Associations between cardiovascular risk factors, hyper- and hypocoagulability

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Chapter 2

Statin treatment reduces the incidence of recurrent pulmonary embolism


Submitted for publication
ABSTRACT

Background 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 VTE patients with a previous episode is lacking. We examined the effect of statin therapy on the recurrence of pulmonary embolism (PE).

Methods By use of the PHARMO Record Linkage System, a Dutch population-based registry of pharmacy records linked with hospital discharge records, patients hospitalized with an acute PE were identified between 1998 and 2008. Prescription based use of statins and vitamin K antagonists was identified starting at hospital discharge and during follow-up. Hospitalizations for recurrent PE, cardiovascular events, and death were assessed by Cox proportional hazard models with statin exposure as a time-varying covariate.

Results We identified 3093 patients with a first episode of PE with a mean age of 61.3 ± 17.0 years. The median duration of vitamin K antagonist treatment was 199 days (45-3793). Twenty-four percent of the VTE patients (n=737) had at least one prescription of statins during the follow-up period and the median duration of statin therapy was 1557 days (5-4055 days). During a median follow up of 1529 days (1-4155), 285 (9.2%) patients experienced a recurrent PE. Treatment with statins reduced recurrent PE (HR 0.48, 95%CI 0.35-0.67), and the protective effect was present both during and after stopping VKA treatment. There was a clear dose-response effect, with the largest risk reduction for the most potent statins. Finally, statin treatment also reduced CVD and all-cause mortality.

Conclusions Statin treatment decreases the risk of recurrent pulmonary embolism, irrespective of VKA treatment. Treatment with statins may be an attractive alternative for anticoagulant treatment in the long-term treatment of pulmonary embolism.
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.\textsuperscript{12} Long-term anticoagulant therapy with vitamin K antagonists is highly effective in preventing VTE, but carries an increased risk of major bleeding. Nevertheless, guidelines recommend indefinite duration of anticoagulant treatment in patients with idiopathic VTE, since the risk of a recurrence is high.\textsuperscript{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 three to six months.\textsuperscript{4,5} Consequently, alternative, safe options to reduce the risk of recurrent VTE are necessary.

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

In a meta-analysis of fourteen, mainly observational studies, it was shown that the use of statins significantly decreased the risk of a first VTE (OR 0.81, 95%CI 0.66-0.99).\textsuperscript{18} Recently, a large placebo controlled randomized trial, consisting of approximately 18000 healthy individuals, reported a 43% reduction in the occurrence of VTE with use of rosvastatin (OR 0.57, 95%CI, 0.37-0.86).\textsuperscript{19} 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.\textsuperscript{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 hospital admissions have been linked to pharmacy records, we assessed whether statin therapy reduces the risk of recurrent VTE and whether this effect is dose-dependent.

METHODS

Setting

All patients were recruited via 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 was retrieved from the Dutch registry for mortality, coordinated by the Central Bureau for Genealogy (www.cbg.nl).

**Patient selection**

All patients, aged 18 years and older with a first hospitalization for PE (ICD I26) between 1998 and 2006, were identified. Previously, the accuracy of using ICD codes for the diagnosis of pulmonary embolism (PE) was validated. Patients were eligible for inclusion if they had a prescription of vitamin K antagonists within 120 days after the diagnosis of PE.

