Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study

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Summary

Background In some studies, venous thromboembolism has been associated with atherosclerosis and with the risk of arterial cardiovascular events such as myocardial infarction and stroke. Other studies, however, do not show this association. To help clarify these discrepant findings, we aimed to investigate the risk of arterial cardiovascular events in patients who were diagnosed with venous thromboembolism.

Methods We undertook a 20-year population-based cohort study using data from nationwide Danish medical databases. After excluding those with known cardiovascular disease, we assessed the risk of myocardial infarction and stroke in 25 199 patients with deep venous thrombosis, 16 925 patients with pulmonary embolism, and 163 566 population controls.

Findings For patients with deep venous thrombosis, the relative risks varied from 1·60 for myocardial infarction (95% CI 1·35–1·91) to 2·19 (1·85–2·60) for stroke in the first year after the thrombotic event. For patients with pulmonary embolism, the relative risks in that year were 2·60 (2·14–3·14) for myocardial infarction and 2·93 (2·34–3·66) for stroke. The relative risks were also raised, though less markedly, during the subsequent 20 years of follow-up, with 20–40% increases in risk for arterial cardiovascular events. Relative risks were similar for those with provoked and unprovoked deep venous thrombosis and pulmonary embolism.

Interpretation Patients with venous thromboembolism have a substantially increased long-term risk of subsequent arterial cardiovascular events.

Introduction

Venous thromboembolism is a common and serious disorder in Western countries, with hospital admission rates that seem to be increasing.1–4 Venous thromboembolic disorders are generally considered to be distinct from thrombotic atherosclerotic diseases, since arterial thrombi consist mainly of platelets, in contrast to venous thrombi, which mainly consist of red blood cells and fibrin.5

In 2003, an association between venous thromboembolism and markers of atherosclerosis was reported, suggesting that both conditions share activation of blood coagulation and platelets.6 In this case-control study, patients with unprovoked venous thromboembolism had a higher prevalence of asymptomatic carotid atherosclerosis than did patients with secondary thrombosis and age-matched and sex-matched hospital controls without venous thrombosis.7 Another case-control study, showing an increased prevalence of coronary calcification in patients with unprovoked venous thromboembolism, supported the observation.7

In contrast, two other studies failed to find a relation between atherosclerosis and venous thromboembolism.8,9 These investigations looked at the risk of subsequent venous thromboembolism in patients with and without non-invasive markers of atherosclerosis.8,9 A cross-sectional autopsy study provided inconclusive data.9 In other reports, patients who had venous thrombosis or pulmonary embolism (especially those with an unprovoked event) had an increased risk of atherosclerotic cardiovascular events.10–15 However, most of these investigations were clinic-based studies from referral centres with few outcomes, and so their interpretation is limited.13–15 Thus whether venous thromboembolism is associated with arterial cardiovascular morbidity, and if so, to what extent, is not clear.

Data on this issue are important, as they could foster the understanding of both venous thrombosis and atherosclerotic disease, and provide further insight into the clinical course of patients with venous thromboembolism. We therefore undertook a large, population-based assessment of the risk of hospitalisation due to acute myocardial infarction and stroke after a diagnosis of venous thromboembolism, using data from Danish medical databases.11–13

Methods

Patients and procedures

With the approval of the Danish Registry Board we obtained data from the Danish National Registry of Patients, which since 1977 has recorded 99.4% of all discharges from Danish acute-care non-psychiatric hospitals.16–18 The recorded information includes: dates of hospital admission and discharge, surgical procedures done, and up to 20 discharge diagnoses, classified according to the International Classification of Diseases,
8th revision (ICD-8) until Dec 31, 1993, and according to the 10th revision thereafter. In all Danish medical registries, patients are identified through the civil registration number. These are unique identifiers, assigned at birth, and stored in the Danish Civil Registration System along with date of birth, residency status, and dates of immigration, emigration, and death (if any).

To form a cohort of individuals with venous thromboembolism and no history of cardiovascular disease, we identified the first recorded inpatient hospital discharge diagnosis of lower limb deep venous thrombosis, or pulmonary embolism, or both, between Jan 1, 1980, and Dec 31, 2005, in all Danish residents aged at least 40 years. Using the civil registration number, we searched the National Registry of Patients to identify and exclude cases with any previous or concurrent discharge diagnosis of cardiovascular disease. We also excluded those with a venous thromboembolism diagnosis during the first three years of the registry’s running (1977–79) to avoid including patients treated for complications or recurrence of previous thromboembolism.

