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Statin treatment and risk of recurrent venous thromboembolism: a nationwide cohort study

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ABSTRACT

Objectives: Statins may decrease the risk of primary venous thromboembolism (VTE), that is, deep vein thrombosis (DVT) and pulmonary embolism (PE) but the effect of statins in preventing recurrent VTE is less clear. The aim of this study was therefore to investigate the association between statin therapy and risk of recurrent VTE.

Design: A prospective cohort study.

Setting: All hospitals in Denmark.

Participants: All patients with a hospital diagnosis of VTE in Denmark during 1997–2009 associated with a warfarin or heparin prescription were identified.

Main outcome measures: Adjusted HR of recurrent hospitalised VTE (ie, fatal or non-fatal DVT or PE) associated with use of statins.

Results: 44 330 patients with VTE were included in the study. Of these 3914 were receiving statin therapy at baseline. Patients receiving statins were older (68±11 compared to 62±18 years), had more comorbidity and used more medications. The incidence rate for recurrent VTE was 24.4 (95% CI 22.8 to 26.2) per 1000 person-years among statin users and 48.5 (95% CI 47.4 to 49.7) per 1000 person-years among non-statin users. Statin use was associated with a significantly lower risk of a recurrent VTE, adjusted HR 0.74 (95% CI 0.68 to 0.80), compared with no statin use. The association between statin use and risk of recurrent VTE was significantly affected by age. Among younger individuals (≤80 years), statin use was associated with lower risk of recurrent VTE, HR 0.70 (95% CI 0.65 to 0.76) whereas in older individuals (>80 years) statin use was significantly associated with higher risk of recurrent VTE, HR 1.28 (95% CI 1.02 to 1.60), p for interaction=<0.0001.

Conclusions: Statin use was associated with a decreased risk of recurrent VTE.

Strengths and limitations of this study

- We lacked data on chemotherapy, obesity, pregnancy and smoking.
- The main strength of our study was the large amount of individuals included.
- The main limitation was the observational nature of the study.

INTRODUCTION

Venous thromboembolism (VTE), that is, deep vein thrombosis (DVT) and pulmonary embolism (PE) are common diseases associated with high morbidity and mortality. Primary VTE has an incidence rate of 1–2/1000 person-years in Western populations[1 2] and more than 30% of patients with VTE experience at least one recurrent episode during the following 5-year period.[3 4] The risk of VTE is influenced by many temporary factors such as surgery,[5] cancer and immobilisation, but if no such conditions are apparent, short-term secondary prophylaxis with anticoagulants may be insufficient in order to prevent recurrent VTE. A first episode of unprovoked VTE is nevertheless followed by 3–6 months of anticoagulant therapy with vitamin K antagonists in order to reduce the risk of recurrent episodes. The risk of major bleeding is the foremost complication of treatment and one of the main reasons for limiting treatment duration to 3–6 months. Statins have been shown to be associated with reduced risk of VTE and may therefore constitute a possible long-term supplement to antithrombotic treatment after VTE.[6 7] The potential role of statins on the coagulation system is currently not clear, but statins may carry an antithrombotic effect by inhibiting the expression of tissue factor and thereby inhibit platelet activation.[6 8–12] A randomised controlled trial of rosuvastatin in the primary prevention of VTE, a meta-analysis, and several observational studies have shown a significant reduction in the risk of VTE associated with the use of statins ranging from 20% to 60%.[13–20] However, another recent meta-analysis including unpublished trials showed no significant effect of statins on the primary risk of VTE.[21]

The effect of statin treatment on prevention of recurrent episodes in patients with a previous VTE is insufficiently investigated. Therefore, the aim of our study was to investigate if statin use could have a preventive effect on recurrent VTE in a nationwide cohort of patients with DVT or PE.

