Heart Disease May Be a Risk Factor for Pulmonary Embolism Without Peripheral Deep Venous Thrombosis

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Background—Heart diseases increase the risk of arterial embolism; whether they increase the risk of pulmonary embolism without peripheral venous thrombosis is less certain.

Methods and Results—We conducted a nationwide, population-based case-control study in Denmark using patients diagnosed with pulmonary embolism and/or deep venous thrombosis between 1980 and 2007. We computed odds ratios to estimate relative risks associating preceding heart disease with pulmonary embolism, pulmonary embolism and deep venous thrombosis, or deep venous thrombosis alone. In this study, 45,282 patients had pulmonary embolism alone, 4,680 had deep venous thrombosis and deep venous thrombosis, and 5,790 had deep venous thrombosis alone; 541,561 were population controls. Myocardial infarction and heart failure in the preceding 3 months conferred high risks of apparently isolated pulmonary embolism (odds ratio, 43.5 [95% confidence interval (CI), 39.6 – 47.8] and 32.4 [95% CI, 29.8 – 35.2], respectively), whereas the risks of combined pulmonary embolism and deep venous thrombosis (19.7 [95% CI, 16.0 – 24.2] and 22.1 [95% CI, 18.7 – 26.0], respectively) and deep venous thrombosis alone (9.6 [95% CI, 8.6 – 10.7] and 12.7 [95% CI, 11.6 – 13.9], respectively) were lower. Left-sided valvular disease was associated with an odds ratio of 13.5 (95% CI, 11.3 – 16.1), whereas the odds ratio was 74.6 (95% CI, 28.4 – 195.8) for right-sided valvular disease. Restricting the analysis to cases diagnosed after 2000 led to lower risk estimates but the same overall pattern.

Conclusion—Heart diseases increase the near-term risk for pulmonary embolism not associated with diagnosed peripheral vein thrombosis. (Circulation. 2011;124:00-00.)

Key Words: case-control studies ■ epidemiology ■ heart diseases ■ pulmonary embolism ■ venous thrombosis

Venous thromboembolism (ie, pulmonary embolism and deep venous thrombosis) has an estimated overall incidence of 1 per 1000 persons per year and a 6% to 12% case fatality rate within 1 month.1–3 Pulmonary embolism often develops as a complication of deep venous thrombosis, stemming from an underlying silent or overt thrombosis in the lower or upper extremities.4 However, ≈40% of patients with pulmonary embolism have no preceding or concurrent diagnosis of peripheral thrombosis, even after careful venous examination.5,6

Clinical Perspective on p ●●●

Several explanations for pulmonary embolism in the absence of peripheral deep venous thrombosis have been postulated. It is possible that the thrombus originated peripherally but became dislodged, so the remainder could not be detected even by sensitive methods.7 Alternatively, there may be other sources of right-sided thrombi, including the heart itself, especially in the setting of cardiac diseases that are notoriously associated with an increased risk of left-side cardiac thromboses and subsequent embolic stroke.8 Indeed, autopsy series have shown that right intracardiac thrombosis may be as common as thrombosis on the left,9–11 and ultrasound surveys have reported a high prevalence of right-side thrombi in patients with acute pulmonary embolism.12–14

A recent cross-sectional hospital database study reported a higher prevalence of heart disease in patients with pulmonary embolism and no accompanying peripheral venous thromboembolism compared with patients who had pulmonary embolism with peripheral venous thromboembolism.7

A longitudinal study of the association between heart disease and pulmonary embolism is needed to further elucidate the hypothesis that sources of thrombi other than those in the peripheral venous system increase the risk of pulmonary embolism. Evidence provided by such a study would improve our understanding of the clinical course of heart disease and may potentially lead to improved understanding and prevention of pulmonary embolism. We therefore undertook a
nationwide population-based case-control study to evaluate whether common heart diseases that increase the risk of left-sided arterial embolism (such as heart failure, myocardial infarction, atrial fibrillation or flutter, and valvular heart disease) are also associated with increased risk of incident pulmonary embolism without apparent peripheral venous thrombosis.