The date of hospital discharge for PE was considered to represent the start of follow-up i.e. cohort entry. Demographic features, including age and gender, were recorded, and previous hospital records potentially associated with a higher risk of VTE (i.e. trauma/ fractures (ICD 800-869, 76-81), malignancy (ICD 150-157,162,172,174,179,180,182,183,185,188, 201-208), pregnancy and pregnancy, labor and delivery related complications (ICD 640-669), myocardial infarction (ICD 410-412), stroke (ICD 433-434), peripheral atherosclerosis, arterial embolism and arterial thrombosis (ICD 440,444), diabetes mellitus (ICD 250), rheumatoid arthritis (ICD 714), pneumonia (ICD 480-488), chronic respiratory failure (490-496), cardiac failure (ICD 428), urinary tract infection (ICD 590,594), nephrolithiasis (ICD 592,594), nephrectomy (ICD 55.5), non-infectious colitis (555-558) prostatectomy, pancreatic disease (ICD 571), liver disease (ICD 571-572), appendectomy (ICD 47), hysterectomy (ICD 68), cholelithiasis (ICD 574) and obesity (ICD 278)) occurring within three months prior to the PE, were retrieved. Hospitalizations (co-morbidity) prior to this period were less likely to have influenced the occurrence of PE on the index date. Furthermore, hospitalizations for cardiovascular events were also assessed during the follow-up period.

**Exposure**

Exposure to medication was determined starting within 120 days after discharge for a first hospitalization for pulmonary embolism and claimed prescriptions of both statins and VKA were used during follow-up. Prescriptions for the drugs contained information on type and dosage.

**Outcome**

The primary outcome of interest was an episode of symptomatic and recurrent pulmonary embolism. Arterial cardiovascular events (i.e. acute coronary syndrome consisting of myocardial infarction and other (sub) acute coronary events, ischemic stroke) as well as all-cause mortality were the secondary outcomes of interest.
**Statistical analyses**

Data was expressed as means ± SD or medians with range, depending on the distribution of the data. Baseline characteristics were compared using t-test for continuous variable and X² test for categorical data. Incidence rates, hazard ratios and number needed to treat were assessed. The strength of the association between statin therapy and outcomes was assessed by use of Cox proportional-hazards regression model, with statin exposure as a time-varying covariate. Statin therapy was assessed as a time-varying covariate to take into account whether or not statin therapy was stopped, interrupted or whether a patient had switched from one statin type to another, so that any potential beneficial effect could only be present while taking statin drugs. 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, allowing for overlap between prescriptions. If a new prescription occurred within 120 days of the theoretical end date of the previous prescription, treatment was considered to have been continued. If the gap was longer or when patients switched between statins, a new treatment episode was assumed. Patients were followed from cohort-entry to the occurrence of a study outcome or end of follow-up data (e.g. prescriptions, hospitalizations) whichever came first. According to the episodes of statin use obtained, patients were classified according to statin exposure status, where patients were classified as either exposed or non-exposed. Secondary analyses were also performed using time-varying covariates for statin exposure during follow-up. The effect of statin was expressed as the adjusted hazard ratio (HR) along with its 95% confidence interval (CI). The influence of possible confounding factors was first analyzed in a univariate model. All variables with a significant association with the outcome (p-value <0.05) were then added to the multivariate model. Using backward modeling, if a significant contribution disappeared in the multivariate model, the variable was removed. The variables assessed were age, gender, previous cardiovascular events, prior hospitalizations associated with an increased risk of PE and vitamin K antagonist therapy (VKA).

The average reduction of serum concentration of low density lipoprotein (LDL) cholesterol by statin therapy varies for the type and daily dose used. To compare the effect of different types of statins at different doses, statin therapy is expressed in potencies. In the present study statin potency was divided in three categories, with the first category being set as the reference category. Drugs with a potency of 1.0-1.3 were classified as potency category 1, drugs with a potency between 1.4 and 1.8 were classified as potency category 2 and drugs with a potency of ≥ 1.9 were classified as potency category 3 (Table 1). Statistical analyses were performed with SAS software (version 6.12; SAS Institute, Inc, Cary, North Carolina).
Table 1. Type, dose and potency of statins

