Thrombosis Research 184 (2019) 99–104

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Initiation of statins and risk of venous thromboembolism: Population-based matched cohort study

Nils Skajaa[a,*], Szimonetta K. Szépligeti[a], Erzsébet Horváth-Puhó[a], Waleed Ghanima[b,c], John-Bjarne Hansen[d,e], Henrik Toft Sørensen[a]

[a] Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark
[b] Department of Medicine, Østfold Hospital, Kalnes, Norway
[c] Department of Hematology, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[d] K.G. Jebsen Thrombosis Research and Expertise Center, Department of Clinical Medicine, Arctic University of Norway, Tromsø, Norway
[e] Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

ARTICLE INFO

Keywords:
Statins
Venous thromboembolism
Pharmacoepidemiology
New-user design
Prevention
Pleiotropic effects

ABSTRACT

Background: The effects of statins in prevention of venous thromboembolism (VTE) is not well established.
Objectives: To examine the risks of first-time VTE in a cohort of patients initiating statin treatment and in a matched general population comparison cohort.
Methods: We conducted a nationwide, population-based, matched cohort study based on data from Danish health registries. The study period was 1 January 2005–31 December 2015. We identified statin initiators (without VTE, myocardial infarction, or ischemic stroke) and sex-, age-, and calendar year-matched (1,3) individuals from the general population (without statin use, VTE, myocardial infarction, or ischemic stroke). We computed cumulative risks and comorbidity-adjusted hazard ratios (HRs) of VTE, myocardial infarction, and ischemic stroke.
Results: Among 601,011 statin initiators and 1,803,033 matched population cohort members during 2005–2015, the cumulative risk after 11 years was 2.8% for VTE (both cohorts), 4.7% *vs.* 2.9% for myocardial infarction, and 7.1% *vs.* 5.2 for ischemic stroke. After adjustment, statin use was associated with a slightly decreased risk of VTE (adjusted HR: 0.95 [95% CI: 0.92–0.97]), driven by a reduced risk of unprovoked VTE (adjusted HR: 0.92 [95% CI: 0.89–0.95]). The reduced risks of VTE were more pronounced among patients who had an imaging examination performed. The adjusted HRs were elevated for myocardial infarction and ischemic stroke.
Conclusion: Statin initiation was associated with a reduced risk of VTE, with no indication of a healthy-user effect. Based on available evidence, statins have weak thromboprophylactic effects.

1. Introduction

Venous thromboembolism (VTE) is common, costly to treat, and associated with severe short and long-term complications [1]. About 10 million cases of VTE occur each year, only surpassed by myocardial infarction and stroke [1].

Despite different thrombus compositions and clinical manifestations, arterial and venous thrombosis often co-occur and share common risk factors [2]; increasing evidence indicates that occurrence of one condition increases the risk of the other [3–6].

Anticoagulation represents the treatment of choice for thromboprophylaxis, but balancing the risk of bleeding is challenging [7]. Statins are effective lipid-lowering drugs used in the prevention of arterial thromboses [8]. However, statins also possess anti-inflammatory and anti-thrombotic effects [9], making them potentially suitable to prevent VTE [10–15].

The JUPITER trial–the only randomized controlled trial (RCT) to test the hypothesis that statins protect against VTE– reported a 43% risk reduction among 17,802 individuals randomized to receive either rosuvastatin 20 mg daily or placebo [10]. However, the event rates were low in this trial and other investigators recognized the need for further evidence [16]. As statins are cost-effective drugs with established effectiveness in preventing arterial thromboses, further RCTs seem unlikely. Large population-based datasets of high quality may instead represent the best available data source. The Danish health registries permit individual-level linkage with almost complete follow-up,

* Corresponding author at: Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark.
E-mail address: nilsskajaa@clin.au.dk (N. Skajaa).

https://doi.org/10.1016/j.thromres.2019.11.003
Received 27 May 2019; Received in revised form 31 October 2019; Accepted 4 November 2019
Available online 06 November 2019
0049-3848/

thereby providing an excellent opportunity to examine this association rigorously [17].

We, therefore, undertook a large, population-based cohort study in Denmark employing a "new-user" design to provide further evidence on the potentially protective effects of statins in VTE prevention.