Methods

Design and Rationale
We chose to study the relation between incident heart disease and pulmonary embolism both with and without preceding deep venous thrombosis, as well as the relation with deep venous thrombosis without pulmonary embolism. Examination of the relation between incident heart disease and these 3 outcomes using the same study design allows comparisons of the strengths of association, which can further elucidate possible mechanisms.

Source Population
Our case-control study was nested in the entire population of Denmark (population, 5.4 million) during the years 1980 to 2007. We obtained data from the Danish National Patient Registry, which contains records of all acute care hospital discharges since January 1, 1977, and outpatient specialist clinics and emergency room visits since January 1, 1995,15 and from the Danish Civil Registration System. The civil registration number, a personal identifier assigned to all Danes at birth and residents at immigration, was used to link records across registries.

Identification of Cases With Venous Thromboembolism
Our approach to ascertaining the outcomes of pulmonary embolism and deep venous thrombosis has been described previously.16,17 The Danish National Patient Registry records civil registration numbers, dates of hospital admission and discharge, and surgical procedures performed. For each discharge, the registry includes up to 20 discharge diagnoses assigned by the discharging physician and classified according to the International Classification of Diseases (ICD), 8th revision until December 31, 1993, and 10th revision thereafter. Among the discharge diagnoses in the Danish National Patient Registry, one is registered as primary and the others as secondary. According to Danish guidelines, the primary diagnosis (called the action diagnosis in the registry) is the main reason for the admission. We obtained from the Danish National Patient Registry all initial discharge diagnoses of venous thromboembolism (see the Appendix for the ICD codes) between January 1, 1980, and December 31, 2007.18–20 The start date of the study was set 3 years after the establishment of the Danish National Patient Registry to enable us to exclude prevalent venous thromboembolism cases. We identified 109,752 inpatients with a first recorded hospitalization for pulmonary embolism (primary and secondary discharge diagnoses) and/or of deep venous thrombosis in a lower limb.

Population Controls
The Danish Civil Registration System updates its records daily, including changes to vital status (dead or alive), date of death, and the home address of all Danish residents.21 For each case, we used risk-set sampling to select 5 population controls from this registry matched to the case on age and sex. We assigned the date of the case’s first hospital admission for venous thromboembolism (pulmonary embolism alone, pulmonary embolism and deep venous thrombosis, or deep venous thrombosis alone) as the index date both for the case and for the case’s matched controls. Thus, in addition to fulfilling the matching criteria, the controls had to be alive on the index date and could not have had a study outcome before this date. A total of 541,561 population controls were included in the study.

Potential Confounders
To classify patients as having unprovoked versus provoked venous thromboembolism, we collected data on preceding inpatient cancer, fractures, trauma, surgery, and pregnancy diagnoses from the Danish National Patient Registry.18–20 We also retrieved data on obesity and psychiatric diseases (as a marker of antipsychotic drug use), which have been reported as risk factors for venous thromboembolism.20 Only diagnoses recorded on and before the index date were included. For cancer, we also included cancer diagnosis 3 months after the index date because occult cancer is a strong risk factor for venous thromboembolism.19 The relevant ICD codes are provided in the Appendix.

Statistical Analysis
We tabulated the frequency and proportion of venous thromboembolism cases and population controls within categories of demographic variables, heart disease history, and candidate confounders. We assessed associations using odds ratios (ORs) with 95% confidence intervals (CIs). Given the risk-set sampling of controls, these ORs provide an unbiased estimate of the corresponding rate ratios. Because we examined multiple outcomes combining pulmonary embolism and deep venous thrombosis, we estimated the ORs using unconditional polytomous logistic regression, with adjustment for the matching factors and covariates. We examined whether the adjusted ORs differed for pulmonary embolism with and without reported deep venous thrombosis. We used Wald statistics to compute P values testing the homogeneity of these adjusted ORs. We repeated all analyses using conditional logistic regression, and no result varied substantially from those presented here.

