Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Risk of Venous Thromboembolism in Statin Users Compared to Fibrate Users in the United Kingdom Clinical Practice Research Datalink (UK CPRD) GOLD

Olulade Ayodele[1], Howard J Cabral[2,3], David D McManus[4], Susan S Jick[1,5]

[1]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA; [2]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA; [3]Biostatistics and Research Design Program, Boston University Clinical and Translational Science Institute, Boston, MA, USA; [4]Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA; [5]Boston Collaborative Drug Surveillance Program, Lexington, MA, USA

Correspondence: Susan S Jick, Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA, Tel +1 (781) 862-6660, Email sjick@bu.edu

Background: A substantial proportion of adults receive statins for treatment of hypercholesterolemia and cardiovascular risk, and statins have been found to improve outcomes in this patient population. However, studies have not consistently demonstrated the potential benefits of statins in preventing venous thromboembolism (VTE). Therefore, we conducted this study to investigate this association.

Methods: We conducted a cohort analysis in a study sample comprised of 40–79-year-old patients with hyperlipidemia who received at least one fibrate or statin prescription between January 1995 and December 2018 in the United Kingdom Clinical Practice Research Datalink (CPRD) GOLD. We evaluated the association between statin use and incident unprovoked VTE, compared to fibrate use, an active comparator, using Kaplan–Meier (KM) analysis, Poisson regression (with and without propensity score matching), and inverse probability of treatment weights (IPTW) marginal structural models (MSM).

Results: In this cohort of 166,292 patients with hyperlipidemia, 0.81% (N=1,353) developed incident unprovoked VTE. In analyses using the KM method, patients who received statins had a slightly lower risk of VTE compared to those who received fibrates (Log rank test: p=0.0524). The adjusted incident rate ratio (95% CI) for VTE, calculated using Poisson regression, controlling for serum cholesterol and other baseline covariates, in patients prescribed statins compared to fibrates was 0.77 (0.45–1.33) in the full cohort, 0.74 (0.38–1.45) in the propensity score matched analysis, and 0.51 (95% conservative CI: 0.34–0.76) in the IPTW MSM analysis.

Conclusion: While the magnitude of effect varied across the different analytic methods, there is consistent evidence for a protective effect of statin use on the occurrence of unprovoked VTE.

Keywords: hyperlipidemia, statin, fibrate, VTE

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common condition that continues to be an important cause of morbidity and mortality.[1] In the United States, over half a million VTE events are treated yearly, with mortality rates as high as 1–6% for DVT and 12–23% for PE.[1–4] Risk factors and proximate causes of VTE are well documented in the literature, including: estrogen use, obesity, chronic kidney disease, autoimmune disorders, cancer, recent surgery, fractures, immobilization and recent pregnancy.[4–8] Since many patients who develop VTE have one or more VTE risk factors or other causes, the challenge in researching drug-induced VTE is thus to determine whether a VTE is due to the pharmacologic agent or to pre-existing comorbid conditions.

Received: 2 August 2024
Accepted: 24 September 2024
Published: 5 October 2024

Over 25% of Americans 40 years and older take HMG COA reductase inhibitors, also known as statins, to treat hypercholesterolemia due to the favorable effects of statins on rates of vascular events, myocardial infarction, stroke, and death, particularly among patients with other cardiovascular risk factors.[9] The lipid-lowering effect of statins have been shown to significantly reduce the risk of arterial embolic events.[10,11] In contrast, to date, randomized and non-randomized studies evaluating the relationship between statin therapy and venous thromboembolic events have found conflicting results.[12–34] Thus, additional studies are needed to further investigate this potential association.

The anti-inflammatory and antioxidant effects of statins are well documented.[34–36] Since the mechanisms of arterial and venous thromboembolism are somewhat related, and statins could potentially have an impact on the coagulation pathway,[33,34] it is conceivable that statin use lowers the risk of VTE. This association was explored over 15 years ago using the General Practice Research Database (GPRD)[5,37] and The Health Improvement Network (THIN)[38] data with inconclusive results. In the earlier versions of the Clinical Practice Research Datalink (CPRD), the GPRD, had limited information on lifestyle factors and covariates to control confounding. Thus, residual confounding could have explained the results of the earlier study. Further, statins were novel during the study period (1991–2000) and not yet widely prescribed, thus there were few exposed cases and overall case counts were low. The THIN study[38] evaluated all VTE and was not restricted to unprovoked VTE which may explain the null findings observed.

A major concern with studying the effect of statin use on the risk of VTE is the presence of confounding, thus we employed propensity score matching which has the advantage of balancing the distribution of measured potential confounders in the exposed and unexposed groups at baseline. We also used marginal structural models (MSMs) to control for time-varying confounding[39–43] by using inverse probability of treatment weights (IPTW) to create a pseudo-population in which exposure is not confounded.

Methods

This retrospective cohort study was conducted using the United Kingdom (UK) CPRD GOLD, a primary care database, established in 1987, of over 725 general practices in the UK.[44] It contains data on a representative sample of more than 11 million UK patients recorded by general practitioners (GPs) using standard software and coding systems. General practitioners are actively involved in health care coordination, serving as gatekeepers of primary care, and directing specialist referrals. Thus, CPRD GOLD data is a rich source of real-world data for health care research. In addition to patient demographic information, CPRD GOLD includes information on patient characteristics like symptoms, body mass index (BMI), laboratory tests, medical diagnoses, treatments (such as prescriptions issued in primary care, including dosage and quantity), hospitalizations, referrals, deaths, and health-related behaviors such as smoking and alcohol use. Large validation studies have demonstrated the accuracy and completeness of data captured in CPRD GOLD for use in pharmacoepidemiologic research.[45,46]

The study sample comprised 641,837 patients aged 40–79 years, who were diagnosed with hyperlipidemia and received at least one fibrate or statin prescription between January 1, 1995, and December 31, 2018, in CPRD GOLD. We restricted this study to patients aged 40–79 years to limit the heterogeneity of the study population. First, hyperlipidemia and treatment for hyperlipidemia is less common in patients younger than 40, and age is associated with both VTE and hyperlipidemia treatment. Restriction also excluded the most complicated population, patients aged 80 and older, who are more likely to have many comorbidities that could confound the Statin-VTE relationship.

We required all patients to have 1 or more years of information in CPRD GOLD before the cohort entry date and at least three lipid profile laboratory tests—the first one within one year before the cohort entry date, the second one within 6 months after the cohort entry date, and the third between 6 and 18 months after the cohort entry date. The cohort entry date was defined as the first date that a statin or fibrate was prescribed with evidence of a diagnosis of hyperlipidemia either before or on the cohort entry date.

We excluded all patients with a diagnosis of cancer (except non-melanoma skin cancer), AIDS, severe liver disease, history of VTE, coagulopathies, vasculitis, or chronic kidney disease recorded prior to the cohort entry date from the study sample.