2. Methods

2.1. Design and setting

We conducted a nationwide, population-based, matched cohort study based on prospectively recorded data obtained from the Danish National Health Service Prescription Database (DNHSPD), the Danish National Patient Registry (DNPR), and the Danish Civil Registration System (CRS). The study period was 1 January 2005 to 31 December 2015. The Danish National Health Service provides tax-supported health care to the entire Danish population and partial reimbursement for prescribed drugs, including statins [18]. Each legal resident is assigned a unique ten-digit civil registration number upon birth or immigration, enabling unambiguous linkage across all data sources and assuring near-complete follow-up [17].

The DNHSPD contains data on all prescriptions redeemed in Danish community and outpatient pharmacies since 1 January 2004 [19]. For each redeemed prescription, the civil registration number, the redemption date, the *Anatomical Therapeutic Chemical Classification System* (ATC) code, type, and quantity of the drug are recorded. Data in the DNPR are coded according to the *International Classification of Diseases* (ICD) *Eighth Revision* (1977–1993), and *Tenth Revision* (thereafter) [20]. Each hospital and outpatient contact is recorded using one primary diagnosis and one or more secondary diagnoses. The availability of data in the DNPR since 1977 for hospital contacts and since 1995 for hospital outpatient clinic contacts permitted individual-level identification of patients' medical histories.

2.2. Statin initiation

We used the DNHSPD and DNPR to assemble a cohort of statin initiators with no history of VTE, myocardial infarction, or ischemic stroke: We first searched the DNHSPD to identify patients who redeemed a statin prescription for the first time between 1 January 2005 and 31 December 2015. The date of the incident statin prescription redemption was defined as the index date. To ensure that only initiators were captured, we excluded patients with a redeemed statin prescription from the start of the DNHSPD registry (1 January 2004) until the start of the study period (1 January 2005). We then searched the DNPR for primary and secondary diagnoses among the statin initiators and excluded those with an inpatient or outpatient diagnosis of VTE, myocardial infarction, or ischemic stroke at any time before or on the index date.

2.3. General population comparison cohort

We identified a general population comparison cohort from the CRS: Since 1968, this registry has recorded changes in vital and migration status for the Danish population [17]. For each statin initiator, we randomly selected three individuals, with replacement, matched on sex, age, and calendar year. To be eligible, general population cohort members had to be alive on the statin prescription redemption date (the index date), have no history of a VTE, myocardial infarction, or ischemic stroke (any time before or on the index date), and have no history of statin use (since 1 January 2004). Persons in the comparison cohort were subsequently assigned an index date corresponding to that of the matched statin initiator. Potential general population cohort members were excluded based on the same DNPR hospital diagnoses used to exclude ineligible statin initiators.

2.4. Outcomes

The primary outcome was a first-time inpatient or outpatient diagnosis of VTE, defined as a composite of deep vein thrombosis and pulmonary embolism. We treated unprovoked and provoked VTE as separate primary outcomes, classifying provoked VTE according to classic predisposing factors (*i.e.*, a diagnosis of cancer within 1 year before the index date, as well as fracture or trauma, surgery, or pregnancy within 90 days before the index date) [21]. According to Danish guidelines, statins are primarily used for secondary prevention of arterial thrombosis [22]. To examine a potential "healthy-user effect"–*i.e.*, healthier individuals may be more likely to receive prophylactic treatments than those less healthy–we included first-time inpatient and outpatient diagnoses of myocardial infarction and ischemic stroke as positive control outcomes.

2.5. Other covariates

For both statin initiators and general population cohort members, we obtained information on the following hospital-diagnosed comorbidities associated with both venous and arterial cardiovascular events as recorded in the DNPR after 1977 and before the index date: heart failure, diabetes, obesity, hypertension, atrial fibrillation, atherosclerosis and other diseases of the arteries, cancer, chronic kidney disease, and liver disease. We also obtained information from the DNHSPD on prescription redemptions before the index date of postmenopausal hormone replacement therapy, antipsychotics, and antithrombotic agents.

