Associations between cardiovascular risk factors, hyper- and hypocoagulability
Rafi, S.

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Chapter 6

Thyroid disease, anti-thyroid or thyreomimetic agents, and the risk of pulmonary embolism

Bregje van Zaane, Alessandro Squizzato, Sara Biere-Rafi, Patrick C. Souverein, Dees PM Brandjes, Harry R Büller, Victor EA Gerdes and Anthonius de Boer

Submitted
ABSTRACT

Context Hyperthyroidism is thought to induce hypercoagulability, whereas a bleeding tendency has been observed in hypothyroidism. However, both disease entities have been associated with an increased risk of venous thrombosis. This discrepancy may be explained by the impact of treatment for thyroid disease.

Objective To evaluate the association between pulmonary embolism (PE) and the start of treatment for thyroid disease.

Design and Setting A nested case-control study was conducted using the PHARMO Record Linkage System, a Dutch population-based pharmacy registry.

Patients Cases were patients hospitalized for PE and the date of hospitalization was set as index date. Controls were gender- and age-matched subjects without a history of PE prior to this index date.

Main outcome measures Odds ratios (ORs) and their 95% confidence intervals (95% CI) were estimated for new use of antithyroid or thyreomimetic agents, or hospitalization for thyroid disease from 12 months before to 12 months after the index date.

Results The study population consisted of 3479 cases and 11830 controls. New use of antithyroid agents or hospitalization for thyrotoxicosis within 6 months after the index date (i.e. untreated hyperthyroidism at the index date) was significantly associated with PE (adjusted OR 3.22; 95% CI 1.12-9.22), whereas a relation between thyreomimetic agents and PE was observed for new use before the index date, especially within the first 3 months after treatment onset (adjusted OR 4.58; 95% CI 1.28-16.43). No association was found for new use of thyreomimetic agents after the index date, or for new use of antithyroid agents before the index date.

Conclusions Our findings suggest that both patients with untreated hyperthyroidism and patients who have recently started with thyreomimetic agents for hypothyroidism are at an increased risk for PE.
INTRODUCTION

Thyroid hormone has many effects on the heart and vascular system, and both hyper- and hypothyroidism have been associated with an increased cardiovascular morbidity. Among this, several case reports have pointed towards a possible relationship between thyroid disease and venous thromboembolism. Thyroid hormone excess has been reported to induce prothrombotic changes, as witnessed by high levels of von Willebrand factor, factor VIII, fibrinogen and plasminogen activator inhibitor-1 in hyperthyroid patients. It is therefore hypothesized that hyperthyroidism may be a risk factor for venous thromboembolism. Inversely, reduced levels of von Willebrand factor and factor VIII have been observed during hypothyroidism.7,8 These effects may, at least in part, protect against venous thromboembolism. Indeed, we have recently shown that high levels of FT4 are associated with an increased risk of venous thrombosis, whereas a reduced risk of venous thrombosis was observed for low levels FT4; all within the normal reference range.9

To date, only two published studies, including one of our own, have assessed the effect of thyroid disease on the occurrence of venous thromboembolism. Remarkably, both studies found that (subclinical) hypothyroidism, but not hyperthyroidism, was associated with an increased risk of venous thromboembolism. These conflicting findings may result from the fact that the impact of treatment was not disentangled in the analysis. In general, thyroid hormone levels gradually decrease to normal levels within 4 to 12 weeks of treatment with antithyroid agents. A simultaneous reduction in procoagulant and anti-fibrinolytic factors may therefore rapidly attenuate the risk of venous thromboembolism in patients treated for hyperthyroidism. In hypothyroidism, treatment entails thyroid hormone substitution therapy with thyreomimetic agents. While normalization of thyroid hormone levels may occur within the first months after treatment onset, the vascular consequences of the increased body weight, hypertension and dyslipidemia, predominantly seen in prolonged thyroid hormone deficiency, may persist. It is therefore uncertain to what extent the transition in coagulation factors during the first months of substitution therapy may affect the risk of venous thromboembolism.

In a nested case-control design, we set out to evaluate the risk of pulmonary embolism associated with thyroid disease, while at the same time analyzing the influence of treatment.

METHODS

Study design and population

Patients with a first hospitalization for pulmonary embolism and control subjects without a history of pulmonary embolism were derived from a large database constructed 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. Data of more than 2 million community-dwelling residents, residing in 25 geographic
areas in the Netherlands are available from 1985 onwards. The medication histories are linked to
hospital admission 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 assembling of the database, drug prescribing and hospitalization data
were used. Drugs were coded according to the Anatomical Therapeutic Chemical Classification (ATC).
The hospital admission and discharge codes were coded according to the International Classification
of Diseases Ninth Revision (ICD 9), Clinical Modification.

Cases were all patients with a first hospitalization for pulmonary embolism (ICD-9 code 415.1).
Verification of whether the diagnosis had been confirmed by objective tests, including computed
tomography or ventilation perfusion scanning, was performed in a random sample of 10% of the
cases by retrieving data on confirmation of the diagnosis. Diagnosis was correctly confirmed in
more than 95% of the cases.

The date of the first hospitalization for pulmonary embolism was considered the index date.
For each case patient, up to 4 control subjects, matched for gender, age (±5 years) and geographic
region, were randomly selected using risk-set sampling, meaning controls did not have a venous
thromboembolism prior to the index date of the matched case. For this study, the population was
restricted to cases and controls of whom data on prescription use and hospitalizations were avail-
able for at least 12 months before and after the index date.