METHODS

Data-sources

In Denmark every resident is, at the time of birth or immigration, provided with a unique and permanent civil registration number, which enables linkage between nationwide administrative registers on the individual level. The Danish National Patient Register was established in 1978 and includes information on all hospitalisations in Denmark since 1978. At discharge, each admission is registered with one primary and if appropriate, one or more secondary diagnoses according to the International Classification of Diseases (ICD): the 10th revision (ICD-10).[22 23] The National Register of Medicinal Product Statistics[24] holds data on every dispensed prescription from pharmacies in Denmark since 1995. Dispensed drugs are registered by the international Anatomical Therapeutic Classification (ATC) system along with information on date and amount dispensed. Information on vital status was obtained from the Danish Civil Registry[25] and causes of death from the Danish Registry of Causes of Death.[26]

Study population

All patients with a hospital diagnosis of VTE between 1 January 1997 and 31 December 2009 (in patients and out patients) were identified. The VTE diagnoses comprised the following ICD-10 codes: I26 (pulmonary embolism), I80 (phlebitis and thrombophlebitis) and I82 (other venous embolism and thrombosis). Patients with any of I82.0 (Budd-Chiari syndrome), I80.0 (phlebitis and thrombophlebitis of superficial vessels of lower extremities) and I80.8 (phlebitis and thrombophlebitis of other sites) were excluded. To ensure a correct diagnosis of VTE we required that a diagnosis of VTE was followed by appropriate anticoagulation therapy and therefore excluded patients who did not claim a prescription of anticoagulation therapy from a pharmacy (heparin or warfarin/marcoumar) within 30 days of the diagnosis of VTE. The follow-up time started 90 days after the inpatient admission date (index date), which we assumed as the date of VTE, and patients were followed until the first occurrence of any of the following: hospitalisation with VTE diagnoses, emigration, death or 31 December 2009. The reason for starting follow-up 90 days after the hospital admission date was to avoid including any workup investigations related to the initial VTE event.

Comorbidity

Comorbidity was defined by hospitalisation diagnoses up to 1 year prior VTE diagnosis. The concomitant diagnoses (ICD-10 codes) of interest were ischaemic heart disease (I20, I23–I25), acute myocardial infarction (I21–I22), atrial flutter/fibrillation (I48), peripheral vascular disease (I70–I74), diabetes mellitus (E10–E14) and malignancies (C00–C97).

Pharmacotherapy

Use of the following drugs was identified: statins (ATC code C10AA), glucose-lowering medications (A10), non-steroidal anti-inflammatory drugs (NSAIDs) (M01), hormone replacement therapy/oral contraceptives (G03), diuretics (C03), low-dose aspirin (B01AC06), clopidogrel (B01AC04), ACE inhibitor/angiotensin II antagonist (C09) and antipsychotics (N05A). Patients were defined as users at baseline if the prescription was redeemed 90 days before or 90 days after the index date. Patients were allowed to initiate and discontinue medications throughout follow-up and hence change exposure status during the study period.

The exposure status was updated approximately every 90 days. The daily dosage of medication is not recorded in the national prescription register. Treatment with vitamin K antagonists (B01AA) and statins were assessed for each day by considering the amount of claimed medications and claiming time interval for up to three consecutive prescriptions. On the basis of these assumptions, we calculated whether patients at any time had tablets available or not. Patients were considered exposed only while taking the medications. This method is described in more detail elsewhere.[27] The minimal dose of warfarin is 1.25 mg and maximal dose is 10 mg. Minimal dose of simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin are 5, 10, 10, 20, 10 and 5 mg, respectively. The maximal dose is 80 mg for all subtypes of statins. The cut-off points for high dosage of simvastatin, lovastatin, pravastatin, fluvastatin and atorvastatin were 20 mg and for rosuvastatin the cut-off point was 10 mg.

Surgery

From The Danish National Patient Register we obtained information on cardiovascular surgery, abdominal surgery and orthopaedic surgery to adjust for the risk of VTE associated with surgery in the multivariate regression analysis. Surgery was included as a time-varying covariate in the models and patients were considered exposed 30 days following the date of surgery.