2.6. Statistical analyses

We characterized the statin initiators and members of the general population cohort by sex, age group (0–40 years, 41–50 years, 51–60 years, 61–70 years, and 71+ years), calendar period (2005–2008, 2009–2012, and 2013–2015), and the other covariates. We also calculated median age at baseline and median follow-up time. We followed both cohorts from the index date until the date of a cardiovascular event (VTE, myocardial infarction, ischemic stroke), death, emigration, or study end (31 December 2015), whichever occurred first. Following an initial cardiovascular event, we continued follow-up for other cardiovascular events, thereby avoiding informative censoring. We censored general population cohort members if a statin prescription was redeemed during follow-up. We used cumulative incidence functions to illustrate cumulative risks of each outcome during follow-up, comparing statin initiators with general population cohort members, accounting for the competing risk of death. For main analyses only, we also calculated incidence rates. Owing to the matched cohort design, we used Cox proportional hazard regression to compute hazard ratios (HRs), controlling for the matching factors by study design (sex, age, and calendar year) and adjusting for the categorical covariates (heart failure, diabetes, obesity, hypertension, atrial fibrillation, atherosclerosis and other diseases of the arteries, cancer, chronic kidney disease, liver disease, postmenopausal hormone replacement therapy, antipsychotics, and antithrombotics). As a supplementary analysis to control for confounding, we calculated the propensity score (the probability of receiving statin treatment) in both cohorts by including the matching factors and the categorical covariates in a logistic regression model. In main analyses only, we then computed propensity-score-adjusted HRs. We tested the proportionality hazard assumption using log-log plots and found some indication of deviations in the initially selected follow-up periods (0–1 years, > 1–5 years, and > 5–11 years). We, therefore, reclassified follow-up time into 0–1 year and 0–11 years for which valid log-log plots were obtained. We computed 95% confidence intervals (CIs) for all estimates.

2.7. Subgroup analyses

We stratified the results based on sex, age group (0–40 years, 41–50 years, 51–60 years, 61–70 years, and 71+ years), calendar period (2005–2008, 2009–2012, and 2013–2015), high potency statins (rosuvastatin and atorvastatin) and low potency statins (simvastatin, lovastatin, pravastatin, and fluvastatin) [23], number of cardiovascular risk factors (0, 1, ≥2), preexisting comorbidities (cancer, diabetes, and chronic kidney disease), and preexisting use of comedications (postmenopausal hormone replacement therapy, antipsychotics, and antithrombotic agents). We also assessed the independent risks of deep vein thrombosis and pulmonary embolism.

2.8. Sensitivity analyses

We performed several sensitivity analyses to test the robustness of our results. First, to reduce misclassification and to improve assessment of the specific effects of statins, we censored statin initiators at the time of the first event they encountered. Second, to emulate an intention-to-treat analysis, we performed an analysis in which general population cohort members were not censored at the time of their first statin prescription redemption. Third, emulating a per-protocol analysis, we censored statin initiators at the time they redeemed their last statin prescription. We assumed that a treatment episode lasted 90 days and allowed a 30-day grace period [23]. Fourth, to improve the positive predictive value of the VTE diagnosis in the DNPR, we performed an analysis, restricting to patients who received an ultrasound or a computed tomography scan during their hospital contact [24]. Finally, we restricted an analysis to patients without previous cardiovascular disease or previous use of cardiovascular drugs.

The ICD and ATC codes used in the study are listed in eTables 1 and 2. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used to conduct all analyses. According to Danish legislation, informed consent and approval from an ethics committee are not required for registry-based studies. The study was approved by the Danish Data Protection Agency (2016-051-000001).

3. Results

Our study included 601,011 statin initiators and 1,803,033 individuals from the general population. Sex and age distributions were similar between the patient and comparison cohorts. Median age at baseline was 62 years (interquartile range 53–69 years) for both statin initiators and general population cohort members. Compared with general population cohort members, statin initiators had a higher burden of cardiovascular risk factors and comorbidities at baseline and used comedications more frequently (Table 1).