<table>
<thead>
<tr>
<th>Type</th>
<th>Dose</th>
<th>Potency</th>
<th>Dose</th>
<th>Potency</th>
<th>Dose</th>
<th>Potency</th>
<th>Dose</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10</td>
<td>1.6</td>
<td>20</td>
<td>1.8</td>
<td>40</td>
<td>2.0</td>
<td>80</td>
<td>2.2</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>10</td>
<td>1.2</td>
<td>20</td>
<td>1.3</td>
<td>40</td>
<td>1.4</td>
<td>80</td>
<td>1.5</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10</td>
<td>1.3</td>
<td>20</td>
<td>1.3</td>
<td>40</td>
<td>1.4</td>
<td>80</td>
<td>1.5</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10</td>
<td>1.8</td>
<td>20</td>
<td>1.9</td>
<td>40</td>
<td>2.1</td>
<td>80</td>
<td>2.4</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10</td>
<td>1.4</td>
<td>20</td>
<td>1.5</td>
<td>40</td>
<td>1.6</td>
<td>80</td>
<td>1.7</td>
</tr>
</tbody>
</table>

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 vitamin K antagonists within 120 days after the PE. Table 2 shows the baseline characteristics of the patients. The mean age of the study population at baseline was $61 \pm 17$ years and 55% was female. Eight percent of patients with pulmonary embolism ($n=238$) had previous cardiovascular events and based on hospitalisation data, 10% ($n=299$) of the patients with PE had a provoked event. Four percent had a malignancy, whereas 8% had a trauma or surgery (Table 2).

Table 2. Baseline characteristics

<table>
<thead>
<tr>
<th>Cases (n=3093)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>61.3 ± 17.0</td>
</tr>
<tr>
<td>Sex, female</td>
<td>1700 (55)</td>
</tr>
<tr>
<td>Idiopathic VTE</td>
<td>2794 (90.3)</td>
</tr>
<tr>
<td>Previous hospitalizations*</td>
<td></td>
</tr>
<tr>
<td>Acute Infection</td>
<td>33 (1.1)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>12 (0.4)</td>
</tr>
<tr>
<td>Surgery</td>
<td>213 (6.9)</td>
</tr>
<tr>
<td>Trauma</td>
<td>30 (1.0)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>13 (0.4)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>238 (8.0)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>125 (4.0)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>8 (0.3)</td>
</tr>
<tr>
<td>Medication use*</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>85 (2.7)</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>473 (15.3)</td>
</tr>
<tr>
<td>Coumarins</td>
<td>136 (4.4)</td>
</tr>
<tr>
<td>Antihypertensives^</td>
<td>1286 (41.6)</td>
</tr>
<tr>
<td>Anti-diabetes drugs^</td>
<td>201 (6.5)</td>
</tr>
</tbody>
</table>

* Hospitalizations and medication use ≤90 days and ≥ 1 day prior to index date
^ Combination of hospitalizations and medication use
The median duration of anticoagulant therapy with vitamin K antagonist was 199 days (45-3793). During a median follow-up of 1529 days (1-4155), 285 (9.2%) patients were admitted to the hospital for a recurrent pulmonary embolism. The median time to recurrence of pulmonary embolism was 400 days (4-3776).

**Effect of statin therapy on recurrent pulmonary embolism**

Seven hundred thirty-seven (23%) VTE patients had at least one prescription of statins during the follow-up period and the median duration of statin therapy was 1557 days (5-4055 days). Figure 1 shows the influence of statin therapy on time to recurrent pulmonary embolism. The time to recurrence was shorter in never users compared to ever users of statin therapy, 351 (4-3776) and 725 (5-3388) days, respectively (p<0.001). The duration of VKA therapy was however somewhat longer among ever compared to never users of statins, 204 days (48-3473) and 198 days (45-3793), respectively (p=0.0049).

Using a cox proportional-hazards regression model, with statin exposure as a time-varying covariate, compared with never users, ever users of statin had a decreased risk of recurrent pulmonary embolism after adjustment for age, gender, vitamin K antagonist therapy and previous cardiovascular events (HR 0.48, 95%CI 0.35-0.67). The number of VTE patients needed to treat to prevent one recurrent pulmonary embolism was 26.
Of the 285 (9.2%) patients with recurrent PE, 198 (6.4%) events occurred after discontinuation of VKA, while 87 (2.8%) patients had a recurrent event during treatment. The effect of statin therapy on recurrent pulmonary embolism was most pronounced during VKA therapy (HR 0.21, 95%CI 0.09-0.47) but also persisted after discontinuation of VKA treatment (HR 0.66, 95%CI 0.46-0.94).