Exposure Statin Use

The primary exposure was the use of statins, defined as receipt of at least one statin prescription identified from medication codes, available in CPRD GOLD. The comparator exposure was the use of a fibrate in the study population, defined as receipt of at least one fibrate prescription. Patients who switched between drugs were followed from cohort entry up to switch date; however, we excluded patients who were taking both drugs concomitantly.

Outcome Incident Idiopathic Venous Thromboembolism (VTE)

The study outcome was incident unprovoked VTE (DVT and PE) determined based on Read codes, defined as the first ever code of VTE in the patient's medical record that occurred after the cohort entry date. Only unprovoked VTE cases were included. These were defined as VTE events that were not triggered by another proximate cause (including codes for pregnancy, immobility, prolonged hospitalization, fractures, multiple traumas, orthopedic surgery involving long bones or pelvis, or other major surgery) in their record in the 90 days prior to their first VTE diagnosis date. Further, we required VTE cases to have 1 or more prescription codes for anticoagulants (including unfractionated heparin, low-molecular-weight heparins [LMWH] and fondaparinux) present after the VTE diagnosis. This requirement was implemented to increase the specificity of our case definition since anticoagulation is a necessary treatment for thromboembolism. The index date was defined as the date of the incident (first ever) VTE diagnosis. Since death is a competing risk for VTE, we also evaluated models for a composite endpoint that comprised an incident unprovoked VTE event or death, separately.

Person-Time Accrual

Patients accrued exposed (statin use) or unexposed (fibrate use) person-time from cohort entry until censoring occurred due to a VTE diagnosis, switching between study drugs, development of an exclusion criteria, patient turned 80 years old, end of CPRD record, December 31, 2018, or death, whichever came first.

Covariates

Information on covariates of interest in this study were derived from the patient records and included known or suspected risk factors for VTE[6,7] present before or at cohort entry: age, smoking status (never, past, current and unknown), BMI (<25, 25–<30, ≥30 kg m^2, unknown), calendar time (to capture secular trends in VTE risk and Statin or Fibrate use), and comorbidities (including diabetes [with/without end-organ damage], cardiovascular disease [myocardial infarction, peripheral vascular disease, Ischemic heart disease, pericardial disease, pulmonary hypertension, coronary heart disease], chronic obstructive pulmonary disease, dementia, peptic ulcer disease, liver disease, connective tissue disease, alcohol abuse disorders, hypertension, and phlebitis). We defined each comorbidity based on the presence of at least one Read code prior to the cohort entry date. We then calculated a Charlson Comorbidity Index (CCI) score, a weighted index, summarizing both the number and to some extent, the severity of 19 chronic conditions[47–49] for each patient in the study. We excluded solid tumor, leukemia and lymphoma, AIDS, chronic kidney disease, and severe liver disease categories when computing the CCI scores because patients with these conditions were already excluded from the study. We categorized the CCI scores into three groups: 1–3, 4, and 5+. Finally, we classified each patient by hyperlipidemia duration calculated as time from the first documented hyperlipidemia diagnosis in each patient's record to cohort entry date (<1 year or 1+ years).

Data Analysis

We generated descriptive statistics for the study sample to examine the distribution and frequencies of patient characteristics, VTE risk factors, and covariates by exposure status. We evaluated covariates that were structurally deemed to be potential confounders of the Statin-VTE association. A covariate was included in the multivariable model if it changed the main effect measure by at least 10%.

We first compared the risk of VTE in statin users compared to fibrate users using Kaplan–Meier analysis with the Log rank test to evaluate time to VTE event. We also calculated VTE incidence rates (IR) based on cumulative follow-up per 1000 person-years (PY) using Poisson regression models and calculated crude and adjusted incidence rate ratios (aIRRs) and 95% confidence intervals (CI), comparing statin use with fibrate use in models, with and without propensity score

matching. Matched statin users and fibrate users were required to have a propensity score within 20% of the standard deviation of the cohort's mean propensity score.

We conducted additional analyses to account for potential time-dependent confounding due to changes in total serum cholesterol level and censoring over time using an IPTW MSM for repeated measures. Using the weighted sample, we then fit a Poisson regression model to estimate adjusted rate ratios (aRRs) and 95% conservative CI comparing statin use with fibrate use. We used robust variance estimators (generalized estimating equation [GEE] in PROC GENMOD) to account for the within-subject correlation.

Separate analyses were also conducted to examine the independent association of duration of statin use (by the number of statin prescriptions) with VTE, using the fibrate use group as the reference category. Finally, we conducted stratified analyses by sex and age group to assess effect measure modification (EMM).

All analyses were conducted using SAS statistical software (version 9.4, Cary, NC: SAS Institute. Inc).

Data Use and Ethical Approval

This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. This study was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency database research (protocol no: 19_161), and the protocol was made available to the journal reviewers upon request. All data accessed complied with relevant data protection and privacy regulations.

This research is exempt from further review and approval under HHS CFR 46.104.

Results

After all exclusions were applied, there were 166,292 patients ages 40–79 years with hyperlipidemia eligible for inclusion in the CPRD GOLD in 1995–2018, of which 164,595 received a statin prescription and 1697 received a fibrate prescription at cohort entry. The distribution of potential VTE risk factors and patient characteristics among statin and fibrate users as well as risk estimates and associated 95% CI for each risk factor are presented in Table 1. At cohort entry, statin users were older than fibrate users; more likely to be female; had more comorbidities including hypertension, COPD, and autoimmune diseases; were more likely to have a history of phlebitis and higher total serum

Table 1 Distribution of Covariates and Univariable Odds Ratios for Statin Users versus Fibrate Users at Cohort Entry Date for Patients with Hyperlipidemia Aged 40–79 Years in CPRD 1995–2018

Characteristics at cohort entry date	Statin Users (N=164,595)	Fibrate Users (N=1,697)	OR (95% CI)
Age (years)			
<50	21,680 (13.1)	376 (22.2)	1.0 (reference)
50–59	50,628 (30.8)	566 (33.4)	1.55 (1.36–1.77)
60–69	60,899 (37.0)	600 (35.4)	1.76 (1.55–2.00)
70+	31,388 (19.1)	155 (9.1)	3.51 (2.91–4.24)
Mean± Std. Dev	61.20 ±9.18	58.19±9.03	1.04 (1.03–1.04)
Sex			
Male	83,199 (50.6)	909 (53.6)	1.0 (reference)
Female	81,396 (49.5)	788 (46.4)	1.13 (1.03–1.24)

(*Continued*)

Table 1 (Continued).