In a subanalysis, we restricted the analysis to cases of pulmonary embolism and deep venous thrombosis diagnosed after January 1, 2000, to reflect the improved diagnostic accuracy of these disorders with increased use of CT scan of the lungs and ultrasound of the legs. In the same time period, the treatment of acute myocardial infarction and heart failure also improved,4,22–24 with less bed rest recommended.

Results
Descriptive data are presented in Table 1 for the 109,752 patients with venous thromboembolism and 541,561 population controls. Among the patients, 59,790 had a diagnosis of deep venous thrombosis only, 45,282 had a diagnosis of pulmonary embolism only, and 4,680 patients had both diagnoses. There were more women than men, and 40% to 50% were >70 years of age. Most cases were unprovoked. The age and sex distributions of patients with unprovoked deep venous thrombosis and/or pulmonary embolism were similar to those for the overall group (data not shown). Compared with controls, all 3 case groups had a higher prevalence of previous hospitalization for heart disease. This difference held true for all cases and for those with unprovoked presentation.

The OR estimates for heart disease differed according to the time before the venous thromboembolic event, with strong associations between heart disease hospitalizations in

Preceding Heart Disease
We used the Danish National Patient Registry to identify history of inpatient heart disease admissions between January 1, 1977, and the index date of cases and their matched controls. The ICD codes used in the study are provided in the Appendix. In accordance with an earlier design,20 we examined the associations between incident, registry-recorded heart disease, and venous thromboembolism within 2 time periods, defined by whether the heart disease had been recorded first within 3 months before the index date or >3 months before.
the 3 months before the index date and thromboembolism and nearly null associations for the time period >3 months before (Table 2). Isolated pulmonary embolism was strongly associated with both acute myocardial infarction (OR, 43.5; 95% CI, 39.6–47.8) and heart failure admission (OR, 32.4; 95% CI, 29.8–35.2) in the 3 months before the index date but much less strongly associated with valvular heart disease hospitalization during that time window (OR, 11.1; 95% CI, 8.9–13.8). However, the latter association differed substantially between left-sided (mitral or aortic) and right-sided (tricuspid or pulmonary) pathology. A diagnosis of left-sided valvular disease was associated with an OR of 13.5 (95% CI, 11.3–16.1), whereas for right-sided valve disease, the OR was 74.6 (95% CI, 28.4–195.8; \( P \) for test of homogeneity = 0.0006).

The ORs associated with myocardial infarction and heart failure admissions in the 3 months before the index date were substantially lower for deep venous thrombosis and deep venous thrombosis with pulmonary embolism than for isolated pulmonary embolism. For incident atrial fibrillation/flutter and valvular disease, the ORs were similar (Table 2).

Much of the association was driven by coincident hospitalization for heart disease and venous thromboembolism. If there was a hospitalization for heart disease within 3 months before the index admission but not during that hospitalization, the relative risk estimates were lower. For acute myocardial infarction, the OR for isolated pulmonary embolism was 6.3 (95% CI, 5.5–7.2); for pulmonary embolism and deep venous thrombosis, 4.2 (95% CI, 2.9–6.0); and for deep venous thrombosis alone, 2.9 (95% CI, 2.4–3.3). The corresponding