We defined provoked venous thromboembolism cases as those with a diagnosed malignancy before or within 90 days after the thrombotic event in the hospital registry, and those with a discharge diagnosis of fracture, surgery, trauma, or pregnancy within 90 days before the hospitalisation for venous thromboembolism.18 The remaining venous thromboembolism cohort members were classified as unprovoked.18

We formed a population-based control cohort using the Danish Civil Registration System.19 For each patient in the venous thromboembolism cohort, five population controls were randomly chosen from the entire registry, matched for sex, age, and municipality of residence. Each control was required to be alive on the date the corresponding case person was first hospitalised with venous thromboembolism, the “index date” for the matched set. With the venous thromboembolism patients, we excluded comparison cohort members with a hospital discharge diagnosis of any cardiovascular disease before the index date. Starting in 1994, the hospital registry included hospital outpatient visits. In Denmark, these data include essentially all outpatient specialist encounters, including visits to cardiologists. This information enabled us to exclude people with venous thromboembolism (and population controls) who had been diagnosed with a prior cardiovascular disease but who had not been hospitalised.

By use of the civil registration number, all members of the two study cohorts were linked to the Civil Registration System and to the National Registry of Patients so as to identify all inpatient hospitalisations after the index dates for acute myocardial infarction or stroke. We did not undertake a separate analysis of haemorrhagic stroke and heart failure, since these can be complications of anticoagulation therapy and venous thromboembolism, respectively. However, we studied stroke (type unspecified) and not solely ischaemic stroke because of the clinical difficulty in separating ischaemic and non-ischaemic cerebrovascular events. We also considered the combined endpoint of acute myocardial infarction and stroke.

Statistical analysis
We assessed the association between venous thromboembolism and later arterial cardiovascular events both overall and separately for unprovoked and provoked thrombotic episodes. We followed the cohorts from the index dates to the occurrence of a hospitalisation for one of the outcome cardiovascular diseases, or to emigration, death, end of December, 2005, or 20 years of follow-up, whichever came first.

To summarise time-to-events, we used Kaplan-Meier analysis to construct survival curves and life table techniques to compute risks of the outcomes. We used proportional hazards regression to compute hazard ratios and 95% CIs as measures of relative risk for the endpoint diagnoses. In all models, we adjusted for age, sex, and index calendar year. In the analyses of provoked venous thromboembolism we also adjusted for recent (within 90 days) pregnancy or surgery (including trauma and fractures), and main types of cancers (respiratory, gastrointestinal, urogenital, central nervous system, breast, haematological, and other cancers). We used the χ² test to compute p values for differences in proportions.

By 1994 the diagnostic approach to venous thromboembolism had become relatively homogeneous in Denmark.20 When we restricted analysis to venous thromboembolism cases diagnosed after 1994 (and their corresponding unaffected population controls), the findings were essentially identical with those obtained with the complete cohorts, and are not presented here. Statistical analyses were done with SAS software (version 9.1).

Role of the funding source
The sponsor had no role in the study design; in the collection, analysis, and interpretation of the data; in the writing of this report; or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
We identified 90 384 individuals with a first discharge diagnosis of venous thromboembolism after age 40 years, and 451 920 population controls. 48 260 (53·4%) venous thromboembolism cases and 108 483 (24·0%) population control cohort members had a discharge diagnosis of cardiovascular disease before, or concurrent with, the index date and were excluded from further analysis. The most common diagnoses in those excluded from the
venous thrombosis and population cohorts were hypertension (29 580), chronic atherosclerotic heart diseases (25 008), acute myocardial infarction (19 380), stroke or transient ischaemic attack (19 378), heart failure (13 423), and angina pectoris (12 145).

Table 1 shows characteristics of the remaining 25 199 patients with deep venous thrombosis, and the 16 925 patients with pulmonary embolism and their population control cohorts. In both groups there were slightly more women than men. Between a third and a half of the two case cohorts were older than 70 years (table 1). As expected, in comparison to controls, more venous thromboembolism patients than population controls had a malignancy, or recent surgery or pregnancy.