Characteristics at cohort entry date	Statin Users (N=164,595)	Fibrate Users (N=1,697)	OR (95% CI)
Cohort entry Year			
1995–1999	10,053 (6.1)	959 (56.5)	1.0 (reference)
2000–2004	53,645 (32.6)	408 (24.0)	12.54 (11.15–14.11)
2005–2009	65,563 (39.8)	205 (12.1)	30.50 (26.19–35.52)
2010–2018	35,334 (21.5)	125 (7.4)	26.97 (22.35–32.53)
Record Length (Years)			
Mean±Std. Dev	15.39 ±5.00	9.69±5.28	1.26 (1.25–1.27)
BMI			
<25 kg/m^2	28,554 (18.6)	289 (17.0)	1.0 (reference)
25–<30 kg/m^2	53,863 (35.0)	628 (37.0)	0.85 (0.74–0.98)
≥30 kg/m^2	46,283 (30.1)	504 (29.7)	0.91 (0.78–1.05)
Unknown	25,115 (16.3)	276 (16.3)	0.91 (0.77–1.08)
Mean±Std. Dev	28.82 ±5.31	28.84 ±5.02	1.00 (1.00–1.00)
Smoking Status			
Non-Smoker	64,271 (39.1)	606 (35.7)	1.0 (reference)
Current smoker	22,226 (13.5)	232 (13.7)	0.90 (0.78–1.05)
Past-Smoker	77,872 (47.3)	856 (50.4)	0.86 (0.77–0.95)
Unknown	226 (0.1)	3 (0.2)	0.71 (0.23–2.22)
Comorbidities			
Hypertension	78,126 (47.5)	747 (44)	1.15 (1.04–1.27)
Diabetes	30,856 (18.7)	431 (25.4)	0.68 (0.61–0.76)
Uncomplicated	557 (0.3)	12 (0.7)	0.48 (0.27–0.85)
End-organ damage	3,491 (2.1)	45 (2.7)	0.80 (0.59–1.07)
Cardiovascular	29,428 (17.9)	423 (24.9)	0.66 (0.59–0.73)
Myocardial infarction	8,048 (4.9)	165 (9.7)	0.48 (0.40–0.56)
Peripheral Vascular Disease	4,350 (2.6)	65 (3.8)	0.68 (0.53–0.88)
Chronic Heart Failure	2,310 (1.4)	49 (2.9)	0.48 (0.36–0.64)
Stroke or TIA	8,764 (5.3)	74 (4.4)	1.23 (0.98–1.56)
Phlebitis	4,377 (2.7)	24 (1.4)	1.90 (1.27–2.85)
Alcohol	6,833 (4.2)	78 (4.6)	0.90 (0.72–1.13)
Drug use	433 (0.3)	5 (0.3)	0.89 (0.37–2.16)
COPD	5,588 (3.4)	39 (2.3)	1.49 (1.09–2.06)

(*Continued*)

Table 1 (Continued).

Characteristics at cohort entry date	Statin Users (N=164,595)	Fibrate Users (N=1,697)	OR (95% CI)
Epilepsy	2,714 (1.6)	23 (1.4)	1.22 (0.81–1.84)
Autoimmune	17,830 (10.8)	137 (8.1)	1.38 (1.16–1.65)
Mild liver disease	403 (0.2)	10 (0.6)	0.41 (0.22–0.78)
Non-melanoma skin cancer	3,845 (2.3)	26 (1.5)	1.54 (1.04–2.27)
Ulcer	6,413 (3.9)	73 (4.3)	0.90 (0.71–1.14)
Charlson comorbidity index score			
CCI: 1–3	142,356 (86.5)	1,493 (88.0)	1.0 (reference)
CCI: 4	15,972 (9.7)	133 (7.8)	1.26 (1.05–1.51)
CCI: 5+	6,267 (3.8)	71 (4.2)	0.93 (0.73–1.18)
CCI score: Mean±SD	2.29±1.12	2.18±1.15	1.10 (1.05–1.15)
Medications			
Antidiabetic	20,202 (12.3)	334 (19.7)	0.57 (0.51–0.64)
Antihypertensive	75,725 (46.0)	696 (41.0)	1.23 (1.11–1.35)
Antipsychotic	36,993 (22.5)	296 (17.4)	1.37 (1.21–1.56)
HRT or OCP	446 (0.3) (0.55)[a]	11 (0.6) (1.40)[a]	0.42 (0.23–0.76) 0.39 (0.21–0.71)[a]
Total serum cholesterol (mmol/L)			
Optimal <5.2	13,069 (7.9)	213 (12.6)	1.0 (reference)
Intermediate 5.2–6.2	46,998 (28.6)	323 (19.0)	2.37 (1.99–2.82)
High >6.2	104,528 (63.5)	1161 (68.4)	1.47 (1.27–1.70)
HPL duration (years)			
<1	130,857 (79.5)	1,467 (86.5)	1.0 (reference)
1+	33,738 (20.5)	230 (13.6)	1.64 (1.43–1.89)
Follow-up duration (years)	7.26±4.13	5.28±3.87	1.15 (1.13–1.16)

Notes: [a]Among females only. Categorical variables are presented as N (%), continuous variables are presented as mean ±SD; Cardiovascular disease includes Ischemic heart disease, Acute coronary syndrome, pericardial disease, pulmonary hypertension, peripheral vascular disease, coronary heart disease; HPL hyperlipidemia.

Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence Interval; CCI, Charlson comorbidity index; COPD, Chronic Obstructive Pulmonary Disease; HRT, Hormone replacement therapy; OCP, oral contraceptive pill; SD, Standard Deviation; TIA, Transient Ischemic Attack.

cholesterol; but were less likely to be diabetic. Fibrate users had more cardiovascular comorbidities and were more likely to smoke than statin users. 0.8% (N=1353) of the overall cohort developed incident unprovoked VTE.

The Kaplan-Meier analysis conducted in the full cohort showed that patients who received statins had a slightly lower risk of VTE compared to those who received fibrates. (Log rank test: p=0.0524) (Figure 1). The results of the Kaplan–Meier analysis in the propensity score matched cohort did not differ materially from the full cohort analysis (Figure 2).

The crude IR of VTE calculated using Poisson regression was lower in statin users compared to fibrate users. The IRs were 1.12 per 1000 PY and 1.68 per 1000 PY for statin and fibrate users respectively. The crude IRR for statin use