Study outcome

A recurrent VTE was defined as a new inpatient or outpatient admission with the diagnosis of VTE (ICD-10 codes I26, I80 or I82, except I82.0, I80.0 and I80.8, which were excluded) together with a claimed prescription of anticoagulants (heparin or vitamin K antagonists) within 30 days before or after the diagnosis, or VTE coded as the primary or contributing cause of death in the death certificate (same ICD-codes as above). For the composite endpoint, VTE and individual

endpoints, patients with DVT or PE, were followed until the first recurrent event of the type of interest, emigration, death or end of study (31 December 2009).

Statistical analysis

Discrete variables were compared using χ^2 test and continuous variables were compared using the t test. We also calculated crude incidence rates for recurrent DVT, PE and VTE as numbers of events/1000 person-years. Multivariable Cox proportional hazard regression models were used to estimate HR for the recurrent DVT, PE and VTE associated with individual risk factors. All models included age, sex, ischaemic heart disease, acute myocardial infarction, atrial flutter/fibrillation, peripheral vascular disease, diabetes mellitus, malignancies, statins, warfarin, low-dose aspirin, clopidogrel, hormone replacement therapy/oral contraceptives, glucose-lowering medications, diuretics, NSAIDs, ACEi/ARB, antipsychotic medications and surgery. In all models, medications and surgery were time-dependent variables, meaning that patients were only considered exposed when they were taking the drugs or 30 days following the date of surgery. Model assumptions—the linearity of continuous variables, the proportional hazards assumption and lack of interactions—were tested and found valid unless otherwise indicated. Tests for interactions (between statin and the different variables) were performed by inclusion of an interaction term in the analysis.

All calculations were performed using SAS V.9.2 (SAS Institute, Cary, North Carolina, USA). A p value <0.05 was regarded statistically significant. Adjusted numbers needed to treat were calculated by using the methods described by Bender *et al*.[28]

RESULTS

A total of 44 330 patients with VTE were included in the study. Of these 3914 (9.7%) received statin therapy and 40 416 did not receive statin therapy at study baseline. The mean follow-up time was 1438 days for the entire study population. In total 225 patients emigrated during follow-up. The baseline characteristics of statin users and non-statin users are presented in table 1. More patients initiated statin therapy during follow-up and altogether 9869 patients received statin therapy in our study at some point in time. At baseline the majority (81%) of statin users were treated with simvastatin (table 2). Patients with statin therapy were older (68±11 compared to 62±18 years), had more concomitant diseases such as diabetes mellitus (15% vs 4%) and peripheral artery disease (7% vs 2%) and used more medications, particularly low-dose aspirin (50% vs 13%), ACEi/ARB (50% vs 15%) and glucose-lowering drug (20% vs 5%), compared to patients without statin therapy.

Table 1 Baseline characteristic

Characteristic	No statin therapy (N=40 416)	Statin therapy (N=3914)
Age (years)—n (%)		
≤50	10 278 (25)	264 (7)
51–60	6623 (16)	575 (15)
61–70	8187 (20)	1190 (30)
71–80	8636 (21)	1304 (33)
>80	6692 (17)	581 (15)
Age, mean(±SD), years	62.1 (±17.7)	68.4 (±11.3)
Women—n (%)	20 816 (52)	1810 (46)
Concomitant diseases*—n (%)		
Ischaemic heart disease	1639 (4)	868 (22)
Acute myocardial infarction	343 (1)	249 (6)
Atrial flutter/fibrillation	2196 (5)	375 (10)
Peripheral artery disease	828 (2)	270 (7)
Diabetes mellitus	1628 (4)	605 (15)
Malignancies	3903 (10)	346 (9)
Concomitant medications†—n (%)		
Low-dose aspirin	5440 (13)	1954 (50)
Clopidogrel	163 (0.4)	276 (7)
Hormone replacement therapy	5281 (13)	335 (9)
ACEi/ARB	6037 (15)	1939 (50)
Glucose-lowering medications	1905 (5)	800 (20)
Diuretics	13 362 (33)	2140 (55)
Antipsychotic medication	2376 (6)	190 (5)
Nonsteroidal anti-inflammatory drugs	10 223 (25)	989 (25)

*Concomitant diseases refer to hospitalisation diagnosis (ICD 10-codes) up to 1 year prior to venous thromboembolism (VTE) hospitalisation.
†Concomitant medications refer to claimed prescription of an agent in the period between 90 days before to hospitalisation and 90 days after first hospitalisation date.
ACEi/ARB, ACE inhibitor/angiotensin II antagonist.