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Table 1. Characteristics of Cases Diagnosed With the 3 Venous Thromboembolism Outcomes (Pulmonary Embolism Alone, Pulmonary Embolism With Preceding Deep Vein Thrombosis, or Deep Vein Thrombosis Alone) and Their Matched Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pulmonary Embolism (n=45282)</th>
<th>Pulmonary Embolism and Deep Venous Thrombosis (n=4680)</th>
<th>Deep Venous Thrombosis Only (n=59790)</th>
<th>Controls (n=541561), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤55</td>
<td>7959 (18)</td>
<td>1391 (30)</td>
<td>18011 (30)</td>
<td>136633 (25)</td>
</tr>
<tr>
<td>56–70</td>
<td>12634 (28)</td>
<td>1487 (32)</td>
<td>17669 (30)</td>
<td>157377 (29)</td>
</tr>
<tr>
<td>≥71</td>
<td>24689 (54)</td>
<td>1802 (38)</td>
<td>24110 (40)</td>
<td>247551 (46)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24638 (54)</td>
<td>2180 (47)</td>
<td>31169 (52)</td>
<td>286223 (53)</td>
</tr>
<tr>
<td>Male</td>
<td>20644 (46)</td>
<td>2500 (53)</td>
<td>28621 (48)</td>
<td>255338 (47)</td>
</tr>
<tr>
<td>Previous cancer*</td>
<td>8330 (18)</td>
<td>646 (14)</td>
<td>9328 (16)</td>
<td>32276 (6.0)</td>
</tr>
<tr>
<td>Hospitalization or hospital clinic visit for surgery†</td>
<td>13817 (31)</td>
<td>1044 (22)</td>
<td>13820 (23)</td>
<td>13578 (2.5)</td>
</tr>
<tr>
<td>Hospitalization or hospital clinic visit for trauma or fracture†</td>
<td>3584 (7.9)</td>
<td>247 (5.3)</td>
<td>3654 (6.1)</td>
<td>3058 (0.6)</td>
</tr>
<tr>
<td>Pregnancy†</td>
<td>226 (0.5)</td>
<td>25 (0.5)</td>
<td>608 (1.0)</td>
<td>710 (0.1)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1763 (3.9)</td>
<td>195 (4.2)</td>
<td>2551 (4.3)</td>
<td>5966 (1.1)</td>
</tr>
<tr>
<td>Psychiatric diseases</td>
<td>1924 (4.3)</td>
<td>177 (3.8)</td>
<td>3376 (5.7)</td>
<td>9966 (1.8)</td>
</tr>
<tr>
<td>Myocardial infarction 3 mo before VTE‡</td>
<td>2538 (5.6)</td>
<td>113 (2.4)</td>
<td>648 (1.1)</td>
<td>633 (0.1)</td>
</tr>
<tr>
<td>&gt;3 mo before VTE§</td>
<td>3598 (8.0)</td>
<td>211 (4.5)</td>
<td>2483 (4.2)</td>
<td>18367 (3.4)</td>
</tr>
<tr>
<td>Heart failure 3 mo before VTE</td>
<td>3299 (7.3)</td>
<td>198 (4.2)</td>
<td>1318 (2.2)</td>
<td>853 (0.2)</td>
</tr>
<tr>
<td>&gt;3 mo before VTE</td>
<td>3559 (7.9)</td>
<td>167 (3.6)</td>
<td>2282 (3.8)</td>
<td>12519 (2.3)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter 3 mo before VTE</td>
<td>2122 (4.7)</td>
<td>199 (4.3)</td>
<td>1257 (2.1)</td>
<td>709 (0.1)</td>
</tr>
<tr>
<td>&gt;3 mo before VTE</td>
<td>2367 (5.2)</td>
<td>114 (2.4)</td>
<td>1991 (3.3)</td>
<td>13620 (2.5)</td>
</tr>
<tr>
<td>Valvular heart disease 3 mo before VTE</td>
<td>365 (0.8)</td>
<td>17 (0.4)</td>
<td>145 (0.2)</td>
<td>166 (0.0)</td>
</tr>
<tr>
<td>&gt;3 mo before VTE</td>
<td>534 (1.2)</td>
<td>21 (0.5)</td>
<td>329 (0.6)</td>
<td>2873 (0.5)</td>
</tr>
</tbody>
</table>

VTE indicates venous thromboembolism.
*Preexisting cancer or a cancer diagnosis within 3 months after VTE/index date.
†Three months before admission/index date.
‡Within 3 months before VTE but not more than 3 months before VTE.
§More than 3 months before VTE.
risk estimates for heart failure and valvular heart disease showed the same pattern, whereas the risk estimates for atrial fibrillation were almost the same with an OR of \(\approx 3.5\) for the 3 outcomes (data not shown). Even stronger associations were seen after the overall analysis was restricted to patients with venous thromboembolism as the second diagnosis in the discharge records, indicating that venous thromboembolism was a complication of the heart disease or another disease recorded in that hospitalization (Table 3).