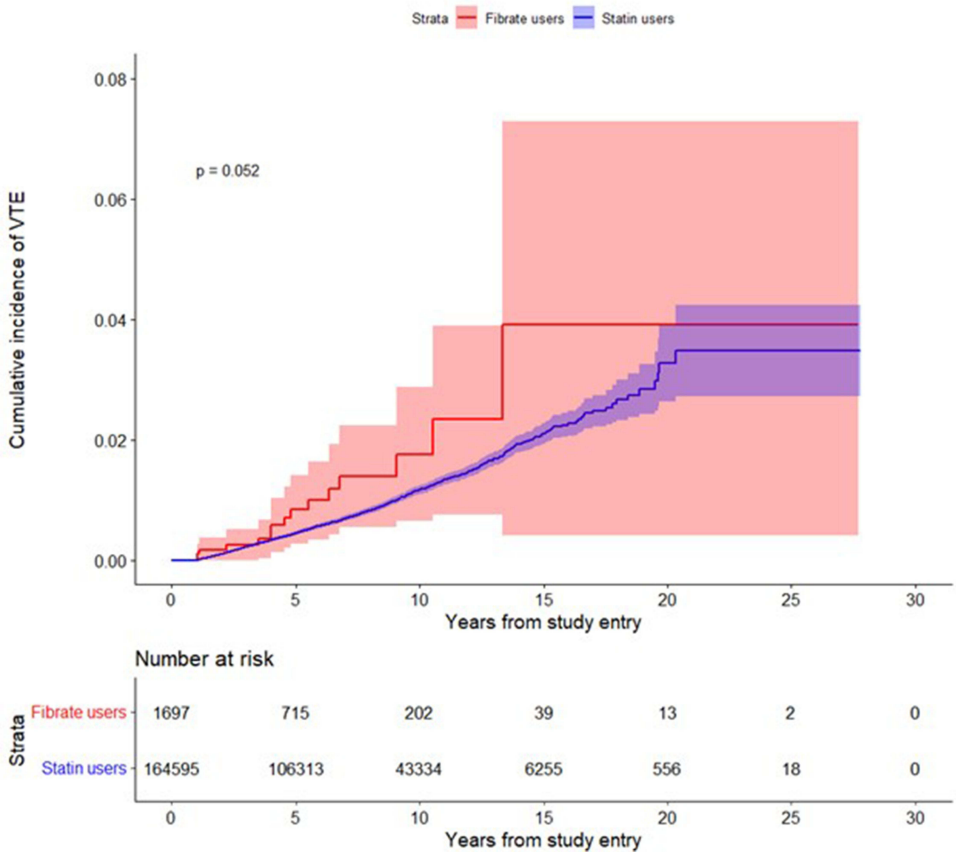

Figure 1 Kaplan-Meier plots for the full study cohort: Association of statins compared to fibrates and incident unprovoked VTE.

compared to fibrate use was 0.67, 95% CI (0.40–1.11). After adjusting for relevant covariates in the multivariable model, the association was slightly less protective: (aIRR=0.77 95% CI (0.45–1.33)). There was a protective effect in males (aIRR=0.61 95% CI (0.30–1.26)) but there was no effect in female statin users (aIRR=0.98 95% CI (0.44–-2.20)), though numbers were small and confidence intervals were wide (Table 2). The protective effect was consistent and observed across all subgroups evaluated in supplemental analyses of duration of statin use by number of prescriptions [data not shown].

Table 3 shows the distribution of baseline characteristics in 1,697 statin users matched 1:1 with fibrate users on propensity score. Characteristics of statin and fibrate users were successfully balanced for most covariates though there remained some imbalance following matching that did not improve on trimming. The results provided, therefore, reflect the untrimmed analyses. The primary difference between the 2 cohorts was that statin users in the matched cohort were more likely to have elevated total serum cholesterol than fibrate users. The risk of VTE was again lower among statin users compared to fibrate users; aIRR=0.74, 95% CI (0.34–1.45) in the multivariable regression models for the propensity score matched analyses but the confidence intervals crossed 1 (Table 4).

The aRR was 0.51 (95% conservative CI: 0.34–0.76) estimated from the IPTW MSM analyses yielded a protective effect and was consistent with the conclusion that statin use decreases the risk of VTE [Supplement 1].

Discussion

We used multiple analytic techniques including Kaplan-Meier and Poisson regression analyses, with and without propensity score matching, and MSM to evaluate the association between statins and risk of VTE using fibrate users as the comparison. Overall, the findings from this study, regardless of methodology or duration of use, suggest that there

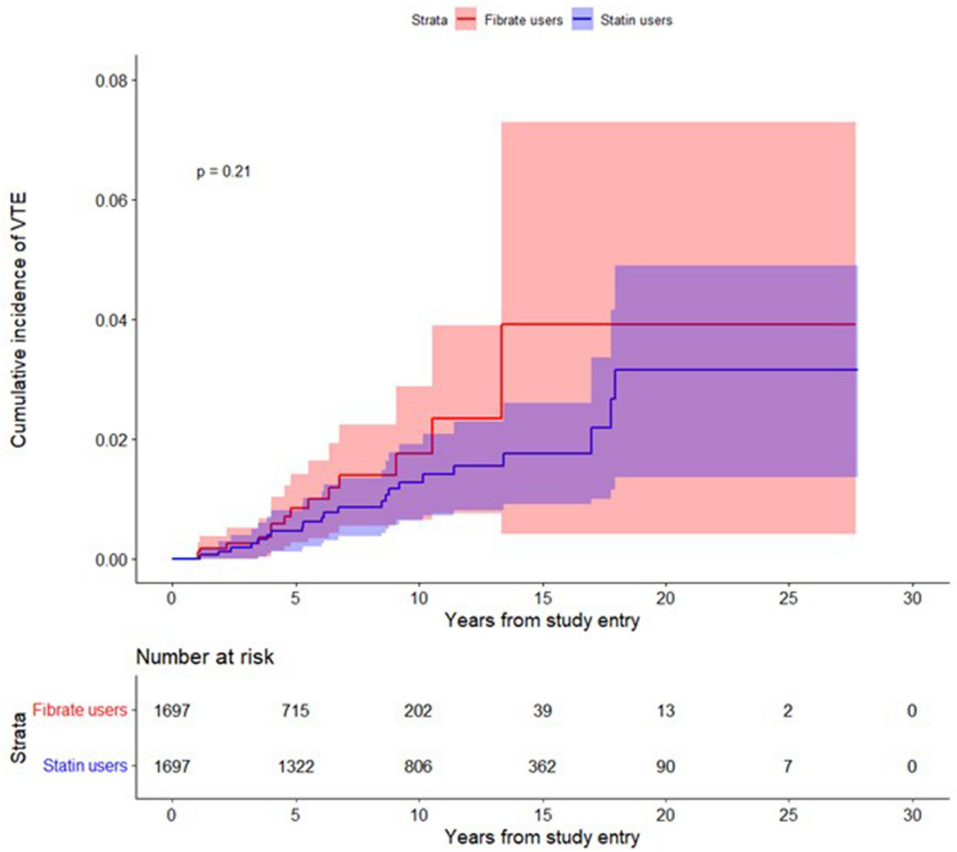

Figure 2 Kaplan Meier plots for the propensity score matched dataset: Association of statins compared to fibrates and incident unprovoked VTE.

is a protective effect of statin use ranging from 20% to 50% reduction in risk of VTE. However, the magnitude of the effect is difficult to establish due to the relatively small size of the non-exposed fibrate group in these data.