Table 2 Type of statin used at baseline

	n	Per cent
Any statin expose	3911	
Simvastatin	3185	81.4
Lovastatin	54	1.4
Pravastatin	208	5.3
Fluvastatin	43	1.1
Atorvastatin	377	9.6
Rosuvastatin	81	2.1

Association between statins and risk of recurrent VTE

The median follow-up time was 1078 days (IQR 361–2271 days) for the entire population, 423 days (IQR 121–1127 days) for those with recurrent VTE and 1285 days (IQR 491–2494 days) for those without recurrent VTE. Recurrent VTE occurred in 8264 (18%) patients, of which 5320 had a recurrent DVT and 3744 had a recurrent PE. The incidence rate of recurrent VTE, DVT and PE are presented in table 3.

For the VTE endpoint statin use was associated with a lower risk of a recurrent VTE, unadjusted HR 0.75 (95% CI 0.70 to 0.81; table 4), adjusted for age and sex, HR 0.74 (95% CI 0.68 to 0.79) and adjusted for all variables, HR 0.74 (95% CI 0.68 to 0.80). A significant interaction was seen between statins and age, p≤0.0001. Statins were associated with a substantially lower risk of recurrent VTE among younger patients, compared with older patients. A significant interaction was also seen between statins and gender, p≤0.0001. Statin use was associated with lower HR in men, compared with women, HR 0.65 (95% CI 0.59 to 0.72) vs HR 0.87 (95% CI 0.78 to 0.98). Further, a significant interaction was also found between statin use and low-dose aspirin, p=0.03. Statin use was associated with significantly lower HR of VTE if administered without low-dose aspirin than if administered with low-dose aspirin, HR 0.70 (95% CI 0.63 to 0.76) compared to 0.82 (95% CI 0.72 to 0.93).

Analysing each endpoint separately, we found that statin use was associated with significantly lower risk of a recurrent DVT, HR 0.66 (95% CI 0.59 to 0.71), as well as recurrent PE, HR 0.87 (95% CI 0.78 to 0.97), compared to no statin use (table 4). The adjusted numbers needed to treat among statin users were 79 for VTE, 392 for PE and 97 for DVT.

A dose–response analysis revealed no significant differential association between low-dose statin use, HR 0.76 (95% CI 0.68 to 0.85) and high-dose statin use, HR 0.71 (95% CI 0.64 to 0.79) on the risk of a recurrent VTE.

DISCUSSION

In our nationwide study comprising over 40 000 patients with prior VTE, statin use was associated with a significant reduction in the occurrence of recurrent VTE. This was found for recurrent DVT as well as for recurrent PE. This is the first study to evaluate the VTE-prophylactic

Table 3 Incidence rate (95% CI)/1000 person-years according to statin use and age