During the 11 years following statin initiation, 9284 patients suffered a VTE (of which 4601 were deep vein thromboses and 4683 were pulmonary emboli), 15,880 a myocardial infarction, and 23,911 an ischemic stroke. For 5179 patients, more than one event occurred. Owing to censoring when a first-ever statin prescription redemption occurred among members of the general population cohort, median follow-up time was slightly shorter in this cohort (5 years [interquartile range 2–8 years]) than in the cohort of statin initiators (6 years [interquartile range 3–8 years]).

Fig. 1 shows cumulative risks during follow-up comparing statin initiators and members of the general population cohort. For VTE, the cumulative risks grew in parallel between the two cohorts. After 11 years of follow-up, the risks were 2.8% for all VTE, 0.9% for provoked VTE, and 1.9% for unprovoked VTE in both cohorts. The risks were higher in the statin initiator cohort than in the general population cohort for myocardial infarction (4.7% *vs* 2.9%) and for ischemic stroke (7.1% *vs* 5.2%). eTable 16 shows corresponding incidence rates for all outcomes.

After adjusting for the covariates during the full follow-up period, first-time statin use was associated with a slightly decreased risk of all VTE (adjusted HR: 0.93 [95% CI: 0.91–0.96]), driven by a reduced risk of unprovoked VTE (adjusted HR: 0.91 [95% CI: 0.88–0.94]). In contrast, the adjusted HR for provoked VTE was close to unity (adjusted HR: 0.99 [95% CI: 0.95–1.04]). Statin use was associated with elevated risks of both myocardial infarction (adjusted HR: 1.41 [95% CI: 1.38–1.44]) and ischemic stroke (adjusted HR: 1.19 [95% CI: 1.17–1.21]). The propensity-score-adjusted HRs were virtually identical with those estimated using traditional regression modelling (Table 2).

Compared with the full follow-up time, the reduction in risk of all VTE was less pronounced in the first year (adjusted HR: 0.96 [95% CI: 0.90–1.03]) (eTable 3). For unprovoked VTE, the relative risks during the first year (adjusted HR: 0.91 [95% CI: 0.84–0.99]) was similar to that for the entire follow-up period. The relative risks of provoked VTE (adjusted HR: 1.11 [95% CI: 0.98–1.25]), myocardial infarction (adjusted HR: 2.25 [95% CI: 2.15–2.35]), and ischemic stroke (adjusted HR: 1.86 [95% CI: 1.79–1.93]) were higher during the first year than during the full follow-up time.

Table 1
Characteristics (N, %) of statin initiators and matched general population cohort members, Denmark, 2005–2015.

Cumulative risks of venous thromboembolism (all, provoked, unprovoked), myocardial infarction, and ischemic stroke in statin initiators and members of the general population comparison cohort.

	Statin initiators (N = 601,011)	General population cohort members (N = 1,803,033)
Sex		
Men	295,868 (49.2)	887,604 (49.2)
Women	305,143 (50.8)	915,429 (50.8)
Age groups, years		
0–40	31,216 (5.2)	93,780 (5.2)
41–50	87,684 (14.6)	263,200 (14.6)
51–60	168,001 (28.0)	504,210 (28.0)
61–70	191,777 (31.9)	574,891 (31.9)
70+	122,333 (20.4)	366,952 (20.4)
Median age (interquartile range)	62 (53–69)	62 (53–69)
Cardiovascular risk factors and comorbidities		
Heart failure	12,587 (2.1)	17,059 (0.9)
Diabetes	86,808 (14.4)	48,129 (2.7)
Obesity	27,106 (4.5)	36,782 (2.0)
Hypertension	88,613 (14.7)	121,741 (6.8)
Atrial fibrillation	26,037 (4.3)	46,810 (2.6)
Atherosclerosis and other diseases of the arteries	24,155 (4.0)	26,684 (1.5)
Cancer	47,318 (7.9)	146,856 (8.1)
Chronic kidney disease	7181 (1.2)	10,091 (0.6)
Liver disease	6626 (1.1)	18,298 (1.0)
Comedications		
Postmenopausal hormone replacement therapy	70,015 (11.6)	193,771 (10.7)
Antipsychotic drugs	33,542 (5.6)	74,561 (4.1)
Antithrombotic agents	117,256 (19.5)	159,490 (8.8)

