Statin treatment and the risk of recurrent pulmonary embolism

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Aims
Patients with idiopathic venous thromboembolism (VTE) have a high recurrence risk during and after stopping anticoagulant treatment. Several studies suggest that treatment with statins reduces the incidence of a first episode of VTE, but data on the effects in patients with a previous episode are lacking. We examined the effect of statin therapy on the risk of recurrent pulmonary embolism (PE).

Methods and results
Using the PHARMO Record Linkage System, a Dutch population-based registry of pharmacy records linked with hospital discharge records, patients hospitalized with an acute episode of PE were identified between 1998 and 2008. Prescription-based use of statins and vitamin K antagonist (VKA) were identified starting at hospital discharge and during follow-up. The association between statin use (time-varying) and the incidence of recurrences, cardiovascular events, and death was assessed using Cox regression analysis. The mean (standard deviation) age was 61 (17) years. The median (range) duration of VKA treatment after acute PE was 199 (45–3793) days. Twenty-four per cent of the patients (n = 737) had at least one prescription of statins during the follow-up period and the median duration of statin therapy was 1557 (5–4055) days. During a median follow-up of 1529 (1–4155) days, 285 (9.2%) patients experienced a recurrence. Treatment with statins was associated with a reduced risk of recurrent PE [adjusted hazard ratio (HR) 0.50, 95% CI: 0.36–0.70], both during and after stopping VKA treatment. A dose–response relationship was shown for potency, with the largest reduction in those with the most potent statins. Finally, statin treatment also reduced the risk for cardiovascular events and all-cause mortality.

Conclusion
Statin treatment decreases the risk of recurrent PE, irrespective of VKA treatment. Treatment with statins may be an attractive alternative for anticoagulant treatment in the long-term treatment of PE.

Keywords
Statins • Recurrent pulmonary embolism • Vitamin K antagonists

Introduction

In spite of many therapeutic advances, venous thromboembolism (VTE), especially pulmonary embolism (PE), remains an important cause of morbidity and mortality in the Western world.1,2 Long-term anticoagulant therapy with vitamin K antagonists (VKAs) is highly effective in preventing VTE, but carries an increased risk of major bleeding. Nevertheless, guidelines recommend extended duration of anticoagulant treatment in patients with idiopathic VTE, since the risk of a recurrence is high.3 In fact, even during anticoagulant treatment, patients with VTE are not fully protected against a second episode of VTE, with a recurrence rate of 3% in the first 3 to 6 months.4,5 Consequently, alternative, safe options to reduce the risk of recurrent VTE are necessary.

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Numerous studies have shown a correlation between atherothrombosis and VTE,6–10 and a potential role of statin therapy in the management of VTE further supports this association.11–16 Although commonly known for their lipid-lowering effects, statins also express inhibitory effects on platelet aggregation, thrombin generation, and fibrinolysis.17

In a meta-analysis of 14, mainly observational studies, it was shown that the use of statins significantly decreased the risk of a first episode of VTE [odds ratio (OR) 0.81, 95% confidence interval (CI) 0.66–0.99].18 Recently, a large placebo-controlled randomized trial, consisting of ≈18 000 individuals with an elevated hsC-reactive protein, reported a 43% reduction in the occurrence of a first episode of VTE with the use of rosuvastatin (OR: 0.57, 95% CI: 0.37–0.86).17 Although these results seem encouraging, the number needed to treat in order to prevent a single, first episode of VTE in healthy individuals is considerable and reaches up to 2000.20 A role of statin therapy in the primary prevention of VTE therefore seems limited. Whether statin therapy might be effective in the secondary prevention of VTE is not known. As a class, statins are generally well tolerated and demonstrate good safety profiles. Therefore, statin therapy may be a promising and relatively safe alternative or supplementary treatment option in VTE patients who require long-term prevention. Using a population-based database, in which pharmacy records have been linked to hospital admissions, we assessed whether statin therapy reduces the risk of recurrent pulmonary embolism in patients with a first episode of pulmonary embolism.

