with surgery or for acute medical illness.

* Nineteen cases and two controls where males are on estrogen/progesterone.

§ Two cases are missing nursing home confinement

Table 2

Risk of Venous Thromboembolism with Lipid Lowering Therapy (Either Statin or Non-Statin) Compared to No Lipid Lowering Therapy

Model	Lipid Lowering Therapy versus no lipid therapy		
	Odds Ratio	95% Confidence Interval	P-value
Unadjusted	0.73	(0.55, 0.96)	0.03
Adjusted for‡:			
BMI	0.70	(0.53, 0.93)	0.01
Trauma / fracture	0.75	(0.56, 0.99)	0.05
Hospitalized +/− surgery†	0.61	(0.44, 0.86)	0.01
Active cancer	0.77	(0.57, 1.04)	0.09
Neurological disease, with leg Paresis	0.72	(0.54, 0.96)	0.03
Pacemaker/ catheter	0.63	(0.47, 0.86)	0.003
Varicose veins	0.75	(0.57, 0.99)	0.04
Nursing home*§	0.75	(0.57, 0.99)	0.04
Prior Superficial Thrombosis	0.75	(0.56, 1.00)	0.05
Oral Contraceptives	0.73	(0.55, 0.96)	0.03
Pregnancy/Postpartum	0.73	(0.55, 0.96)	0.03
Estrogen/Progesterone/Oral Contraceptives	0.73	(0.55, 0.97)	0.03
Diabetes	0.70	(0.53, 0.93)	0.01
CHF	0.71	(0.54, 0.95)	0.02
Angina/MI	0.59	(0.44, 0.79)	0.0005
Stroke	0.68	(0.51, 0.91)	0.008
Peripheral Vascular Disease	0.70	(0.53, 0.92)	0.01
Ever Smoker	0.73	(0.55, 0.97)	0.03
Warfarin	0.73	(0.55, 0.96)	0.02
Heparin	0.73	(0.55, 0.97)	0.03
All of the above factors	0.67	(0.43, 1.04)	0.08

‡Modeling was done using conditional logistic, however all models were adjusted for age at event or index since the matching was within ± 1 year; there were no missing values.

†In hospital or within 92 days of previous hospitalization compared to no hospitalization in the past 92 days. Within the 3 months prior, the hospitalization occurred in the contest of a surgery or an acute medical illness (2 level variable).

*All nursing home patients including those in hospital or in hospital in the previous 92 days.

§Two cases are missing nursing home confinement data

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Table 3

Risk of Venous Thromboembolism with Statin and Non-Statin Lipid Lowering Therapy Compared Individually to No Lipid Lowering Therapy

Model	Statin Lipid Lowering Therapy			Non-Statin Lipid Lowering Therapy		
	Odds Ratio	95% Confidence Interval	P-value	Odds Ratio	95% Confidence Interval	P-value
Unadjusted	0.78	(0.57, 1.07)	0.12	0.72	(0.45, 1.14)	0.16
Adjusted for[‡]: BMI	0.76	(0.55, 1.04)	0.09	0.71	(0.44, 1.13)	0.15
Trauma / fracture	0.78	(0.57, 1.08)	0.14	0.75	(0.47, 1.21)	0.24
Hospitalized+/− surgery[†]	0.60	(0.41, 0.89)	0.01	0.65	(0.37, 1.13)	0.13
Active cancer	0.86	(0.61, 1.20)	0.36	0.71	(0.43, 1.18)	0.19
Neurological disease, with Leg paresis	0.80	(0.58, 1.10)	0.17	0.68	(0.42, 1.10)	0.12
Pacemaker/ catheter	0.65	(0.46, 0.92)	0.01	0.71	(0.43, 1.17)	0.18
Varicose veins	0.80	(0.58, 1.10)	0.16	0.74	(0.46, 1.17)	0.20
Nursing home[*§]	0.80	(0.59, 1.10)	0.17	0.72	(0.45, 1.15)	0.17
Prior Superficial Thrombosis	0.80	(0.58, 1.11)	0.18	0.72	(0.45, 1.16)	0.18
Oral Contraceptives	0.78	(0.57, 1.07)	0.12	0.72	(0.45, 1.14)	0.16
Pregnancy/Postpartum	0.78	(0.57, 1.07)	0.12	0.72	(0.45, 1.14)	0.16
Estrogen/Progesterone/Oral Contraceptives	0.79	(0.58, 1.09)	0.15	0.71	(0.45, 1.14)	0.16
Diabetes	0.75	(0.54, 1.02)	0.07	0.72	(0.45, 1.15)	0.17
CHF	0.74	(0.54, 1.03)	0.07	0.75	(0.47, 1.21)	0.24
Angina/MI	0.63	(0.45, 0.87)	0.005	0.61	(0.38, 0.99)	0.04
Stroke	0.73	(0.53, 1.00)	0.05	0.69	(0.43, 1.10)	0.11
Peripheral Vascular Disease	0.75	(0.55, 1.03)	0.08	0.69	(0.43, 1.10)	0.12
Ever Smoker	0.78	(0.57, 1.07)	0.13	0.72	(0.45, 1.14)	0.16
Warfarin	0.77	(0.57, 1.06)	0.11	0.72	(0.45, 1.14)	0.16
Heparin	0.79	(0.57, 1.09)	0.15	0.73	(0.46, 1.18)	0.20

Model	Statin Lipid Lowering Therapy			Non-Statin Lipid Lowering Therapy		
	Odds Ratio	95% Confidence Interval	P-value	Odds Ratio	95% Confidence Interval	P-value
All of the above factors	0.66	(0.41, 1.08)	0.10	0.71	(0.34, 1.47)	0.36

‡Modeling was done using conditional logistic, however all models were adjusted for age at event or index since the matching was within ± 1 year; there were no missing values.

†In hospital or within 92 days of previous hospitalization compared to no hospitalization in the past 92 days. Within the 3 months prior, the hospitalization occurred in the contest of a surgery or an acute medical illness (2 level variable).

*All nursing home patients including those in hospital or in hospital in the previous 92 days.

§Two cases are missing nursing home confinement data.