Associations between cardiovascular risk factors, hyper- and hypocoagulability
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Chapter 4

High proportion of patients with venous thrombo-embolism already have an indication for statin therapy

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ABSTRACT

Introduction Recent data suggests an association between venous thrombo-embolism (VTE) and cardiovascular disease (CVD), and a protective effect of statin therapy on VTE. It is however unclear how many VTE patients already require statin treatment. The proportion of VTE patients with an indication for statin therapy was assessed and compared to matched control subjects.

Methods Consecutive VTE patients aged > 40 years were enrolled and matched to controls without VTE. The total number of subjects with either documented CVD, statin use, or with an increased risk of CVD, assessed by an established European risk prediction algorithm (SCORE), was compared between VTE patients and controls.

Results Hundred fifty-seven VTE patients and 364 controls were enrolled. The mean age was 60 ± 11 years. Thirty-one (20%) VTE patients had a history of CVD, compared to 19 (5%) controls (p<0.001). Twenty-seven VTE patients and forty-two controls (without CVD) received statins (21% and 12% respectively p=0.009). Among the non-statin users, 3 (3%) VTE patients and 2 (1%) controls had diabetes and were ≥50 years (p=0.06). Of the remaining subjects, ten (11%) VTE patients and 57 controls (19%) had a high risk SCORE (p=0.02). Overall, 71 (45%) VTE patients had an indication for statin therapy compared to 120 (33%) controls (p=0.008).

Conclusion Although the exact role of statin therapy for the prevention of recurrent VTE remains to be elucidated, the present study illustrates that in a substantial proportion of VTE patients, statin therapy is already indicated for the prevention of CVD.
INTRODUCTION

Venous thrombosis is a common disease entity, associated with considerable morbidity and mortality. Prior studies have shown that patients with venous thromboembolism (VTE) have a two- to threefold higher incidence of subsequent cardiovascular disease (CVD) [1,2], which is most evident for unprovoked VTE. An association between venous and arterial thrombosis is further supported by shared risk factors [3-8]. For decades differences in localisation and clinical presentation have implied a different mechanism of disease as well as distinct management strategies. At present, however, similar treatment options are considered. The efficacy of drugs that have shown great benefit in the primary and secondary prevention of CVD, such as lipid lowering compounds, is being studied for the prevention of VTE [9-14]. Recently, in the large randomized placebo controlled Jupiter trial, rosuvastatin reduced the risk of a first episode of VTE in apparently healthy individuals who had an increased hsCRP level [15].

The risk of recurrence is substantial in patients with idiopathic VTE [16], with a recurrence rate of 20–25% in three to five years, and therefore life-long anticoagulant therapy is often recommended [17]. This however comes at the expense of an increased risk of bleeding complications [18]. Since evidence supports a protective effect of statin therapy, VTE patients requiring long-term treatment, especially those with a relative contraindication for anticoagulant therapy, could potentially benefit from this new treatment option.

At the same time, it is unclear how many VTE patients already use statins or have an indication for statin therapy. We, therefore, assessed the total number of patients with documented VTE who were either treated with statins or who had an indication for statin therapy because of an increased risk of cardiovascular mortality. These findings were compared to numbers in matched controls derived from the general population.