Overall, venous thromboembolism was a clear marker of subsequent risk of each of the arterial cardiovascular endpoints (table 2). For patients with deep venous thrombosis, the relative risks during the first year after the thrombotic event were 1·60 (95% CI 1·35–1·91) for myocardial infarction and 2·19 for stroke (1·85–2·60); the relative risks were higher for pulmonary embolism (table 2).

Some venous thromboembolism patients had a high absolute risk of arterial cardiovascular events. In those with pulmonary embolism who were older than 70 years, the risk of myocardial infarction or stroke in the first year of follow-up was 3·96% versus 1·59% for the comparison cohort (relative risk 2·57; 95% CI 2·13–3·10). By contrast, in patients aged 40–55 years with pulmonary embolism, the relative risk over the first follow-up year was higher (3·68; 2·23–6·08), but the increase in risk was small: the absolute risks were 0·88% versus 0·24% in the control cohort.
After the first year of follow-up, the excess relative risks persisted, but at a lower level, roughly 20–40% above risks in the control cohort (table 2). 1–5 years after deep venous thrombosis, the relative risk for myocardial infarction or stroke was 1.33 (95% CI 1.24–1.43); this fell to 1.04 (0.99–1.09) 16–20 years after the event. After pulmonary embolism, the relative risks were similar during these two periods (data not shown).

Tables 3 and 4 summarise the risk estimates for unprovoked and provoked venous thromboembolism, respectively. The relative risks for arterial cardiovascular events were similar in the two analyses. As in the overall analysis, the excess risks were lower for deep venous thrombosis than for pulmonary embolism, and the modest, long-term associations were also present. The relative risks for unprovoked deep venous thrombosis fell slowly over the long-term follow-up (figure), whereas for unprovoked pulmonary embolism the excess relative risk appeared more constant. For patients with a provoked presentation, there was no evidence of a substantial change over time after the first year (figure).

In general we did not identify any major differences in relative risks between females and males. However, the relative risk estimates for the first year of follow-up tended to be slightly higher for females than males for both unprovoked and provoked pulmonary embolism (data not shown).

**Discussion**

Our large nationwide population-based study provides strong evidence that patients with venous thromboembolism have an increased risk of subsequent arterial cardiovascular events, compared with population controls. The excess risk was most pronounced during the first year of follow-up, persisted for up to 20 years, and was noted after both deep venous thrombosis and pulmonary embolism. The relative risks were similarly high in patients with unprovoked venous thromboembolism and in those with provoked disease.

Our population-based data are largely consistent with the initial observations of higher prevalences of asymptomatic carotid plaques or coronary calcifications in patients with unprovoked deep venous thrombosis than in matched hospital controls. The cross-sectional

### Table 3: Risks of arterial cardiovascular disease in patients with unprovoked venous thromboembolism, and in population controls

<table>
<thead>
<tr>
<th>Event</th>
<th>Deep venous thrombosis cohort (n=18,087)</th>
<th>Deep venous thrombosis population control cohort (n=66,637)</th>
<th>Pulmonary embolism cohort (n=11,043)</th>
<th>Pulmonary embolism population control cohort (n=40,043)</th>
<th>Adjusted relative risk (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>273</td>
<td>1961</td>
<td>517</td>
<td>7051</td>
<td>1.87 (1.62–2.17) 1.25 (1.19–1.31)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>138</td>
<td>961</td>
<td>289</td>
<td>3627</td>
<td>1.74 (1.42–2.13) 1.18 (1.10–1.27)</td>
</tr>
<tr>
<td>Stroke</td>
<td>137</td>
<td>1118</td>
<td>234</td>
<td>3861</td>
<td>2.01 (1.63–2.48) 1.29 (1.21–1.38)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>59</td>
<td>489</td>
<td>127</td>
<td>1627</td>
<td>1.60 (1.82–2.18) 1.34 (1.21–1.48)</td>
</tr>
<tr>
<td>2–20 years’ follow-up</td>
<td>207</td>
<td>1984</td>
<td>433</td>
<td>566</td>
<td>1.82 (1.38–2.38) 1.26 (1.06–1.51)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>107</td>
<td>427</td>
<td>240</td>
<td>2635</td>
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<tr>
<td>Acute myocardial infarction</td>
<td>38</td>
<td>196</td>
<td>135</td>
<td>1322</td>
<td>1.22 (0.80–1.87) 1.17 (0.89–1.53)</td>
</tr>
<tr>
<td>Stroke</td>
<td>72</td>
<td>249</td>
<td>111</td>
<td>1459</td>
<td>2.62 (1.84–3.73) 1.38 (1.10–1.73)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>33</td>
<td>98</td>
<td>55</td>
<td>578</td>
<td>2.59 (1.53–4.39) 1.45 (1.01–2.09)</td>
</tr>
</tbody>
</table>