3.1. Additional analyses

The association of statin use with a reduction in risk of unprovoked VTE was slightly stronger in men than in women. In contrast, for myocardial infarction and ischemic stroke, the adjusted HRs were higher in men than in women (Table 2). For all conditions under study, the relative risks attenuated with increasing age (eTables 4–5). We found no substantial modification of associations between calendar periods for VTE. For myocardial infarction and ischemic stroke, the associations were stronger in the most recent calendar period (eTable 6). Statin potency did not materially affect the associations with VTE (eTable 7). In analyses stratified by cardiovascular risk factors before baseline, the adjusted HRs were lower for all VTE, provoked

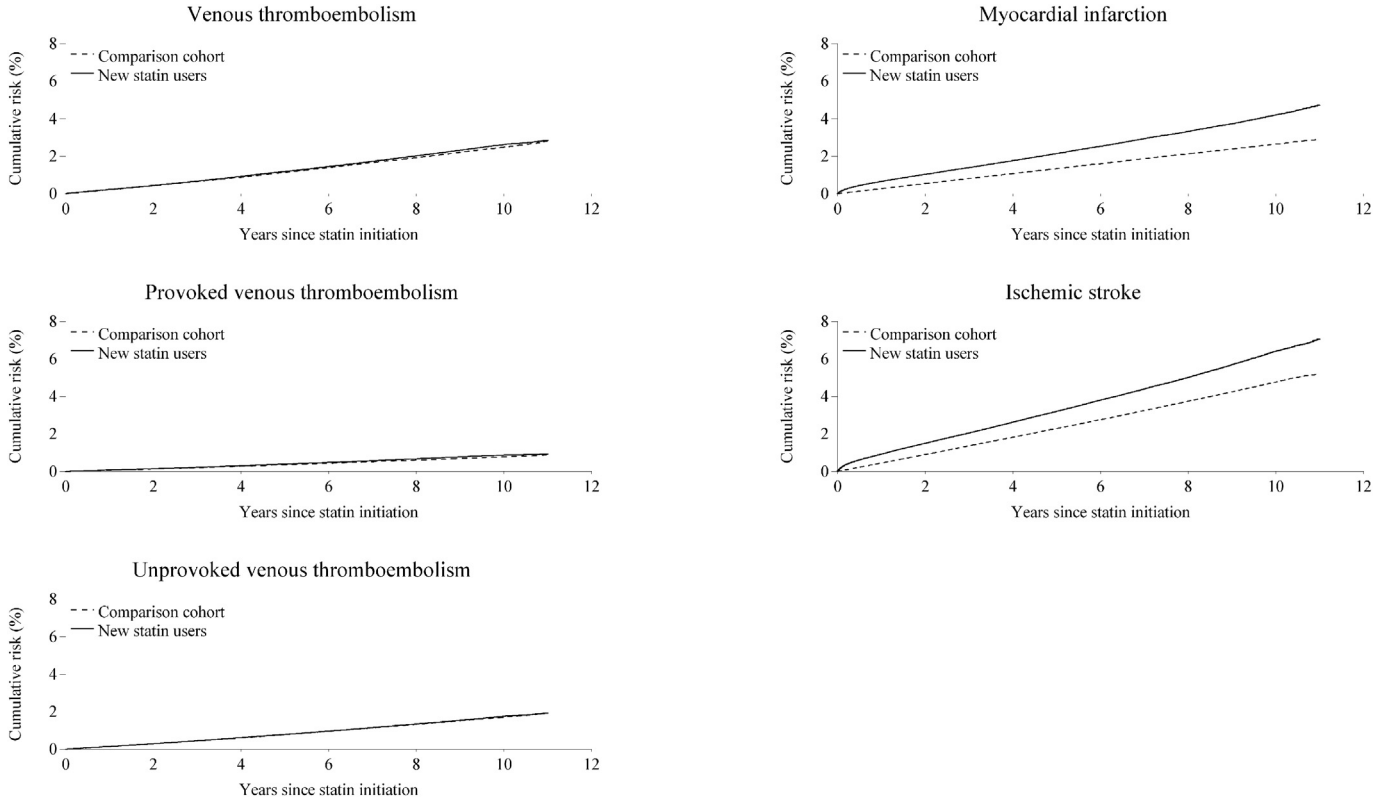

Fig. 1.