Methods

Setting

Data were obtained from the PHARMO Record Linkage System (Pharmo Institute, Utrecht, the Netherlands; available at http://www.pharmo.nl). This system includes demographic details and complete medication histories of Dutch community pharmacies. The medication histories are linked to hospital discharge records. Because virtually all patients in the Netherlands are registered with a single community pharmacy, pharmacy records are essentially complete insofar as prescription drug use is concerned. For the purpose of this study, drug prescribing data and hospitalization data were used. Drugs were coded according to the Anatomical Therapeutic Chemical Classification. The hospital admission and discharge codes were coded according to the International Classification of Diseases Ninth Revision (ICD 9), Clinical Modification. Data on all-cause mortality were retrieved from the Dutch registry for mortality, coordinated by the Central Bureau for Genealogy (www.cbg.nl).

Patient selection

All patients with a first hospitalization for pulmonary embolism (ICD 126) between 1998 and 2008 were identified. Previously, the accuracy of using ICD codes for the diagnosis of PE was validated.31 Patients were eligible for inclusion if they had a prescription of VKA within 120 days after the diagnosis of PE.

The date of hospital discharge for pulmonary embolism was considered to represent the start of follow-up, i.e. cohort entry. Demographic features, including age and gender, were recorded, and potential risk factors for PE, such as trauma, surgery, and malignancy, occurring within 3 months before the occurrence of PE were retrieved by ICD codes. Also information on previous cardiovascular events, and peripheral vascular and cerebrovascular disease was assessed.

Exposure

Exposure to medication was determined, starting after discharge for a first hospitalization for PE and including claimed prescriptions of statins (C10AA) used during the follow-up. Prescriptions for the drugs contained information on the type and the dosage.

Outcome

The primary outcome of interest was an episode of symptomatic recurrent PE. Arterial cardiovascular events, myocardial infarction (ICD 410–412), stroke (ICD 433–434), peripheral atherosclerosis, arterial embolism and arterial thrombosis (ICD 440, 444), and cardiac failure (ICD 428), as well as all-cause mortality, were the secondary outcomes of interest.

Statistical analyses

Patients were followed from cohort entry to the occurrence of a study outcome or censoring (last available prescription or admission in PHARMO record linkage System or in the Dutch registry for mortality), whichever came first. The association between statin therapy and study outcome (i.e. recurrent PE, arterial cardiovascular events, all-cause mortality) was first explored by means of the Kaplan–Meier method and formally tested using the log-rank test. For this analysis, patients were divided into two groups: never and ever users of statins according to their medication status during the follow-up period. Since this method does not take into account whether statin treatment was initiated, ceased, or interrupted, we subsequently performed Cox regression analyses with time-varying statin therapy. For this analysis daily usage of statins was assessed based on pharmacy prescriptions, calculating statin treatment episodes. A treatment episode was defined as a series of subsequent prescriptions, and allowing for overlap between prescriptions. If a new prescription was given within 100 days of the theoretical end date of the previous prescription, treatment was considered to have continued. If the gap was longer, a new treatment episode was assumed. The effect of statin was expressed as the hazard ratio (HR) along with its 95% CI. A multivariable Cox regression model was used to adjust for potential confounders such as age, gender, previous cardiovascular events, provoking factors for pulmonary embolism <3 months before the first episode of PE (such as surgery and trauma), and VKA therapy as a time-varying covariate. Inclusion in the final model that constantly contains statin therapy was determined by backward stepwise elimination.

The mean reduction in the serum concentration of low-density lipoprotein (LDL) cholesterol by statin therapy varies between 10% (fluvastatin 5 mg) to 58% (rosuvastatin 40 mg).22 To compare the effect of different types of statins at different doses, statin therapy was expressed in potencies based on LDL-cholesterol reduction.22 Three potency categories were made: potency I—LDL cholesterol reduction of <20%; potency
II—LDL cholesterol reduction of 20–40%; and potency III—LDL cholesterol reduction >40% (Table 1). Patients without statin therapy were set as the reference group. Furthermore, we categorized the duration of statin therapy after the index PE into four groups (no statin use, 0–2 years, 2–5 years, and >5 years), with the category ‘no statins’ as reference. We examined the association between the occurrence of pulmonary embolism and potency or duration of statin therapy (time-varying) by means of Cox regression analysis and we adjusted for potential confounders, i.e. age, gender, prior statin use, prior hospitalizations associated with PE, and VKA therapy as a time-varying covariate. Inclusion in the final model that constantly contains potency or duration of statin therapy was determined by backward stepwise elimination.