METHODS

Study design

A case-control study was performed to evaluate the proportion of VTE patients with an indication for treatment with statins, among patients with a recent episode of provoked or unprovoked venous thromboembolism (VTE). The study had been approved by the local medical ethics committees. All patients were enrolled at a minimum of three months and maximally one year after the VTE event. All inclusions took place in the period between February 2009 and September 2010 at the Academic Medical Centre, Amsterdam, the Netherlands (AMC), the University Hospital Leuven, Belgium (UZL), and the University of Insubria, Varese, Italy. All consecutive patients aged 40 years and older, diagnosed with a first or recurrent episode of either deep venous thrombosis (DVT) or pulmonary embolism (PE), were enrolled after informed consent had been obtained. The diagnosis of PE was confirmed by a multislice CT scan or ventilation perfusion scintigraphy, and
DVT was diagnosed by ultrasonography. VTE was classified as unprovoked if it occurred in the absence of any recent trauma, hospitalization, pregnancy, use of oral anticonceptives or surgery (i.e., occurring within 3 months before the event), and in the absence of a malignancy that was diagnosed before the event. Subjects were classified as having a positive history of CVD if a history of coronary heart disease, cerebrovascular disease or peripheral arterial disease was documented in their medical charts. Blood sampling only took place in individuals without a history of CVD and in those in whom no indication for statin therapy had yet been made by treating physicians. A fasting blood sample was obtained on one occasion (including glucose, total cholesterol, LDL-cholesterol and HDL-cholesterol and triglyceride levels). Total cholesterol (TC) levels, LDL cholesterol and triglyceride levels were considered to be increased when they exceeded the 95th percentile of the reference values of the concerning age categories. HDL levels were considered to be low when they were below the 5th percentile of the reference values of the concerning age categories. Dyslipidemia was considered to be present if lipid levels exceeded the 95th percentile or were below 5th percentile of the reference values or if use of lipid lowering drugs was reported. Diabetes mellitus was defined as fasting glucose levels > 7.0 mmol/L or the use of diabetes medication. Blood pressure, weight and height were measured and the body mass index (BMI) was calculated. Hypertension was defined a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg during a single measurement or if use of anti-hypertensives was reported.

To further specify the expected risk associated with these risk factors, the 10-year cardiovascular mortality risk was calculated with The European risk prediction system, Systemic Coronary Risk Evaluation (SCORE) in subjects with no history of CVD, who had no diabetes and who did not use statin therapy [19]. This risk score results in a percentage as a risk estimate for cardiovascular death and is based on age, sex, smoking habits, systolic blood pressure and either total cholesterol or cholesterol/HDL ratio. It estimates the total mortality due to ischemic heart disease and stroke. A score between 5 and 10% confers an intermediate risk in which intervention can be considered. A score of higher than 10% confers a high risk, necessitating intervention. Statin therapy was considered to be medically ‘indicated’ in subjects already using statins, subjects with a history of CVD, patients with diabetes of 50 years and older, and finally in subjects with an intermediate or high risk.

Control subjects were a representation of the general Dutch population, consisting of healthy employees of Dutch companies, who underwent screening for cardiovascular risk factors. The controls were not allowed to have a history of venous thromboembolism and were matched for gender and age.

Statistical analysis

Data was analyzed using SPSS Statistical Software version 16.0. Baseline characteristics were summarised in case of normally distributed data by means and standard deviations (SD) and by using medians and ranges in case of skewed distributed data. Student’s t-test was applied for continuous variables and by $\chi^2$-test for discrete variables.
RESULTS

Baseline characteristics of the study population are shown in Table 1. A total of 157 consecutive patients with documented VTE were compared to 394 age- and gender matched controls. The mean age of the study population was 60 (±11) years and 61% was male. The average time from diagnosis of VTE till inclusion in the study was 5.2 (± 2.9) months. In 61% of VTE patients the event was unprovoked. The two most common provoking factors for VTE were immobilisation either in relation to trauma or surgery (33%) and malignancy (10%). Forty-one percent of the VTE patients had a DVT, 36% had suffered from a PE, whereas in 23% a combination of DVT and PE was present. Twenty percent of the patients had a recurrent episode of VTE.

Cardiovascular disease was more prevalent among VTE patients. Thirty-one (20%) VTE patients had a history of CVD, compared to 19 (5%) controls (p<0.001). Forty-seven VTE patients and controls (both without a history of CVD) received statins (30% and 13%, respectively, p=0.009). Furthermore, among both the cases and controls, subjects with CVD were on average 10 years older compared to non-CVD subjects not on statins (70 and 60 years respectively). Statin users without a history of CVD (both VTE patients and controls) were on average 5 years older than subjects not treated with statins. Among the VTE patients who had a positive history of CVD, the majority suffered from an unprovoked VTE (58%), which was similar to that in VTE patients without a previous CVD, 63% (p=0.93).