The crude effects (crude IRR (95% CI)) of statins on the risk of VTE compared to fibrates were 0.67 (0.40–1.11) in the standard regression model and 0.76 (0.39–1.47) in the propensity score matched analyses. After controlling for serum cholesterol and other baseline covariates, the aIRR in the Poisson regression analysis was still protective in the full cohort

Table 2 Incidence Rates and Incidence Rate Ratios for Statin Use Compared to Fibrate Use and Risk of Incident Unprovoked VTE Stratified by Age and Sex in Patients with Hyperlipidemia Age 40–79 Years in CPRD 1995–2018

Exposure at cohort entry date	Cases N=1,353	Person-Years N=1,203,770.28	IR per 1,000 PY (95% CI)	Crude IRR (95% CI)	Adjusted IRR (95% CI)
All Patients					
Fibrates	15	8,957.07	1.68 (1.08–2.97)	1.0 (reference)	1.0 (reference)
Statins	1,338	1,194,813.22	1.12 (1.06–1.18)	0.67 (0.40–1.11)	0.77 (0.45–1.33)
Males					
Fibrates	8	4,549.03	1.76 (0.88–3.52)	1.0 (reference)	1.0 (reference)
Statins	653	608,909.80	1.07 (0.99–1.16)	0.61 (0.30–1.22)	0.61 (0.30–1.26)

(*Continued*)

Table 2 (Continued).

Exposure at cohort entry date	Cases N=1,353	Person-Years N=1,203,770.28	IR per 1,000 PY (95% CI)	Crude IRR (95% CI)	Adjusted IRR (95% CI)
Females					
Fibrates	7	4,408.04	1.59 (0.76–3.33)	1.0 (reference)	1.0 (reference)
Statins	685	5,85,903.41	1.17 (1.09–1.26)	0.74 (0.35–1.55)	0.98 (0.44–2.20)
Age <60 years					
Fibrates	6	5,182.41	1.16 (0.52–2.58)	1.0 (reference)	1.0 (reference)
Statins	415	557,765.72	0.74 (0.68–0.82)	0.64 (0.29–1.44)	0.85 (0.36–1.98)
Age ≥60 years					
Fibrates	9	3,774.65	2.38 (1.24–4.58)	1.0 (reference)	1.0 (reference)
Statins	923	637,047.49	1.45 (1.36–1.55)	0.61 (0.32–1.17)	0.63 (0.31–1.26)

Notes: *Adjusted for age, sex, Charlson comorbidity index, propensity score, cohort entry year, BMI, cardiovascular disease, hypertension, diabetes, myocardial infarction, chronic heart failure, COPD, autoimmune disease, liver disease, phlebitis, duration of Hyperlipidemia and total cholesterol.
Abbreviations: CI, Confidence Interval; IR, Incidence rate; IRR, Incidence Rate Ratio; PY, Person-Years.

Table 3 Distribution of Covariates at Cohort Entry Date and Univariable Odds Ratios for Incident Unprovoked VTE in Statin Users Compared to Fibrate Users Matched on Propensity Score, in Patients with Hyperlipidemia Age 40–79 Years in CPRD 1995–2018

Characteristics at Cohort Entry Date	Statin Users (N=1,697)	Fibrate Users (N=1,697)	OR (95% CI)
Age (years)			
<50	399 (23.5)	376 (22.2)	1.0 (reference)
50–59	631 (37.2)	566 (33.4)	1.03 (0.86–1.24)
60–69	495 (29.2)	600 (35.4)	0.74 (0.60–0.90)
70+	172 (10.1)	155 (9.1)	0.99 (0.75–1.30)
Mean±Std. Dev	57.41±9.20	58.19±9.03	0.99 (0.88–1.63)
Sex			
Male	909 (53.6)	909 (53.6)	1.0 (reference)
Female	788 (46.4)	788 (46.4)	NA
Cohort Entry Year			
1995–1999	903 (53.2)	959 (56.5)	1.0 (reference)
2000–2004	473 (27.9)	408 (24.0)	2.37 (1.64–3.41)
2005–2009	217 (12.8)	205 (12.1)	2.10 (1.24–3.55)
2010–2018	104 (6.1)	125 (7.4)	0.73 (0.32–1.70)
Length of Record (years)			
Mean±Std. Dev	9.85±5.06	9.69±5.28	1.03 (0.99–1.05)

(*Continued*)

Table 3 (Continued).

Characteristics at Cohort Entry Date	Statin Users (N=1,697)	Fibrate Users (N=1,697)	OR (95% CI)
BMI			
<25 kg/m^2	326 (19.2)	289 (17.0)	1.0 (reference)
25–<30 kg/m^2	608 (35.8)	628 (37.0)	0.86 (0.71–1.05)
≥30 kg/m^2	500 (29.5)	504 (29.7)	0.89 (0.73–1.08)
Unknown	263 (15.5)	276 (16.3)	0.85 (0.68–1.07)
Mean±Std. Dev	28.73±5.03	28.84±5.02	1.00 (1.00–1.00)
Smoking Status			
Non-Smoker	598 (35.2)	606 (35.7)	1.0 (reference)
Current smoker	217 (12.8)	232 (13.7)	0.95 (0.76–1.18)
Past-Smoker	878 (51.7)	856 (50.4)	1.04 (0.90–1.21)
Unknown	4 (0.2)	3 (0.2)	1.33 (0.30–5.99)
Comorbidities			
Hypertension	690 (40.7)	747 (44)	0.87 (0.76–1.00)
Diabetes	402 (23.7)	431 (25.4)	0.91 (0.78–1.07)
Diabetes-uncomplicated	11 (0.6)	12 (0.7)	0.92 (0.40–2.08)
Diabetes end-organ damage	38 (2.2)	45 (2.7)	0.83 (0.53–1.31)
Cardiovascular disease	416 (24.5)	423 (24.9)	0.98 (0.83–1.15)
Myocardial infarction	177 (10.4)	165 (9.7)	1.09 (0.86–1.37)
Peripheral Vascular Disease	55 (3.2)	65 (3.8)	0.83 (0.57–1.21)
Chronic Heart Failure	59 (3.5)	49 (2.9)	1.22 (0.82–1.81)
Stroke or TIA	55 (3.2)	74 (4.4)	0.73 (0.51–1.05)
Phlebitis	20 (1.2)	24 (1.4)	0.83 (0.45–1.52)
Alcohol	94 (5.5)	78 (4.6)	1.21 (0.89–1.64)
Drug use	6 (0.4)	5 (0.3)	1.20 (0.37–3.93)
COPD	40 (2.4)	39 (2.3)	1.03 (0.66–1.59)
Epilepsy	21 (1.2)	23 (1.4)	0.91 (0.50–1.67)
Autoimmune	130 (7.7)	137 (8.1)	0.94 (0.73–1.21)
Mild liver disease	11 (0.6)	10 (0.6)	1.10 (0.47–2.59)
Non-melanoma skin cancer	28 (1.6)	26 (1.5)	1.08 (0.63–1.84)
Ulcer	69 (4.1)	73 (4.3)	0.94 (0.67–1.33)

(*Continued*)

Table 3 (Continued).