	Any statin use			No statin use		
	VTE	DVT	PE	VTE	DVT	PE
Age (years)						
≤50	7.4 (5.9 to 9.1)	4.6 (3.5 to 6.1)	3.5 (2.6 to 4.8)	46.8 (45.8 to 47.8)	28.6 (27.9 to 29.4)	19.3 (18.7 to 20.0)
51–60	29.8 (25.4 to 34.9)	17.5 (14.3 to 21.3)	11.8 (9.3 to 14.9)	44.8 (43.8 to 45.8)	27.5 (26.7 to 28.3)	18.6 (18.0 to 19.2)
61–70	30.4 (26.7 to 34.5)	16.4 (13.9 to 19.4)	13.9 (11.6 to 16.7)	45.0 (44.0 to 46.0)	27.7 (27.0 to 28.5)	18.6 (18.0 to 19.2)
71–80	36.6 (32.1 to 41.8)	16.2 (13.3 to 19.6)	21.3 (18.0 to 25.2)	44.6 (43.6 to 45.6)	27.6 (26.8 to 28.4)	18.3 (17.7 to 18.9)
>80	52.2 (42.1 to 64.8)	19.7 (14.0 to 27.7)	33.1 (25.4 to 43.1)	44.3 (43.3 to 45.2)	27.3 (26.5 to 28.0)	18.2 (17.7 to 18.8)
All	24.4 (22.8 to 26.2)	12.7 (11.5 to 13.9)	12.3 (11.1 to 13.5)	48.5 (47.4 to 49.7)	30.3 (29.4 to 31.1)	19.6 (19.0 to 20.3)

DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 4 HRs of venous thromboembolism associated with statin use

Outcome	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted† HR (95% CI)
Venous thromboembolism	0.75 (0.70 to 0.81)	0.74 (0.68 to 0.79)	0.74 (0.68 to 0.80)
Deep venous thrombosis	0.61 (0.55 to 0.67)	0.63 (0.57 to 0.70)	0.66 (0.59 to 0.71)
Pulmonary embolism	0.93 (0.84 to 1.04)	0.86 (0.77 to 0.95)	0.87 (0.78 to 0.97)

*Adjusted for gender and age.
†Adjusted for gender, age, low-dose aspirin, clopidogrel, surgery, ischaemic heart disease, acute myocardial infarction, atrial flutter/fibrillation, peripheral vascular disease, diabetes mellitus, malignancies, hormone replacement therapy, diuretics, glucose-lowering medication, ACE inhibitors/angiotensin II antagonists, non-steroidal anti-inflammatory drugs (NSAID) and antipsychotic medication.

effect of statin among participants with previous VTE on such a large population. Whether statins can be used as prophylaxis in patients with a previous VTE is an upcoming discussion. To our knowledge, two previous observational studies have focused on the influence of statins on the risk of recurrent thromboembolic events. Biere-Rafi *et al* recently used a Dutch population-based registry of pharmacy records linked with hospital discharge records and found that among 3039 patients with PE statin use was associated with decreased risk of recurrent pulmonary embolism (HR 0.50 (95% CI 0.36 to 0.70)).[29] Delluc *et al* investigated the association between statin use and recurrent VTE on a small population of 432 participants and found no association.[30]

There are six subtypes of statins available on the market and it has not been clear if any reduction of VTE should be a class effect of statins or if it may differ between agents. In our study 80% of statin users were treated with simvastatin. We could therefore not explore a potential difference in effects between statins. However, a previous case–control study by Ramacharan *et al*,[19] with 4538 cases of first time VTE, verified by scanning and with the case's partners as controls, found that simvastatin, pravastatin and atorvastin were associated with lower risk of VTE. Doggens *et al*[16] found simvastatin to reduce the risk of VTE, but they were unable to find the same association for pravastatin. The recent study by Biere-Rafi *et al* showed that statins with the strongest potency, that is, atorvastatin and rosuvastatin, were associated with the greatest protection against a recurrent PE. In our study, however, we could not confirm such a differential association nor could we identify a dose–response relation between statin dosages and the risk of VTE. The lack of dose–response relationship may be explained by the fact that the maximum effect of statins on the risk of VTE is reached already at low dose of statins. Further studies are warranted to investigate this subject.