Among the VTE patients without CVD and who were not treated with statins, BMI (28.9 kg/m2 ±7.5 and 25.6 kg/m2 ± 3.6, respectively, p<0.001), and glucose levels (5.3 mmol/l (3.7-10.2) and
5.1 mmol/l (3.1-11.9) respectively, p=0.006) were higher compared to the controls. On the other hand, mean levels of total cholesterol (6.01 mmol/l ± 1.08 and 5.49 mmol/l ±1.07, p<0.001) and LDL cholesterol (3.74 mmol/l ± 0.93 and 3.43 mmol/l ± 0.97, p=0.007) were slightly higher among controls. HDL cholesterol and triglyceride levels were not different between the two groups (Table 2). Dyslipidemia, hypertension and diabetes mellitus were equally prevalent among VTE patients and controls (Table 1).

Table 2. (Laboratory) measurements in subjects without a history of cardiovascular disease and not using statins

<table>
<thead>
<tr>
<th></th>
<th>VTE (n=97)</th>
<th>Controls (n=303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>5.49 ± 1.07</td>
<td>6.01 ± 1.08</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.48 ± 0.42</td>
<td>1.57 ± 0.42</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.43 ± 0.97</td>
<td>3.74 ± 0.93</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.25 (0.41-9.03)</td>
<td>1.39 (0.47-8.01)</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.3 (3.7-10.2)</td>
<td>5.1 (3.1-11.9)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>150.2 ± 96.5</td>
<td>138.7 ± 20.7</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>96.6 ± 103.7</td>
<td>85.0 ± 10.9</td>
</tr>
</tbody>
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\[a p<0.05, VTE; venous thromboembolism\]

**Cardiovascular risk assessment and indication for statins**

The CVD mortality risk was assessed in all subjects not receiving statin therapy, who did not have diabetes or a history of CVD. The median 10-year risk of fatal cardiovascular disease in VTE patients was 3% (0.1-31), which was comparable to the control subjects (3%, 0.1-98, p=0.17). The percentage of VTE patients with an increased cardiovascular mortality (10-year cardiovascular mortality risk >5%) risk score (37%) was similar to that in the controls (37%) (p=0.99). However, the number of subjects with a high 10-year cardiovascular mortality risk of >10% was higher among controls than VTE patients (19% and 11% respectively, p=0.02) (Table 3).

Subsequently we evaluated which patients were using or had an indication for statin therapy. Among the 157 VTE patients, 31 (20%) patients had documented CVD, 27 (21%) patients without previous CVD received statins, 3 patients had diabetes and were older than 50 years, and another 35 patients had a potential indication for statins, based on the intermediate to high cardiovascular mortality risk. This means that a total of 96 (61%) patients with VTE had an indication for statin treatment or were already using statins. Among the 364 control subjects, 19 (5%) had CVD, 42 (12%) were using statins, 2 subjects had diabetes and were aged 50 years or older, and 110 had a high cardiovascular risk. A total of 173 (48%) of the control persons therefore had an indication for, or were already using statins (p=0.004 for difference between the two groups).

After excluding individuals with an intermediate risk, 71 (45%) of the VTE patients and 120 (33%) of the controls had a definite indication for statin therapy (Table 3) (p=0.008). At least 8% of the VTE patients were not receiving statin therapy (reaching up to 24% patients if VTE patients with an intermediate risk are also included), in spite of a clearly increased cardiovascular mortality risk.
The number of subjects with a statin indication was comparable among VTE patients with provoked and unprovoked disease. VTE patients with a history of CVD, non-CVD patients using statin therapy, diabetes patients aged >50 years and VTE patients with a risk >5%, 59 (61%) patients with unprovoked VTE compared to 32 (58%) patients with provoked VTE (p=0.31) used statins or had a statin indication. After excluding individuals with an intermediate risk, the number of VTE patients requiring statin therapy reduced to 39 (41%) in patients with unprovoked VTE and to 27 (49%) in patients with provoked VTE (p=0.30). Compared to the control subjects, the percentage of VTE patients with either provoked or unprovoked VTE who had an indication for statin therapy, was not