Characteristics at Cohort Entry Date	Statin Users (N=1,697)	Fibrate Users (N=1,697)	OR (95% CI)
Charlson comorbidity index score			
CCI: 1–3	1,454 (92.3)	1,493 (88.0)	1.0 (reference)
CCI: 4	94 (6.0)	133 (7.8)	0.94 (0.70–1.25)
CCI: 5+	28 (1.8)	71 (4.2)	0.93 (0.55–1.56)
CCI score: Mean±Std. Dev	2.10±1.12	2.18 (1.15)	0.94 (0.88–1.00)
Medications			
Antidiabetic	307 (18.1)	334 (19.7)	0.90 (0.75–1.07)
Antihypertensive	633 (37.3)	696 (41.0)	0.85 (0.74–0.98)
Antipsychotic	296 (17.4)	296 (17.4)	1.00 (0.84–1.20)
HRT or OCP	18 (1.1) (2.3)[a]	11 (0.6) (1.40)[a]	1.70 (0.78–3.71) 1.70 (0.78–3.71)[a]
Total cholesterol (mmol/L)			
Optimal <5.2 mmol/L	83 (4.9)	213 (12.6)	1.0 (reference)
Intermediate 5.2–6.2 mmol/L	333 (19.6)	323 (19.0)	2.79 (2.05–3.79)
High >6.2 mmol/L	1,281 (75.5)	1,161 (68.4)	3.22 (2.40–4.30)
Mean±Std. Dev	7.13±4.49	7.00±1.85	1.02 (0.98–1.05)
HPL duration (years)			
<1	1,460 (86.0)	1,467 (86.5)	1.0 (reference)
1+	237 (14.0)	230 (13.6)	0.96 (0.79–1.18)
Follow-up duration (years)	10.18±5.68	5.28±3.87	1.26 (1.23–1.28)

Notes: [a]Among females only. Categorical variables are presented as N (%), continuous variables are presented as mean±SD.
Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence Interval; CCI, Charlson comorbidity index; HPL, Hyperlipidemia; TIA, Transient Ischemic Attack; HRT, Hormone replacement therapy; NR, Not Applicable; OCP, oral contraceptive pill; SD, Standard Deviation.

Table 4 Propensity Score-Matched Analyses: Incidence Rate Ratio of Incident Unprovoked VTE in Statin Users Compared to Fibrate Users in Patients with Hyperlipidemia Age 40–79 Years in CPRD 1995–2018

Exposure at cohort entry date	VTE cases N=37	Person-Years N=26,225.66	IR per 1,000 PY (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
Fibrates	15	8,957.07	1.68 (1.08–2.97)	1.0 (reference)	1.0 (reference)
Statins	22	17,268.60	1.27 (0.84–1.94)	0.76 (0.39–1.47)	0.74 (0.38–1.45)

Notes: *Adjusted for Age, Charlson comorbidity index, cohort entry year, cardiovascular disease, BMI and total cholesterol.
Abbreviations: CI, Confidence Interval; IR, Incidence rate; IRR, Incidence Rate Ratio; PY, Person Years.

(0.77 (0.45–1.33)) and remained unchanged in the propensity score matched analysis (0.74 (0.38–1.45)). In the MSM analysis the aRR was 0.51 (95% conservative CI: 0.34–0.76).

Our findings are consistent with other studies that have shown a protective effect between statin use and VTE.[13,24,50,51] Herrington et al,[51] found a 50% risk reduction in statin users compared to non-users in the Heart and

Estrogen/Progestin Replacement Study (HERS). The JUPITER trial showed that rosuvastatin was associated with a 43% reduction in all VTE and 39% reduction in unprovoked (without a known malignant condition, trauma, hospitalization, or surgery) VTE.[24] After this randomized controlled trial (RCT), multiple subsequent studies also found protective effects though they were not as strong. A meta-analysis conducted by Squizzato et al,[29] which evaluated statins and fibrates (and other lipid-lowering drugs) using data from three RCTs, three cohort studies and eight case-control studies, concluded that statins reduced the risk of VTE (adjusted odds ratio (OR) 0.81, 95% CI 0.66–0.99), while fibrate use was associated with an increase in VTE risk. Rahimi et al[13] conducted a meta-analysis of published and unpublished evidence from 29 RCTs and concluded that statins likely only provide a moderate reduction in the risk of VTE events in contrast with the previous suggestion of a large protective effect (pooled OR 0.89, 95% CI 0.78–1.01; p=0.08). In a systematic review and network meta-analysis covering the period from 1966 to February 2017,[52] the pooled risk ratio for VTE was 0.87 (95% CI 0.77–0.98; p=0.022) when statin use was compared with placebo in 27 RCTs.

Previous studies suggest that most of the protective effect of statins on VTE is not related to cholesterol levels but is possibly associated with their antithrombotic and antiplatelet properties including their effect on blood coagulation parameters, thrombus burden, vein wall scarring, neutrophil migration, and reduced platelet aggregation.[25,53] Further, statins have been associated with reduction in numerous inflammatory biomarkers including CRP, IL-6, IL-8, MCP-1, and PAI-1, suggesting that the effects of statins on VTE are mediated through an anti-inflammatory mechanism.[18,25] Our study adjusted for baseline cholesterol levels and time-varying cholesterol levels; however, future studies should evaluate other time-varying covariates.

Previous observational studies have been criticized for selection bias whereby statin users might be different, for example, more health conscious than non-users, which could result in a spurious protective effect of statin use.[19,38] By comparing statin use to fibrate use in this study, we minimized this bias since both cohorts have the same therapeutic indication (underlying hyperlipidemia diagnosis). There may still be residual confounding by severity between statin and fibrate users, however, one would expect that patients with more severe hyperlipidemia would have received statins, thus underlying disease severity would not explain the results of this study.

Of all patients (N=8213) who had a history of myocardial infarction (MI) at baseline in the full cohort, 8048 (98%) received a statin and 165 (2%) received a fibrate. However, the proportion of patients that had a MI before the cohort entry date was higher among fibrate users than statin users. We could not find a plausible explanation for this. Since statins are prescribed for secondary prevention of MI, we would expect a higher proportion of patients with a history of MI to receive a statin. We explored whether this distribution differed by calendar time or patient age at cohort entry date, but the distributions were similar across both. We evaluated the first documented statin or fibrate exposure at cohort entry; therefore, statin intolerance was not an issue in this study. It is possible that other unmeasured confounders were present, such as patient reluctance and physician preference that influenced their choice to forgo the standard of care (statin prescription) for a patient with a previous MI. This needs to be evaluated further.

Some limitations of this study should be mentioned. We did not evaluate statin dose in this study. In clinical practice, statin dose may be modified over time, but unless there is statin intolerance, patients tend to continue using prescribed statins regardless of cholesterol levels and therefore dose of statin may be a more appropriate time-varying covariable rather than any statin use. We did assess the effect of duration of statin use. The protective effect remained consistent across all durations of continuous use (data not shown).