VTE, myocardial infarction, and ischemic stroke among patients with ≥2 cardiovascular risk factors compared with patients without cardiovascular risk factors. No effect modification was observed for unprovoked VTE (eTable 8). For individual comorbidities, the adjusted HRs for VTE were largely similar in patients with preexisting cancer, diabetes, or chronic kidney disease, as well as in patients using

Table 2
Events and risks of venous thromboembolism (all, provoked, unprovoked), myocardial infarction, and ischemic stroke, and hazard ratios comparing statin initiators with general population cohort members during full follow-up time (0–11 years), among all and according to sex.

	Statin initiators N = 601,011		General population comparison members N = 1,803,033		Hazard ratios (95% CI)[b]		
	Events	Risk (95% CI)[a]	Events	Risk (95% CI)	Crude	Adjusted	PS-adjusted
Venous thromboembolism							
All	9284	2.84 (2.75–2.93)	22,952	2.79 (2.71–2.86)	1.01 (0.99–1.04)	0.93 (0.91–0.96)	0.94 (0.92–0.97)
Men	4368	2.80 (2.66–2.93)	11,210	2.84 (2.73–2.96)	0.99 (0.95–1.02)	0.90 (0.87–0.94)	
Women	4916	2.88 (2.75–3.02)	11,742	2.73 (2.64–2.82)	1.04 (1.00–1.07)	0.96 (0.92–0.99)	
Unprovoked venous thromboembolism							
All	6196	1.92 (1.84–2.01)	15,761	1.92 (1.86–1.98)	0.99 (0.96–1.02)	0.91 (0.88–0.94)	0.91 (0.88–0.94)
Men	2857	1.87 (1.75–1.99)	7780	1.98 (1.89–2.08)	0.94 (0.89–0.98)	0.86 (0.82–0.90)	
Women	3339	1.99 (1.87–2.10)	7981	1.87 (1.80–1.95)	1.04 (0.99–1.08)	0.95 (0.91–0.99)	
Provoked venous thromboembolism							
All	3088	0.93 (0.88–0.98)	7191	0.88 (0.84–0.92)	1.07 (1.02–1.12)	0.99 (0.95–1.04)	1.01 (0.97–1.06)
Men	1511	0.95 (0.88–1.02)	3430	0.88 (0.81–0.95)	1.10 (1.03–1.17)	1.01 (0.94–1.08)	
Women	1577	0.91 (0.84–0.99)	3761	0.88 (0.83–0.94)	1.04 (0.98–1.11)	0.98 (0.92–1.05)	
Myocardial infarction							
All	15,880	4.72 (4.57–4.86)	26,014	2.89 (2.83–2.96)	1.60 (1.57–1.63)	1.41 (1.38–1.44)	1.39 (1.36–1.41)
Men	9945	6.09 (5.83–6.35)	16,499	3.77 (3.66–3.88)	1.60 (1.56–1.64)	1.44 (1.40–1.49)	
Women	5935	3.44 (3.30–3.57)	9515	2.07 (2.00–2.15)	1.60 (1.55–1.65)	1.36 (1.31–1.41)	
Stroke							
All	23,911	7.05 (6.89–7.22)	45,524	5.20 (5.12–5.28)	1.36 (1.34–1.38)	1.19 (1.17–1.21)	1.17 (1.15–1.19)
Men	12,492	7.36 (7.15–7.58)	23,387	5.51 (5.38–5.64)	1.40 (1.36–1.43)	1.22 (1.19–1.25)	
Women	11,419	6.77 (6.51–7.03)	22,137	4.91 (4.80–5.02)	1.32 (1.29–1.35)	1.16 (1.13–1.19)	

Abbreviation: CI, confidence interval; PS, propensity score.

[a] Cumulative incidence per 1000 statin initiators or general population cohort members.

[b] Crude hazard ratios: controlled for matching factors (age, sex, calendar year); adjusted hazard ratios: controlled for matching factors and adjusted for heart failure, diabetes, obesity, hypertension, atrial fibrillation, atherosclerosis and other diseases of the arteries, cancer, chronic kidney disease, liver disease, postmenopausal hormone replacement therapy, antipsychotics, and antithrombotic; propensity score-adjusted hazard ratios: adjusted for propensity scores.