**DISCUSSION**

Since recent studies suggest that statin treatment reduces the risk of VTE, we assessed the proportion of VTE patients who already have an indication for statin therapy. The present study shows that in a substantial number of VTE patients, statin therapy is already prescribed or indicated based on their CVD risk. Forty-five percent of the studied VTE population had an indication for statin therapy, which was more than in the control population (33%).

Our findings confirm previous reports describing an association between CVD and VTE [1,2]. Not only was there a higher prevalence of CVD necessitating statin therapy in VTE patients, also in the patients without CVD, the use of statin therapy was more prevalent in VTE patients than controls. In subjects without proven CVD and not using statin therapy, cardiovascular mortality risk based on the SCORE, was comparable between VTE patients and the control group. Given the fact that these prediction models have not been validated for this specific patient population, these outcomes should be interpreted with caution. Furthermore, the present study confirms previous reports which show the association between CVD and VTE is most evident for unprovoked VTE [1], since the prevalence of CVD was highest in subjects with unprovoked VTE.

Nevertheless, although evidence on an association between VTE and CVD is accumulating, 8% (possibly reaching up to 24%) of the VTE patients had an indication for statin therapy, but this was not recognised by the treating physicians.

**Table 3.** SCORE in VTE patients and controls without previous CVD or statin use

<table>
<thead>
<tr>
<th>SCORE</th>
<th>VTE</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects, n (%)</td>
<td>94 (60%)</td>
<td>301 (83%)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.73% (0.07-31.4)</td>
<td>3.40% (0.05-98.0)</td>
</tr>
<tr>
<td>Intermediate and high (5-10%)</td>
<td>35 (37%)</td>
<td>110 (37%)</td>
</tr>
<tr>
<td>High (&gt;10%)</td>
<td>10 (11%)</td>
<td>57 (19%)</td>
</tr>
</tbody>
</table>

Score; Systemic Coronary Risk Evaluation
Score was calculated in subjects without CVD, not using statins or diabetes medication
Overlapping risk factors for CVD and VTE most likely directly underlie the combined risk of both arterial and venous thrombosis. Numerous classical risk factors have previously been associated with VTE, and the association has been most consistent for obesity [3, 5-7,20]. In the present study indeed BMI was on average higher in the VTE patients. Whether or not diabetes mellitus and hypertension are associated with VTE is not clear [5-7,20]. Although our findings suggest a similar prevalence of diabetes and hypertension, glucose levels were on average significantly higher among the VTE patients than controls. No clear association between dyslipidemia, lipid levels and VTE was seen, which is supported by literature [5-7]. The potential mechanisms by which statins are thought to prevent VTE is not by improvements in lipid profile, but instead have been explained by effects on the vascular endothelium, platelet aggregation, specific coagulation factors, fibrin generation, fibrinolysis and inflammation [21,22].

The present study had some limitations which were associated with the design of the study. Although patients were prospectively included, statin therapy and previous cardiovascular events were collected in a retrospective manner. The exact indication as well as the time of initiation of statins could not be evaluated.

In summary, trials assessing which patients could potentially benefit from statin therapy next to their conventional therapy with anticoagulants are expected in the near future. The present study however shows that a substantial proportion of the VTE patients are being treated with statins or have a clear indication for statin therapy to prevent CVD. Therefore, irrespective of a potential place for statins in the prevention of recurrent VTE, a high number of VTE patients already has an indication for statin therapy. The present findings should further increase awareness among treating physicians of the increased CVD risk in VTE patients.
REFERENCES