Association between statin therapy and risk of cardiovascular events and all-cause mortality

Thirteen percent (n=398) of the VTE population died during follow-up. The number of deaths in never users was higher than in ever users of statin therapy: 324 (14%) and 74 (10%), respectively (HR 0.51; 95%CI 0.39-0.66). Furthermore, statin therapy had a protective effect irrespective of VKA therapy (HR during VKA: 0.50, 95%CI 0.26-0.95, and HR 0.51, 95%CI 0.38-0.67 without VKA therapy). The number of VTE patients needed to treat to prevent one death (of any cause) was 25.

As expected, the number of VTE patients with a history of CVD was higher among the patients using statins compared to non-statin population, 147 (20%) and 91 (4%), respectively (p<0.0001). Nevertheless, statin use was associated with a lower occurrence of cardiovascular events during follow-up compared to the patients that did not use statins, 622 (26%) and 314 (43%), respectively (HR 0.73, 95%CI 0.62-0.87). The reduction in cardiovascular events was most pronounced during vitamin K antagonist therapy (HR 0.60; 95%CI; 0.43-0.83), although this effect persisted after cessation of vitamin K antagonist therapy (HR 0.80; 95%CI 0.65-0.98). The number of VTE patients needed to treat with statins to prevent one CVD was 6.

Association between potency of statin and risk of pulmonary embolism

Finally, the influence of the potency of statins and the effect on recurrent PE was assessed. The most frequently used potency of statin therapy was 1.4-1.8, which was prescribed to 547 (74%) of the VTE patients. Less patients used lower (1.0-1.3) or higher potency (≥ 1.9) drugs (135 (18%) and 55 (7%), respectively).

There was a clear potency-dependent effect of statins on recurrent PE, with the largest protection observed in strongest potency category. Compared to the lowest potency (1.0-1.3), the most potent statins (≥ 1.9) seemed to be associated with the largest reduction in recurrent PE (HR 0.28, 95%CI 0.07-1.15), followed by the 1.4-1.8 category (HR 0.43, 95% CI 0.29-0.63), although this association of the highest potency group did not reach statistical significance. The effect of potency was also evident for cardiovascular events (potency ≥ 1.9: 37% reduction (statistically not significant) and potency 1.4-1.8: 28% reduction), whereas for mortality the most potent drugs (potency ≥ 1.9) showed a non-significant reduction of 35% and statins with a potency of 1.4-1.8 showed a larger reduction (50%).
DISCUSSION

In an analysis based on over 3000 patients with a first episode of pulmonary embolism, with a median follow-up of 1529 days, statin therapy was associated with an approximately 50% reduction in the occurrence of recurrent pulmonary embolism. This beneficial effect was present during and after VKA treatment. Furthermore, there was a dose-dependent effect on recurrent events of pulmonary embolism, with the greatest reduction associated with high potency drugs. Finally, during follow-up, statin therapy resulted in a 30% reduction in cardiovascular events and a 50% reduction in all-cause mortality in patients with pulmonary embolism.

Several studies have analysed the effect of statin therapy on the prevention of a first episode of venous thromboembolism. Both observational as well as case-controls studies showed risk reductions ranging from 22% to 58%.11-16 Recently, in the large randomized placebo-controlled Jupiter trial, rosvustatin 20 mg was associated with a risk reduction of 43% (95% CI 0.37-0.86) of VTE in almost 18,000 apparently healthy individuals.19 A recent meta-analysis showed an overall reduction of 20% (95% CI 0.66-0.99) on primary VTE among statin users.18 Although the reduction in VTE with use of statins may seem consistent and relatively large, with an VTE incidence of around 1 in 1000, this results in a high number needed to treat of over 2000.20 In the present study the number of VTE patients needed to treat to prevent one single recurrent episode was only 26. If cardiovascular events and all-cause mortality are taken into account, the number needed to treat will drop even further.