A two-tailed P-value of 0.05 was considered to indicate statistical significance. Statistical analyses were performed with the SAS software (version 6.12; SAS Institute, Inc., Cary, NC, USA).

Results

We identified 3093 patients who were admitted to the hospital for a first episode of pulmonary embolism during 1998 and 2008, and who had a prescription of VKA within 120 days after the pulmonary embolism. Table 2 shows the baseline characteristics of the patients. The mean age (standard deviation) of the study population at baseline was 61 (17) years and 55% were female. Eight per cent of patients with an episode of PE (n = 238) had previous cardiovascular events. Based on hospitalization data, 10% (n = 299) of the patients with PE had a provoked event.

The median duration (range) of anticoagulant therapy with VKA was 199 (45–3793) days. During a median follow-up of 1529 (1–4155) days, 285 (9.2%) patients were admitted to the hospital for a recurrent episode of PE. The median time to the recurrence of PE was 400 (4–3776) days.

Association between statin therapy and recurrent PE

Seven hundred and thirty-seven (23%) PE patients had at least one prescription of statins during the follow-up period and the median duration of statin therapy was 1557 (5–4055) days. Figure 1 shows the influence of statin therapy on the time to the recurrence of PE. The time to recurrence was shorter in never users compared with ever users of statin therapy, 351 (4–3776) and 725 (5–3388) days, respectively (P < 0.001). The duration of VKA therapy was somewhat longer among ever users compared with never users of statins, 204 (48–3473) days and 198 (45–3793) days, respectively (P = 0.005).

Using a Cox proportional-hazards regression model with statin exposure as a time-varying variable, statin therapy was associated with a reduced risk of a recurrent episode of PE after adjustment for gender, VKA therapy, and previous cardiovascular events (HR: 0.50, 95% CI: 0.36–0.70) (Table 3).

Of the 285 (9.2%) patients with recurrent pulmonary embolism, 198 (6.4%) events occurred after discontinuation of VKA, while 87 (2.8%) patients had a recurrent event during treatment. The protective effect of statin therapy on recurrent pulmonary embolism

<table>
<thead>
<tr>
<th>Type of statin</th>
<th>Dose</th>
<th>Patients with a first episode of pulmonary embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All (n = 3093)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age (years), mean ± SD (range)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>238 (8.0)</td>
<td>1700 (55)</td>
</tr>
<tr>
<td>Surgery</td>
<td>213 (6.9)</td>
<td>136 (4.4)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>125 (4.0)</td>
<td>33 (1.1)</td>
</tr>
<tr>
<td>Acute infection</td>
<td>33 (1.1)</td>
<td>18 (0.6)</td>
</tr>
<tr>
<td>Trauma</td>
<td>30 (1.0)</td>
<td>7 (0.2)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>13 (0.4)</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>12 (0.4)</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>8 (0.3)</td>
<td>0 (–)</td>
</tr>
<tr>
<td>Medication usea, n (%)</td>
<td>Antihypertensive</td>
<td>1286 (41.6)</td>
</tr>
<tr>
<td></td>
<td>Antiplatelet</td>
<td>473 (15.3)</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>284 (9.2)</td>
</tr>
<tr>
<td></td>
<td>Antidiabetic</td>
<td>201 (6.5)</td>
</tr>
<tr>
<td></td>
<td>Vitamin K antagonist</td>
<td>136 (4.4)</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
<td>85 (2.7)</td>
</tr>
</tbody>
</table>

SD, standard deviation; n, number.aHospitalizations and medication use between 1 and 90 days prior to the first episode of PE.
was most pronounced during VKA therapy (adjusted HR: 0.22, 95% CI: 0.10–0.50), but also persisted after the discontinuation of VKA treatment (adjusted HR: 0.69, 95% CI: 0.48–0.99).

The most frequently used potency category of statin therapy was potency category I (20–40% LDL cholesterol reduction), which was prescribed to 547 (74%) of the patients. There was a potency-dependent effect of statins on recurrent pulmonary embolism, with the largest protection observed in strongest potency category (Figure 2). Adjusted for gender, VKA therapy and previous cardiovascular events, compared with non-statin users, the most potent statin category (III) was associated with the largest reduction in the recurrence of PE (HR: 0.29, 95% CI: 0.07–1.16) followed by potency category II (HR: 0.44, 95% CI: 0.30–0.65), and the lowest potency category (HR: 0.88 95% CI: 0.50–1.54). Although the association of the highest and lowest potency group when compared with non-statin users did not reach statistical significance, the P-for-trend was highly significant ($P < 0.001$).