Table 3
Events and risks of venous thromboembolism and hazard ratios comparing statin initiators with general population cohort members during full follow-up period (0–11 years), restricted to diagnoses confirmed with ultrasound or computed tomography scan.

	Statin initiators N = 601,011		General population cohort members N = 1,803,033		Hazard ratios (95% CI)[b]	
	Events	Risk (95% CI)[a]	Events	Risk (95% CI)	Crude	Adjusted
Venous thromboembolism (ultrasound or CT scan confirmed)	6267	1.94 (1.86–2.02)	16,833	2.06 (1.99–2.12)	0.93 (0.90–0.96)	0.88 (0.85–0.90)

Abbreviation: CI, confidence interval; CT, computed tomography.
[a] Cumulative incidence per 1000 statin initiators or general population cohort members.
[b] Crude hazard ratios: controlled for matching factors (age, sex, calendar year); adjusted hazard ratios: controlled for matching factors and adjusted for heart failure, diabetes, obesity, hypertension, atrial fibrillation, atherosclerosis and other diseases of the arteries, cancer, chronic kidney disease, liver disease, postmenopausal hormone replacement therapy, antipsychotics, and antithrombotics.

postmenopausal hormone replacement therapy, antipsychotics, and antithrombotic agents (eTables 9–10). Finally, the adjusted HRs were similar for deep vein thrombosis and pulmonary embolism (eTable 11).

3.2. Sensitivity analyses

In analyses in which members of the statin initiator cohort were censored when they experienced their first outcome and in analyses in which general population cohort members were not censored when they redeemed a statin prescription, results were similar to those for the main analyses (eTables 12–13). Conversely, when we censored statin initiators 90 days following their last redeemed statin prescription (allowing a 30-day grace period), the adjusted HRs were lower than those in the main analyses for all VTE, provoked VTE, and unprovoked VTE (eTable 14). Similarly, when we required the diagnosis of VTE to be accompanied by an ultrasound or computed tomography scan (68% of patients with all VTE), the adjusted HRs lowered (adjusted HR: 0.89 [95% CI: 0.86–0.92]) (Table 3). When restricting to patients without previous cardiovascular disease or use of cardiovascular drugs, the associations were slightly less pronounced (eTable 15).

4. Discussion

In this nationwide, population-based cohort study in Denmark, we found that first-time statin initiators were at decreased risk of unprovoked VTE compared with statin non-initiators from the general population. The beneficial effects of statins were greater when the VTE diagnoses were verified by an ultrasound or computed tomography scan. The relative risk reduction did not differ by statin potency or between deep vein thrombosis and pulmonary embolism. At the same time, the risks of myocardial infarction and ischemic stroke were higher among statin initiators than among members of the general population, indicating no “healthy-user effect”.

Strengths of our study included its large size and use of prospectively recorded and clinically-derived hospital data with virtually no loss to follow-up. The positive predictive values for VTE, myocardial infarction, and ischemic stroke in the DNPR are high and appropriate for research purposes [24]. Approximately 30% of VTEs observed in the current study lacked an imaging procedure. This is likely explained by either a lack of imaging registration to the DNPR or outcome misclassification. In any case, misclassification in this regard would be non-differential, directing the effect estimates towards the null. When we used a stricter definition of VTE (requiring validation through an ultrasound or a computed tomography scan), the beneficial effects of statins were greater, thus strengthening the evidence of a relative risk reduction in statin users compared with the general population. Our data on statin use originated from prescriptions redeemed at community pharmacies [19] and statin users in Denmark reportedly have high compliance rates [25].

The main study limitation was the lack of random assignment of drug exposure, which makes residual and uncontrolled confounding possible. Indeed, bias by indication was a main type of bias in our study, exemplified by the large baseline differences. These differences are expected in a routine clinical setting as statins are indicated for the secondary prevention of arterial thrombosis [22]. While we controlled for much confounding in this regard, any uncontrolled confounding by smoking and high body mass index likely led to conservative estimates of the true beneficial effects of statins [27]. Likewise, in accordance with previous reports [27], we observed no indication of a “healthy-user effect” in our cohort, since the relative risks of myocardial infarction and ischemic stroke were higher among statin users than among the general population. Moreover, we implemented a “new-user design” that excluded prevalent users already in the design-phase [26]. Further, the organization of the Danish health care system with unfettered access to care across all socioeconomic gradients and ethnic groups reduced the likelihood of confounding by socioeconomic status.