It is possible that we missed some cases in this study; a cohort study assumes complete follow-up of all exposed and unexposed patients and correct identification of all cases that develop. However, some cases may have been missed if the GP did not receive complete documentation of the event. Further, misclassification of the outcome "unprovoked VTE" may have occurred. Misclassification of PE is unlikely since a documented PE diagnosis is expected to be objective, but outcome misclassification is still a possibility for DVTs. To address this concern, we required receipt of anticoagulation as part of the case definition to validate the diagnosis of VTE.

There are many competing risks for unprovoked VTE, including death, but we expected this to be non-differential with respect to exposure status. We analyzed a composite endpoint of VTE or death (data not shown) which led to grossly similar findings, strengthening our conclusion that statin use prevents these negative outcomes in patients with hyperlipidemia.

We also evaluated time-varying confounding using MSM analyses, however, the results did not change the conclusion of a protective effect of statin use on the occurrence of VTE.

We only included patients who had total cholesterol measures at the three specified time points, therefore selection bias may have occurred if the association differed between all patients and patients who were followed up more consistently, and the results may not be generalizable to all hyperlipidemia patients. Our analysis of patients who did not have regular cholesterol labs yielded similar results (data not shown), thus this bias was not likely to have had a material effect on the results.

Important confounders were identified using the expert input of physicians and documented evidence in the literature and CPRD is a longitudinal primary care database with high accuracy of diagnoses and completeness of drug prescription data. However, the potential for residual covariate misclassification or unmeasured confounding is still present. The relatively smaller size of the non-exposed fibrate population and limited information on unmeasured covariates that may predict statin use were limitations in our study; however, we believe these confounders would not completely explain our results given the consistent finding of a protective effect of statins using different analytic methods and the comparable results in clinical trials as well as other observational studies.

In conclusion, in this study of 40–79-year-old patients with hypercholesterolemia, we found evidence that statin use is associated with lower risk of incident unprovoked VTE, potentially as a result of pleiotropic anti-inflammatory or anticoagulatory effects.

This study contributes to a growing body of evidence supporting the use of statins in primary prevention of VTE. Considering the reasonable safety profile, broad pleiotropic and cardioprotective effects of the drug class, further studies of statin use are warranted to inform every day clinical practice.

Acknowledgments

This study was based on the PhD thesis of Olulade Ayodele, which was published as: The use of pharmacologic agents and venous thromboembolic outcomes, Ayodele, Olulade Adeola (2021), 2021-08-27T18:02:51Z

Dr. Ayodele has approved this publication.

Disclosure

Dr David McManus reports grants/personal fees Bristol Myers Squibb/Pfizer, Heart Rhythm Society, Avania, Boehringer Ingelheim, and Fitbit, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Nicholson M, Chan N, Bhagirath V, Ginsberg J. Prevention of Venous Thromboembolism in 2020 and Beyond. *J Clin Med*. 2020;9(8):2467. doi:10.3390/jcm9082467
2. Fowkes FJ, Price JF, Fowkes FG. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. *Eur J Vasc Endovasc Surg*. 2003;25(1):1–5. doi:10.1053/ejvs.2002.1778
3. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: a review of estimated attributable healthcare costs. *Thrombosis Research*. 2016;137:3–10. doi:10.1016/j.thromres.2015.11.033
4. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23). doi:10.1161/01.CIR.0000078468.11849.66
5. Huerta C, Johansson S, Wallander MA. García Rodríguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. *Arch Intern Med*. 2007;167(9):935. doi:10.1001/archinte.167.9.935
6. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A. The prevalence of risk factors for venous thromboembolism among hospital patients. *Arch Intern Med*. 1992;152(8):1660–1664. doi:10.1001/archinte.1992.00400200092017
7. Goldhaber SZ. Risk factors for venous thromboembolism. *J Am Coll Cardiol*. 2010;56(1):1–7. doi:10.1046/j.0306-5251.2001.01523.x
8. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. *Thromb Res*. 2009;123(Suppl 4):S11–S17. doi:10.1016/S0049-3848(09)70136-7
9. Gu Q, Paulose-Ram R, Burt VL, Kit BK Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012.
10. Baigent C, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670–1681. doi:10.1016/S0140-6736(10)61350-5
11. Sørensen HT, Horvath-Puho E, Søgaard KK, et al. Arterial cardiovascular events, statins, low-dose aspirin and subsequent risk of venous thromboembolism: a population-based case-control study. *J Thromb Haemost*. 2009;7(4):521–528. doi:10.1111/j.1538-7836.2009.03279.x
12. Glynn RJ, Danielson E, Fonseca FAH, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med*. 2009;360(18):1851–1861. doi:10.1056/NEJMoa0900241
13. Rahimi K, Bhala N, Kamphuisen P, et al. Effect of statins on venous thromboembolic events: a meta-analysis of published and unpublished evidence from randomised controlled trials. *PLoS Med*. 2012;9(9):e1001310. doi:10.1371/journal.pmed.1001310