Of the 737 PE patients using statins during the follow-up period, 121 (16%) were prescribed statins after their first PE for 2 years, 326 (44%) between 2 and 5 years, and 290 (39%) for >5 years.

### Table 3  Risk of recurrent pulmonary embolism, all-cause mortality, and cardiovascular events with use of statins

<table>
<thead>
<tr>
<th></th>
<th>Crude HR 95% CI</th>
<th>Adjusted HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent pulmonary embolism</td>
<td>0.54 (0.39–0.75)</td>
<td>0.50 (0.36–0.70)$^a$</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.63 (0.48–0.81)</td>
<td>0.53 (0.41–0.69)$^b$</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>0.86 (0.73–1.02)</td>
<td>0.73 (0.62–0.87)$^c$</td>
</tr>
</tbody>
</table>

HR, hazard ratio; 95% CI, 95% confidence interval.

$^a$Adjusted for gender, previous cardiovascular events, and VKA therapy (time-varying).

$^b$Adjusted for age, gender, provoking factors <3 months before the first episode of PE, and VKA therapy (time-varying).

$^c$Adjusted for age, gender, previous cardiovascular events, and VKA therapy (time-varying).
Association between statin therapy and risk of cardiovascular events and all-cause mortality

Thirteen per cent (n = 398) of the study population died during the follow-up; 324 (14%) and 74 (10%) in the group of never users and ever users of statin therapy (P = 0.009), respectively. In the multivariate Cox regression model, statin therapy was associated with a reduced risk for mortality (HR: 0.53; 95% CI: 0.41–0.69) (Table 3). Furthermore, statin therapy had a protective effect irrespective of VKA therapy (adjusted HR during VKA therapy: 0.49, 95% CI: 0.26–0.95; and adjusted HR after the cessation of VKA therapy: 0.54, 95% CI: 0.41–0.72).

As expected, the number of PE patients with a history of cardiovascular disease (CVD) was higher among the patients using statins compared with patients not using statins, 147 (20%) and 91 (4%), respectively (P < 0.0001). During follow-up, 622 (26%) of the patients who used statins experienced a cardiovascular event when compared with 314 (43%) of the patients who did not use statins. In the multivariable Cox regression analysis, statin use was associated with a lower risk for the occurrence of cardiovascular events compared with no statin use during follow-up (HR: 0.73, 95% CI: 0.62–0.87) (Table 3). The reduction in cardiovascular events was most pronounced during VKA therapy (adjusted HR: 0.60; 95% CI: 0.44–0.83), and was borderline statistically significant after the cessation of VKA (adjusted HR: 0.82; 95% CI: 0.67–1.01).

Discussion

In this analysis based on over 3000 patients with a first episode of PE and a median follow-up of 1529 days, statin therapy was associated with an ~50% reduction in the occurrence of recurrent PE. This beneficial effect was present during and after VKA treatment. Furthermore, there was an inverse dose-response relationship between potency of statin therapy and the incidence of recurrences. Finally, during follow-up, statin therapy was associated with a 30% reduction in cardiovascular events and a 50% reduction in all-cause mortality in patients with PE.
Pulmonary embolism is a relatively common disease that is associated with a substantial mortality rate of 5–15%.\textsuperscript{1,2} Especially recurrent PE carries a very high mortality rate. Preventive strategies are therefore mandatory. VKA treatment effectively reduces the risk of recurrences to 2–3%.\textsuperscript{3} After stopping treatment, over a period of five years, the recurrence rate of VTE may be as high as 30%, especially in patients with idiopathic events.\textsuperscript{23} Since patients with a high recurrence rate are difficult to identify, extended anticoagulant treatment is recommended after a first idiopathic VTE.\textsuperscript{3} This therapy, however, carries a considerable risk of major bleeding, especially in the elderly. Clinical practice could greatly benefit from alternative medication that reduces the risk of PE on the one hand and have little side effects on the other. Our findings suggest that statins may form this attractive option for long-term treatment, both as a supplement and as an alternative of VKA for long-term treatment. In the high-risk population of patients with PE, statins reduced recurrent events, not only after stopping anticoagulant treatment, but also during VKA. Furthermore, statins are relatively safe and have little side effects.