A hospital encounter for myocardial infarction or heart failure >3 months before the pulmonary embolism and/or deep venous thrombosis was associated with only slightly elevated ORs. For atrial fibrillation, the ORs were \(\approx 1\), whereas for valvular heart disease, the ORs were <1 for pulmonary embolism with deep venous thrombosis and for deep venous thrombosis alone.

After restriction of the analysis to patients with unprovoked venous thromboembolism, the risk estimates showed the same relative pattern as for the overall venous thromboembolism outcomes (data not shown). Limiting the overall analysis to the time period after 2000 showed the same pattern, but with lower relative risks. Isolated pulmonary embolism was still associated with both acute myocardial infarction (OR, 10.1; 95% CI, 8.1–12.7) and heart failure (OR, 19.3; 95% CI, 16.5–22.6). The association with valvular disease still differed substantially between left- and right-sided pathology. A diagnosis of left valvular disease was associated with an OR of 5.7 (95% CI, 4.1–8.0) and right-sided valvular disease (OR, 37.5; 95% CI, 7.4–191.3; \(P\) for homogeneity =0.03).

### Discussion

In this large population-based case-control study, inpatient diagnoses of heart disease were associated with a markedly increased risk of venous thromboembolism in the subsequent 3 months. The relative risk was particularly high for isolated pulmonary embolism without a concurrent diagnosis of primary deep venous thrombosis. The association was substantially higher for right-sided than for left-sided valvular disease. The increased relative risks associated with myocardial infarction and heart failure seem to extend beyond 3 months past the initial hospitalization for heart disease, but the associations were much weaker over the long term. The risk estimates were substantially more pronounced when episodes of venous thromboembolism were the second diagnoses in the record, indicating that venous thromboembolism was a complication of the heart disease and not vice versa. The risk estimates were lower but showed the same patterns for the period 2000 forward, a period of greater diagnostic accuracy for pulmonary embolism and deep venous thrombosis and shorter bed rest after myocardial infarction and chronic heart failure.

The increase in the risk of deep venous thrombosis, alone or associated with pulmonary embolism, after a cardiac diagnosis is consistent with the fact that several heart diseases induce venous stasis and elevated systemic venous pressure.\(^{25}\) The remarkable increase in the risk of apparently isolated pulmonary embolism in the 3 months after incident heart disease suggests that several heart diseases may directly cause the development of symptomatic embolism without apparent peripheral thrombosis.
Previous studies of heart diseases as a risk factor for isolated pulmonary embolism with heart disease have not been conclusive. Using a study design based on the entire longitudinal hospital history of cases and controls, we found stronger associations than reported in a small hospital-based cross-sectional study from Italy.7 Prandoni et al7 conducted a cross-sectional study and reported ORs of 1.15 for the association of venous thromboembolism with valvular heart disease and 1.28 for the association with coronary heart disease. The study was based on 9019 patients with pulmonary embolism alone and 2157 patients with both pulmonary embolism and deep venous thrombosis who served as a control group. This difference in design partly explains the increased risk. A British case-control study reported relative risk estimates similar to ours for the association of cardiovascular events with subsequent venous thromboembolism after 3 months, but the analysis did not take into consideration the time intervals to venous thromboembolism.28 The reduced risk associated with a diagnosis of atrial fibrillation and valvular disease ≥3 months before the index date might be explained by anticoagulation therapy.29 Several issues should be taken into consideration in the interpretation of our data. The main strengths of our study are its large size, its well-defined population, Denmark’s uniformly organized healthcare system with complete population coverage, and the use of population-based controls.

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The proportion of isolated pulmonary embolism was higher than expected,7 and we lacked clinical data on how often the presence of peripheral deep venous thrombosis was assessed in patients with a diagnosis of pulmonary embolism. Asymptomatic deep venous thrombosis is common in this setting, occurring in 20% to 30% of patients with pulmonary embolism.8 Based on data from general practitioners’ records, a British study found that only 6% of its sample of venous thromboembolism patients had both deep venous thrombosis and pulmonary embolism recorded.28 It is thus likely that the presence of a pulmonary embolism, physicians do not pursue a separate deep venous thrombosis diagnosis because it would not change the recommended treatment.