Pulmonary embolism is a relatively common disease that is associated with a high mortality rate of 5-15%.1,2 Especially recurrent pulmonary embolism carries a very high mortality rate. Preventive strategies are therefore mandatory. VKA treatment effectively reduces the risk of recurrences to around 3%.4,5 After stopping treatment, over a period of three to five years, the recurrence rate of VTE reaches up to 30%, especially in patients with idiopathic events.23 Since patients with a high recurrence rate are difficult to identify, lifelong anticoagulant treatment is recommended after a first idiopathic VTE.3 This therapy however carries a considerable risk of major bleeding, especially in the elderly. Clinical practice could greatly benefit from other medication options that reduce the risk of pulmonary embolism on the one hand and have little side effects on the other. Our study shows that statins may form this attractive option for long-term treatment, since in the high-risk population of patients with pulmonary embolism, statins reduced recurrent events, not only after stopping anticoagulant treatment, but also during VKA. Furthermore, statins are safe and have little side effects. Also, high risk VTE patients in whom anticoagulation is relatively contraindicated might benefit from statin therapy, although the period conferring the highest risk should still be covered by use of conventional anticoagulant therapy.

Why would statins have an effect on recurrent pulmonary embolism? 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.\(^7\)

In our study, the median duration of anticoagulant treatment was 199 days, which is in agreement with the current Dutch guidelines, that recommend a treatment duration of 6 months.\(^4\) 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 percent of the patients experienced a recurrent PE during 4 years of follow-up. Almost three percent (2.9\%) of the patients had a PE during anticoagulant treatment, which is consistent with other studies.\(^4,5\) After stopping anticoagulant therapy, 6.4\% patients had a recurrent PE. In the Worcester Venous Thromboembolism Study,\(^25\) the recurrence rate of PE was 5.9\% during three years of follow-up, although other studies indicate a higher risk.\(^3\)

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 and mortality due to PE. Statins are known to reduce mortality in patients with a history of cardiovascular disease, and especially cardiovascular death, as was shown in the large CTT-meta-analysis.\(^26\) Furthermore, a recent cohort study showed that statin therapy also reduced all-cause mortality in patients with pneumonia, with an adjusted hazard ratio of 0.67 (95\% CI 0.49-0.91).\(^27\)

The main strength of our study was the large cohort of unselected patients with pulmonary embolism, which were followed for a relatively long period with complete data on medication use and hospitalizations. The study design has some obvious limitations, which are inherent to all population based registry studies. The diagnosis of pulmonary embolism was derived from ICD-codes, which could raise concern about the accuracy. However, Cazes et al.\(^21\) recently showed that ICD discharge diagnosis codes yield satisfactory sensitivity for identifying objectively confirmed PE. Since comorbidity could only be assessed through data on hospitalisations, patients with provoking factors for pulmonary embolism, such as immobilisation, waist circumference, BMI and smoking will be underestimated. Nevertheless, this will be the case for both patients and controls and it is unlikely that this will have influenced outcome. Next, we only assessed patients with pulmonary embolism, leaving out patients with venous thrombosis of the legs. Since patients were retrieved through hospital admissions, and venous thrombosis of the legs is increasingly being treated out of hospital, including these patients in our analysis would have introduced a selection bias.

Although a protective effect of statins on venous thrombosis still has to be established, prevention of recurrent pulmonary embolism will lead to a larger reduction of mortality. 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 events have an increased risk of VTE, which only leads to an underestimation of our results. Nevertheless, there is a clear need for a randomised placebo controlled trial of statin therapy in patients with VTE.
In conclusion, statin treatment decreases the risk of recurrent pulmonary embolism substantially, both during and after VKA treatment. Treatment with statins may be an attractive addition to or alternative for anticoagulant treatment in the long-term treatment of pulmonary embolism.
REFERENCES