Why would statins have an effect on recurrent PE? Statins not only lower LDL-cholesterol, they also reduce tissue factor expression and thrombin generation, and attenuate fibrinogen cleavage. Furthermore, statins increase the activity of the transcription factor Kruppel-like factor 2 (KLF-2), thereby promoting thrombomodulin expression on endothelial cells, which enhances the activity of the protein C anticoagulant pathway.\textsuperscript{17}

In our study, the median duration of anticoagulant treatment was 199 days, which is in agreement with the current Dutch guideline, that recommends a treatment duration of 6 months.\textsuperscript{24} The individual duration of therapy after a first episode of PE, however, greatly varied, which was probably due to patient characteristics and preference of the treating physician. Nine per cent of the patients experienced a recurrent episode of PE during 4 years of follow-up. Almost 3% (2.9%) of the patients had an episode of PE during anticoagulant treatment, which is consistent with other studies.\textsuperscript{4,5} After stopping anticoagulant therapy, 6.4% patients had a recurrent episode of PE. In the Worcester Venous Thromboembolism Study,\textsuperscript{25} the recurrence rate of PE was 5.9% during three years of follow-up, although other studies indicate a higher risk.\textsuperscript{23}

Interestingly, statin treatment reduced all-cause mortality in the patients with PE by 50%. Unfortunately, we could not specify the cause of death, but most likely, the reduction will be caused by reduced cardiovascular mortality including PE. Statins are known to reduce mortality in patients with a history of CVD, and especially cardiovascular death, as was shown in the large Cholesterol Treatment Trialist-meta-analysis.\textsuperscript{38} Furthermore, a recent cohort study showed that statin therapy also reduced all-cause mortality in patients with pneumonia, with an adjusted HR of 0.67 (95% CI: 0.49–0.91).\textsuperscript{27}

The main strength of our study was the large cohort of unselected patients with PE who were followed for a relatively long period. The study design has some obvious limitations, which are inherent to all population-based registry studies. The diagnosis of PE was derived from ICD codes, which could raise a concern about the accuracy. However, Casez et al. recently showed that ICD discharge diagnosis codes yield satisfactory sensitivity for identifying objectively confirmed PE.\textsuperscript{21} Furthermore, to reduce misclassification, we only included patients in whom VKA treatment was started following PE. Since patients were retrieved through hospital admissions, we may have missed patients with recurrent PE, because they may have been treated as outpatients. In The Netherlands, however, guidelines clearly recommend in-hospital treatment of PE, unlike patients with venous thrombosis.\textsuperscript{24} Moreover, recurrent PE carries a high mortality risk and will be a clear indication for hospitalization. Because of frequent outpatient treatment, patients with venous thrombosis of the leg were left out of our study. Although a protective effect of statins on venous thrombosis still has to be established, prevention of recurrent PE will lead to a larger reduction in mortality. Since comorbidity could only be accessed through data on prescriptions and hospitalizations, the presence of major provoking factors for PE, such as immobilization, BMI, and smoking will certainly be underestimated. This is illustrated by the 10% of patients registered with a provoking event in our study, and by the relatively low number of recurrent episodes of PE during the follow-up. Nevertheless, in the Jupiter study, the beneficial effect of rosuvastatin was present in both idiopathic and provoked VTE. Finally, a prescription bias of statins is very likely, since patients with an increased cardiovascular risk will be prone to receive this medication. On the other hand, patients with cardiovascular risk factors have an increased risk of VTE, which only leads to an underestimation of our results. Nevertheless, there is a clear need for a randomized placebo-controlled trial of statin therapy in patients with VTE.

In conclusion, statin treatment is associated with a substantially lower risk of recurrent PE, both during and after VKA treatment. Statins may be effective as an adjunctive therapy to anticoagulant drugs in high-risk patients with PE or as an alternative to anticoagulant drugs in the long-term secondary prevention of PE. These results need to be confirmed by properly designed, randomized, placebo-controlled trials.

### Authors’ contributions

S.B.R., B.A.H., and P.W.K. interpreted the results and drafted the manuscript. B.A.H. performed the statistical analysis. All authors participated in the interpretation of the final results and editing of the manuscript. All authors read/reviewed and approved the final version of the manuscript.

### Conflicts of interest: none declared.

### References


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