Therefore, in our study, patients with pulmonary embolism may be less likely to also receive a deep venous thrombosis diagnosis. If the rate of such underdiagnosis is independent of preceding heart disease (ie, is nondifferential) and the heart...
disease associations with pulmonary embolism and venous thromboembolism are lower than the heart disease associations with isolated pulmonary embolism, the underdiagnosis would bias our estimates of association for isolated pulmonary embolism toward the null. A similar phenomenon was found in the Italian study. However, serious bias would have been introduced if there was a differential diagnostic approaches to heart disease and deep venous thrombosis among the 2 pulmonary embolism groups. Most likely, patients with pulmonary embolism with and without venous thrombosis had the same cardiac diagnostic approach during the venous thromboembolism hospitalization in the recent decades, in contrast to patients with isolated deep venous thrombosis, in whom the use of echocardiographic examinations would most likely be lower than in the presence of pulmonary embolism. At the time of the index hospitalization, we found elevated relative risk estimates for venous thromboembolism as secondary diagnoses as a marker for complications to already diagnosed heart disease. We also found that if the heart disease occurred within 3 months before the index hospitalization, but not during the same index hospitalization, the risk estimates showed the same relative pattern.

A weakness is that our data on diagnoses were obtained from a medical database, which may not be entirely accurate. Of patients listed in discharge registries with a diagnosis of venous thromboembolism, 15% to 20% might not fulfill strict clinical criteria for the disease. Therefore, the exposure and covariate data should have little nondifferential misclassification, resulting in little bias. Overall, 2 issues speak for a causal association between right-sided heart disease and the risk of isolated pulmonary embolism. First, diagnoses of isolated pulmonary embolism were substantially more frequent for right-sided valvular heart disease compared with left-sided valvular heart disease. Second, the estimates for acute myocardial infarction and heart failure were higher for isolated pulmonary embolism as a primary diagnosis than for pulmonary embolism and deep venous thrombosis. These distinct patterns would be expected to arise from a causal association but are unlikely to arise from an underlying bias.

Conclusions

We found that patients with heart disease are at increased short-term risk of venous thromboembolism. This result seemed most apparent for isolated pulmonary embolism and suggests that common heart diseases may directly account for the development of pulmonary embolism. In patients with pulmonary embolism and no apparent deep venous thrombosis, sources of emboli should be sought and appropriate targeted treatment instituted.

Appendix

International Classification of Diseases Codes Defining Venous Thromboembolism


International Classification of Diseases Codes Defining Heart Diseases


International Classification of Diseases Codes Defining Comorbidities


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The study obtained support from the Department of Clinical Epidemiology’s Research Foundation and a grant from the Danish Research Agency (grant No. 271-05-0511).

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

It is well established that heart diseases such as atrial fibrillation increase the risk of arterial embolism. However, whether heart diseases similarly increase the risk of pulmonary embolism without peripheral venous thrombosis is less certain. Using Danish medical databases, we conducted a nationwide population-based case-control study of 45,282 patients with embolism alone, 4,680 patients with pulmonary embolism and lower-limb deep venous thrombosis, 59,790 with deep venous thrombosis alone, and 541,561 population controls. Myocardial infarction and heart failure in the preceding 3 months conferred remarkably high risks of apparently isolated pulmonary embolism, with odds ratios of 43.5 (95% confidence interval, 39.6–47.8) and 32.4 (95% confidence interval, 29.8–35.2), respectively. There was a particularly strong association of right-sided valvular disease with isolated pulmonary embolism (odds ratio, 74.6; 95% confidence interval, 58.4–90.5). We conclude that heart disease is associated with an increased short-term risk of venous thromboembolism, including isolated pulmonary embolism. Because common heart diseases may directly account for the development of pulmonary embolism, in patients with pulmonary embolism and no apparent deep venous thrombosis, cardiac sources of emboli should be considered and appropriate treatment instituted. 
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