To our knowledge, this is the largest single study reporting on the risk of VTE in first-time statin users compared with the general population. The JUPITER trial is the sole RCT to date to test the hypothesis that statins modify risk of later VTE [10]. A meta-analysis aggregating adverse event reports from published and unpublished statin trials (22 trials, 146,353 participants) reported a slight risk reduction (odds ratio: 0.89 [95% CI: 0.78–1.01]) of VTE [14]. Newer findings from a meta-analysis–including results from both experimental and observational studies–indicate effect sizes ranging from a 10% to a 30% risk reduction [15]. Thus, our main findings largely agree with those from previous reports and provide further evidence of a protective effect of statins on the risk of first-time VTE.

We found weak evidence of a sex difference in VTE prevention with statins, with risks slightly lower in men than in women. Although we found the greatest risk reduction among patients aged 61–70 years, patients older than age 70 also benefitted. Similarly, the Cholesterol Treatment Trialists' Collaboration recently reported beneficial statin treatment effects on major arterial cardiovascular events irrespective of age [28]. Statins thus may be a useful therapy among patients of all ages.

Conflicting evidence exists regarding the effects of statins on deep vein thrombosis and pulmonary embolism, with some studies reporting a larger risk reduction for deep vein thrombosis than for pulmonary embolism [10,13,15], and others not finding such heterogeneity [14]. Our study was large enough to adequately assess the independent risks of deep vein thrombosis and pulmonary embolism and found that these risks did not differ substantially. Although some evidence indicates that high potency statins have a greater preventive effect than low potency statins [10,23], our findings did not suggest such differential effects.

The mechanisms by which statin modulates risk of VTE are numerous and have been reviewed elsewhere [29,30]. In short, the lipid-lowering, anti-inflammatory, and anti-thrombotic properties of statins likely each play roles. First, improved nitric oxide regulation, mediated through cholesterol lowering, improves endothelial function [29]. Second, statins suppress inflammation by reducing proinflammatory cytokines and c-reactive protein levels [29]. Finally, statins lower both

tissue factor and plasminogen activator inhibitor 1 expression, thereby reducing thrombin generation and thrombotic susceptibility. Conversely, through promotion of Knuppel-like factor 2 activity, statins enhance thrombomodulin expression. They thereby improve the protein C antithrombotic pathway and Factor Va inactivation [29–31].

In conclusion, this large population-based matched cohort study found that first-time statin initiation was associated with a slightly reduced risk of unprovoked VTE, independent of statin potency. The risks of deep vein thrombosis and pulmonary embolism were similar. The evidence of reduced risk was strengthened when an ultrasound or computed tomography scan verified the VTE diagnosis. Statins are safe, cost-effective drugs with established beneficial effects in the prevention of arterial thrombosis. Based on the currently available evidence, statins have weak thromboprophylactic effects.

Author contributions

H.T.S., W.G., and J.B.H conceived the study idea. H.T.S and N.S. designed the study and directed the analyses, which were conducted by E.H.P. and S.K.S. All authors participated in the discussion and interpretation of the results. N.S. reviewed the literature, organized the writing, and wrote initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. H.T.S is the guarantor.

Acknowledgements

K.G. Jebsen Thrombosis Research and Expertise Center is supported by an independent grant from Stiftelsen Kristian Gerhard Jebsen.

Sources of funding

The authors report no targeted funding for this study.

Declaration of competing interest

The authors report no conflicts of interest for this study. The Aarhus University Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies has any relation to the present study. Dr. Ghanima reports receiving grants and lecture honoraria from Novartis, Bayer, and Pfizer/BMS, and lecture and advisory board honoraria from MSD, Novartis and Amgen. None of these grants or honoraria is relevant to the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.11.003.

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