14. Doggen CJ, Lemaitre RN, Smith NL, Heckbert SR, Psaty BM. HMG CoA reductase inhibitors and the risk of venous thrombosis among postmenopausal women. *J Thromb Haemost*. 2004;2(5):700–701. doi:10.1111/j.1538-7836.2004.00696.x
15. Wells PS, Gebel M, Prins MH, Davidson BL, Lensing AW. Influence of statin use on the incidence of recurrent venous thromboembolism and major bleeding in patients receiving rivaroxaban or standard anticoagulant therapy. *Thromb J*. 2014;12(1):26. doi:10.1186/1477-9560-12-26
16. Kunutsor SK, Seidu S, Khunti K. Statins and primary prevention of venous thromboembolism: a systematic review and meta-analysis. *Lancet Haematol*. 2017;4(2):e83–e93. doi:10.1016/S2352-3026(16)30184-3
17. Gaertner S, Cordeanu E-M, Nouri S, Mirea C, Stephan D. Statins and prevention of venous thromboembolism: myth or reality? *Arch Cardiovasc Dis*. 2016;109(3):216–222. doi:10.1016/j.acvd.2015.11.007
18. Li L, Sun T, Zhang P, Tian J, Yang K. Statins for primary prevention of venous thromboembolism (Review). *Cochrane Database Syst Rev*. 2011. doi:10.1002/14651858.CD008203.pub2
19. El-Refai SM, Black EP, Adams VR, Talbert JC, Brown JD. Statin use and venous thromboembolism in cancer: a large, active comparator, propensity score matched cohort study. *Thromb Res*. 2017;158:49–58. doi:10.1016/j.thromres.2017.08.001
20. Khemasuwan D, Chae YK, Gupta S, et al. Dose-related effect of statins in venous thrombosis risk reduction. *Am J Med*. 2011;124(9):852–859. doi:10.1016/j.amjmed.2011.04.019
21. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet*. 2012;380(9841):9841):565–571. doi:10.1016/S0140-6736(12)61190-8
22. Pai M, Evans NS, Shah SJ, Green D, Cook D, Crowther MA. Statins in the prevention of venous thromboembolism: a meta-analysis of observational studies. *Thromb Res*. 2011;128(5):422–430. doi:10.1016/j.thromres.2011.05.012
23. Ashrani AA, Barsoum MK, Crusan DJ, Petterson TM, Bailey KR, Heit JA. Is lipid lowering therapy an independent risk factor for venous thromboembolism? A population-based case–control study. *Thromb Res*. 2015;135(6):1110–1116. doi:10.1016/j.thromres.2015.04.005
24. Perez A, Bartholomew JR. Interpreting the JUPITER trial: statins can prevent VTE, but more study is needed. *Cleve Clin J Med*. 2010;77(3):191–194. doi:10.3949/ccjm.77a.09077
25. Wallace A, Albadawi H, Hoang P, et al. Statins as a preventative therapy for venous thromboembolism. *Cardiovascular Diagnosis and Therapy*. 2017;7(Suppl S3):S207–S218. doi:10.21037/cdt.2017.09.12
26. Agarwal V, Phung OJ, Tongbram V, Bhardwaj A, Coleman CI. Statin use and the prevention of venous thromboembolism: a meta-analysis. *Int J Clin Pract*. 2010;64(10):1375–1383. doi:10.1111/j.1742-1241.2010.02439.x
27. Nguyen CD, Andersson C, Jensen TB, et al. Statin treatment and risk of recurrent venous thromboembolism: a nationwide cohort study. *BMJ Open*. 2013;3(11):e003135. doi:10.1136/bmjopen-2013-003135
28. Biere-Rafi S, Hutten BA, Squizzato A, et al. Statin treatment and the risk of recurrent pulmonary embolism. *Eur Heart J*. 2013;34(24):1800–1806. doi:10.1093/eurheartj/eht046
29. Squizzato A, Galli M, Romualdi E, et al. Statins, fibrates, and venous thromboembolism: a meta-analysis. *Eur Heart J*. 2010;31(10):1248–1256. doi:10.1093/eurheartj/ehp556
30. Ray JG, Mamdani M, Tsuyuki RT, Anderson DR, Yeo EL, Laupacis A. Use of statins and the subsequent development of deep vein thrombosis. *Arch Intern Med*. 2001;161(11):1405–1410. doi:10.1001/archinte.161.11.1405
31. Lacut K, Le Gal G, Abalain JH, Mottier D, Oger E. Differential associations between lipid-lowering drugs, statins and fibrates, and venous thromboembolism: role of drug induced homocysteinemia? *Thromb Res*. 2008;122(3):314–319. doi:10.1016/j.thromres.2007.10.014
32. Lacut K, Oger E, Le Gal G, et al. Statins but not fibrates are associated with a reduced risk of venous thromboembolism: a hospital-based case-control study. *Fundam Clin Pharmacol*. 2004;18(4):477–482. doi:10.1111/j.1472-8206.2004.00252.x
33. Ramcharan AS, Van Stralen KJ, Snoep JD, Mantel-Teeuwisse AK, Rosendaal FR, Doggen CJ. HMG-CoA reductase inhibitors, other lipid-lowering medication, antiplatelet therapy, and the risk of venous thrombosis. *J Thromb Haemost*. 2009;7(4):514–520. doi:10.1111/j.1538-7836.2008.03235.x
34. Rodriguez AL, Wojcik BM, Wrobleski SK, DD M Jr, Wakefield TW, Diaz JA. Statins, inflammation and deep vein thrombosis: a systematic review. *J Thromb Thrombolysis*. 2012;33(4):371–382. doi:10.1007/s11239-012-0687-9
35. Jezovnik MK, Pavel P. Statins and Venous thromboembolism. e-journal of the ESC Council for Cardiology Practice; 2010.
36. Diamantis E, Kyriakos G, Quiles-Sanchez LV, Farmaki P, Troupis T. The Anti-Inflammatory Effects of Statins on Coronary Artery Disease: an Updated Review of the Literature. *Curr Cardiol Rev*. 2017;13(3):209–216. doi:10.2174/1573403X13666170426104611
37. Yang CC, Jick SS, Jick H. Statins and the risk of idiopathic venous thromboembolism. *Br J Clin Pharmacol*. 2002;53(1):101–105. doi:10.1046/j.0306-5251.2001.01523.x
38. Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. *Br J Clin Pharmacol*. 2009;67(1):99–109. doi:10.1111/j.1365-2125.2008.03308.x
39. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*. 2000;11(5):561–570. doi:10.1097/00001648-200009000-00012
40. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11(5):550–560. doi:10.1097/00001648-200009000-00011
41. Hernán MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med*. 2002;21(12):1689–1709. doi:10.1002/sim.1144
42. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656–664. doi:10.1093/aje/kwn164
43. Pazzagli L, Linder M, Zhang M, et al. Methods for time-varying exposure related problems in pharmacoepidemiology: an overview [published correction appears in Pharmacoepidemiol Drug Saf. *Pharm Drug Saf*. 2018;27(2):148–160. doi:10.1002/pds.4372
44. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827–836. doi:10.1093/ije/dyv098
45. García Rodríguez LA, Pérez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol*. 1998;45(5):419–425. doi:10.1046/j.1365-2125.1998.00701.x
46. Lawrenson R, Todd JC, Leydon GM, Williams TJ, Farmer RD. Validation of the diagnosis of venous thromboembolism in general practice database studies. *Br J Clin Pharmacol*. 2000;49(6):591–596. doi:10.1046/j.1365-2125.2000.00199.x

47. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8
48. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676–682. doi:10.1093/aje/kwq433
49. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47(11):1245–1251. doi:10.1016/0895-4356(94)90129-5
50. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;2013(1):CD004816. doi:10.1002/14651858.CD004816.pub5
51. Herrington DM, Vittinghoff E, Lin F, et al. Statin therapy, cardiovascular events, and total mortality in the Heart and Estrogen/Progestin Replacement Study (HERS). *Circulation*. 2002;105(25):2962–2967. doi:10.1161/01.cir.0000019406.74017.b2
52. Birdal O, Saygı M, Doğan R, Tezen O, Karagöz A, İH T. Risk of Venous Thromboembolism with Statins: evidence Gathered via a Network Meta-analysis. *Balkan Med J*. 2023;40(5):324–332. doi:10.4274/balkanmedj.galenos.2023.2023-5-26
53. Violi F, Calvieri C, Ferro D, Pignatelli P. Statins as antithrombotic drugs. *Circulation*. 2013;127(2):251–257. doi:10.1161/CIRCULATIONAHA.112.145334