We found an interesting modification of the effects associated with statins as dependent on age, and the antithrombotic effect of statins seemed to decrease with increasing age. Statin use among patients over 80 years of age was not significantly associated with a lower risk of recurrent VTE. Notably, increasing age in itself seemed to be protective against a recurrent VTE in our study. An explanation for the limited effect associated with statins in elderly patients could therefore be due to a lower baseline risk of VTE among elderly, compared with younger individuals. Another reason could be that patients over 80 have lower exposure to statins, by being less likely to be prescribed with statins, as seen in table 1, or had lower compliance compared to those under 80. However, lower compliance is not likely to be a major reason, since a previous study has shown that elderly patients had better compliance with statins compared to younger patients.[31]

Interestingly, a recent randomised study, Aspirin for preventing the recurrence of venous thromboembolism (WARFASA) study, found that aspirin was effective in preventing unprovoked recurrent VTE after discontinuation of vitamin K antagonists.[32] We investigated if adding statins to low-dose aspirin may be effective in reducing the risk further and we found that, although to a significantly less degree, statins were associated with lowered risks of VTE also among patients receiving aspirin. Further, our data suggest that statins may be as effective as aspirin in preventing VTE in patients with prior VTE and because they carry a lower risk of bleeding they may constitute an attractive alternative to aspirin in some patients. Ultimately, a randomised trial investigating the effect of aspirin, statin and the combination of the two agents for secondary prophylaxis after VTE should therefore be performed.

The exact mechanism underlying any protective effects of statins on risk of VTE is unknown. Some believe statins may carry an antithrombotic effect by inhibiting the expression of tissue factor and thereby inhibiting platelet activation.[6 8–12] Others have earlier suggested that the effect of statin beside the cholesterol lowering effect is due to 'healthy user effect'.[33 34] Thus, persons who receive treatment with statins have a healthier lifestyle or/and a lower risk profile. In our population we cannot rule out a 'healthy user effect', although a recent Danish paper suggested that statin users do not have healthier lifestyle compare with non-statin users.[35]

Strengths and limitations

The main strength of our study was the large amount of individuals included. The Danish National Patient Registry, as well as the National Prescription Registry have proven to be accurate in other settings[36 37] and the validity of the inpatient diagnoses of VTE has been investigated by Severinsen *et al*, who found a positive predictive value of 75% (95% CI 71.9% to 77.9%).[38] The

validity of outpatient diagnoses is unknown. To increase the likelihood of a correct VTE diagnosis we therefore only included patients with VTE diagnoses together with redemption of a prescription of anticoagulants (heparin or warfarin/marcoumar). Still we cannot exclude that the initial diagnosis of VTE was not in error because of the presence of other diseases (cellulitis, arthritis) mimicking VTE. Also statin users could have been taking dietary supplements or other over-the-counter medications not available in the records. These might have influenced the VTE recurrence rate.

The main limitation was the observational nature of the study. We tried to identify the most important risk factors for VTE and adjusted for them in our multivariable analyses. However, we lacked data on, for example, chemotherapy, obesity, pregnancy and recent trauma, which may have influenced our results. Unfortunately, we also lacked access to data on smoking. However, a meta-analysis from *Circulation*[39] indicates that smoking does not increase the risk of VTE. But smokers are less likely to be exposed to statins.[40] Smoking could have confounded our results and have led to overestimating the effect of statin use on the risk of VTE. Smoking is a well-known cardiovascular risk factor and by adjusting our analyses with cardiovascular diseases and cardiovascular medications we have tried to minimise the confounding effects of smoking on our results. Finally, low-dose aspirin and NSAIDs are available as over-the-counter medications; hence some patients may have been misclassified as non-users. The amount of over-the-counter low-dose aspirin in Denmark is probably low since low-dose aspirin, which is used almost exclusively for secondary prevention of cardiovascular disease, is generally prescribed by physicians, being reimbursable by up to 85% through the National Health Insurance Programme.

The observational nature of our study makes it difficult to draw a definite conclusion on whether or not statins lower the risk of recurrent VTE, but our results indicate that statins could prevent recurrent episodes of VTE.

CONCLUSION

In our study with over 40 000 patients with a previous VTE, we found that the use of statins was associated with significantly lowered risk of a recurrent VTE compared to no use of statins. Further studies on the effect of statins on prevention of recurrent VTE episodes are warranted. In particular a randomised clinical trial investigating the effect of statins on the recurrence of VTE is needed to establish the effect of statins in this clinical context.

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