Data are number of events, unless otherwise specified. *Adjusted for sex, age, and year of venous thromboembolism diagnosis.

### Table 4: Relative risks of arterial cardiovascular disease in patients with provoked venous thrombosis or pulmonary embolism, and in population controls

<table>
<thead>
<tr>
<th>Event</th>
<th>Deep venous thrombosis cohort (n=7,112)</th>
<th>Deep venous thrombosis population control cohort (n=27,038)</th>
<th>Pulmonary embolism cohort (n=5,888)</th>
<th>Pulmonary embolism population control cohort (n=22,603)</th>
<th>Adjusted relative risk (95% CI)*</th>
</tr>
</thead>
<tbody>
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Data are number of events, unless otherwise specified. *Adjusted for sex, age, and year of venous thromboembolism diagnosis, pregnancy, surgery up to 90 days before hospitalisation for venous thromboembolism, malignancy (respiratory, gastrointestinal, urogenital, central nervous system, breast, haematological and other cancers) before, or up to 90 days after, the venous thrombotic episode.
nature of these analyses and their reliance on preclinical markers of atherosclerosis necessarily limits their potential to clarify the time course and clinical impact of the association—important issues that we were able to address. Our findings are likewise consistent with a follow-up study of 151 venous thrombosis patients and 151 clinic controls that reported a relative risk of arterial cardiovascular events of 2·86 (95% CI 1·07–7·62).14 In contrast, two cohort studies investigating the association between subclinical markers of atherosclerotic disease and subsequent development of venous thromboembolism failed to find such an association.8,9 One of these8 reported a direct association between arterial cardiovascular and venous thrombotic events during follow-up while the other9 identified an inverse relationship.

In contrast to some previous studies,11,12 we found an increased risk of subsequent arterial cardiovascular events not only in patients with unprovoked venous thromboembolism, but also in those with thrombosis secondary to pregnancy, surgery, or other predisposing conditions. Unlike those previous studies, we did not include use of hormone-replacement therapy or oral contraceptives as predisposing factors in women. However, since the associations for venous thrombosis we noted were similar in men and women, differences in inclusion or exclusion criteria between studies could not explain the differences in findings. Our population-based analysis included all patients with a hospital diagnosis of venous thromboembolism and so was free from the potential distortions of selection and response factors, which can complicate clinic-based cohorts or use of hospital controls.5,13,15,16

The mechanism underlying the association between venous thromboembolism and atherosclerotic disease is not clear. It is not plausible that venous thromboembolism in itself causes myocardial infarction and stroke. Rather, the association we find must be due to shared risk factors or aetiologic pathways, or both.5 With the exception of obesity, there is only weak and inconsistent evidence that venous and atherosclerotic diseases share common risk factors such as diabetes, hypertension, hyperlipidaemia, and cigarette smoking.5,18,22–28 Nonetheless, the increased risk of myocardial infarction and stroke for both provoked and unprovoked venous thromboembolism is consistent with underlying common prothrombotic mechanisms such as thrombogenesis, endothelial damage, or inflammation.21 Acute arterial events such as these are associated with activation of platelets and blood coagulation, and a role of this prothrombotic state in the promotion of venous thrombosis is plausible.5,14 Atherosclerosis itself seems also related to a hypercoaguable state, though perhaps to a lesser extent.20 This weaker relationship could explain why the clinical arterial events have been more consistently associated with risk of venous thromboembolism than with (subclinical) markers of atherosclerosis. In any case, similar biological triggers could be responsible for activating coagulation and inflammatory pathways in both arterial disease and venous thromboembolism.21

However, differences in the aetiology of ischaemic stroke and myocardial infarction could complicate this inference. Ischaemic strokes are more often caused by emboli originating from the heart, the aorta or the carotid arteries than by local thrombi within the brain.16 By contrast, rupture of coronary atherosclerotic plaques and local thrombi are the cause of most myocardial infarctions.22 Therefore, the mechanism behind the association between venous thromboembolism and myocardial infarction could differ from that between deep venous thrombosis and pulmonary embolism, and stroke. Other examples of conditions associated with both arterial and venous thromboembolic disorders are hyperhomocysteinaemia, inherited thrombophilia, antiphospholipid antibodies, and various infections such as those due to Chlamydia pneumoniae.5,28,32

Our study has both strengths and limitations. We studied important clinical arterial cardiovascular events, and our risk estimates are derived from a population-based cohort study, in a setting with a national health service with free access to health care that largely removed referral and diagnostic biases. The large population we studied was well-defined, and the follow-up was complete.
because our design relied on computerised registries with complete nationwide coverage. We had access to the entire hospital discharge registry history and, since 1994, outpatient clinic data as well. We did not include cardiovascular deaths in our analysis. The Danish National Registry of Patients records patients for whom cardiac arrest occurred outside hospital if there was an admission for a resuscitation attempt. However, patients with a myocardial infarction or stroke who died suddenly outside the hospital without a previous admission would not have been judged to have developed the study endpoints.

The validity of our findings depends ultimately on the accurate coding of venous thromboembolism and of cardiovascular endpoints. In administrative databases, the predictive value of a discharge diagnosis of pulmonary embolism and myocardial infarction has been reported to be 90%,15,16 though slightly lower for stroke and venous thrombosis.17,18 However, lack of specificity of the outcome diagnosis would bias our risk estimates towards the null, probably more for stroke than for myocardial infarction.

The cancer and procedure data we used to define provoked venous thromboembolism have high validity, making the specificity of this classification quite high.19 Any misclassification between a provoked and unprovoked venous thromboembolism will attenuate the difference in the relative risk estimates between the two groups. Our use of routine data might actually be a strength. The study itself could not have affected the diagnostic process, although it is certainly possible that the clinicians making the cardiovascular diagnoses were affected by the previous medical history (including that of thromboembolism). We did not have data on use of oral anticoagulation therapy, widely used in patients with venous thromboembolism, which reduces the risk of myocardial infarction and stroke.20 All these biases will tend to be conservative, and result in underestimation of the strength of the association between venous thromboembolism and arterial cardiovascular events.

Our findings could have clinical implications. Our data showed an increased relative risk of cardiovascular disease in patients with venous thromboembolism comparable to that of other conventional risk factors21–24 for arterial cardiovascular events—at least during the first year of follow-up. However, the value of preventive measures against myocardial infarction and stroke in patients with venous thromboembolism is uncertain. Two ongoing studies are evaluating the effect of aspirin on the long-term treatment of venous thromboembolism.1

A few observational studies have shown that statins might reduce the risk of venous thromboembolism,4 but the role of these drugs specifically for the prevention of myocardial infarction and stroke in patients with venous thromboembolism has not yet been explored.6

Thus, we find strong evidence that venous thromboembolism is associated with an increased long-term risk of arterial cardiovascular events irrespective of the presence or absence of classic risk factors for venous thromboembolism. Common risk factors or pathways are most likely responsible for the association. Future studies are needed to further clarify the association, and to evaluate its implications for clinical practice.

Contributors
HTS was the principal investigator and lead author in the conception and design of the study, analysis of the data and drafting of the manuscript. EH-P and LP coordinated the data collection and did the statistical analysis. JAB participated in the study design, provided statistical suggestions, and participated in the interpretation of the results. PP participated in the conception and design of the study and the interpretation of the data. All authors took part in reviewing and editing the entire manuscript, and approved the final version of the manuscript.

Conflict of interest statement
We declare that we have no conflict of interest.

Acknowledgments
The study obtained support from the Western Danish Research Forum for Health Sciences and a grant from the Danish Research Agency (grant no. 271-05-0511).

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