**Definition of exposure**

For all cases and controls, we identified dispensings for antithyroid (ATC codes H03B and H03C) or
thyreomimetic agents (ATC code H03A), as well as admissions for thyrotoxicosis (ICD 9 code 242)
or hypothyroidism (ICD 9 code 244). In order to identify individuals with either active (untreated)
thyroid disease or recent start of treatment for thyroid disease, new use of thyroid-related drugs or
hospitalizations within 12 months before and 12 months after the index date was analyzed. New use
was defined as first ever use, or recurrent use if the time interval between the preceding treatment
episode and the new prescription exceeded 12 months.

For hyperthyroidism, this meant that those individuals who were identified as new users of
antithyroid agents or those who were hospitalized for thyrotoxicosis before the index date, had
experienced hyperthyroidism prior to the date of treatment onset or hospitalization, and were
treated for hyperthyroidism at the index date (i.e. decreasing or already normal levels of thyroid
hormone prior to the index date). Those individuals identified as new users of antithyroid agents,
or hospitalized for thyrotoxicosis after the index date, especially in the first months, were likely to
have active and untreated hyperthyroidism at the index date.

For hypothyroidism, those individuals who were identified as new users of thyreomimetic
agents without previous use of antithyroid drugs or those who were hospitalized for hypothyroid-
ism before the index date, had experienced hypothyroidism prior to the date of treatment onset or
hospitalization, and were treated for hypothyroidism at the index date (i.e. increasing levels of
thyroid hormone relative to prior to treatment). Those individuals identified by treatment onset or hospitalization after the index date, were likely to have untreated hypothyroidism at the index date.

By using ICD codes for hospitalization, information on conditions potentially associated with a higher risk of venous thromboembolism (i.e. pregnancy, malignancy, trauma, acute infections, surgery, cardiovascular disease, heart failure, inflammatory bowel diseases) occurring in the 3 months prior to the index date, was retrieved. This 3-month period was used since hospitalizations (co-morbidity) prior to this period were less likely to have influenced the occurrence of pulmonary embolism on the index date. In addition, use of platelet inhibitors (i.e aspirin, clopidogrel bisulfate, dipyridamole), vitamin K antagonists and heparin, as well as all other medication that may influence the occurrence of pulmonary embolism (i.e. statins, NSAID’s, anti-diabetics), were identified using medication histories.

**Statistical analysis**

Continuous variables were reported as means or medians (range), depending on the distribution of the data. Categorical variables were presented as numbers (percent). Odds ratios (ORs) and their 95% confidence intervals (CIs) for the risk of pulmonary embolism associated with new use of thyroid agents and hospitalization for thyroid disease were estimated using conditional logistic regression. Individuals without thyroid disease, i.e. those who had never been treated with antithyroid or thyreomimetic agents, or hospitalized for thyroid disease, up to 12 months after the index date, were used as reference. The analysis was stratified for treatment onset or hospitalization within 12 months before and 12 months after the index date in order to evaluate the effect of untreated thyroid disease and treatment onset. To investigate a time relationship, the analysis was further stratified for different time intervals between the date of new prescription or hospitalization, and the index date (≤ 3 months, ≤ 6 months, and ≤ 12 months).

The influence of potential confounding factors was analyzed by evaluating the influence of a potential confounder on the effect estimate of the exposure of interest. If a change in crude OR of more than 5% was found for any of the independent factors, these variables were added to the multivariate model. Statistical analysis was performed with the use of SPSS 15.0 software package (SPSS Inc, Chicago, IL, USA).

**RESULTS**

**Patient characteristics**

Patient characteristics are summarized in Table 1. The database consisted of 4494 cases and 16802 control subjects. Drug prescription data and hospitalization data of at least 12 months before and 12 months after the index date were available for 3479 cases and 11830 controls. These subjects formed the basis of the present analysis. Matching ensured that age and gender distribution in cases and controls were comparable; mean age in the cases was 59 (18-94) years and 57.6% were women.
New use of antithyroid agents or hospitalization for thyrotoxicosis

In total, 12 (0.3%) case patients and 23 (0.2%) control subjects were identified as new users of antithyroid agents during the study period (Table 2). One case patient and 3 control subjects were hospitalized for thyrotoxicosis in the 12 months after the index date; no individuals were hospitalized in the 12 months before the index date. The number of individuals without thyroid disease was 3303 (94.9%) in the cases and 13391 (96.3%) in the control subjects.

New use of antithyroid agents or hospitalization for thyrotoxicosis after the index date was analyzed, a clear time-dependent relation was observed. Treatment onset or hospitalization within the first three months after the index date resulted in a crude odds ratio of 3.46 (95% CI 0.57-21.10), which gradually decreased with extension of the time interval. After adjustment for potential confounding factors a significant association between pulmonary embolism and new use of antithyroid agents or hospitalization within 6 months after the index date was observed (OR 3.22; 95% CI 1.12-9.22).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=3479</td>
<td>N=11830</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>59 (18-94)</td>
<td>58 (18-96)</td>
</tr>
<tr>
<td>Gender, female, n (%)</td>
<td>2003 (57.6)</td>
<td>6903 (58.4)</td>
</tr>
<tr>
<td>Previous hospitalizations, n (%)a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Infection</td>
<td>58 (1.7)</td>
<td>16 (0.1)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>22 (0.6)</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12 (0.3)</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>13 (0.4)</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>118 (3.4)</td>
<td>38 (0.3)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>12 (0.3)</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>Surgery</td>
<td>224 (6.4)</td>
<td>113 (1.0)</td>
</tr>
<tr>
<td>Trauma</td>
<td>36 (1.0)</td>
<td>13 (0.1)</td>
</tr>
<tr>
<td>Medication use, n (%)a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparins</td>
<td>89 (2.6)</td>
<td>24 (0.2)</td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td>519 (14.9)</td>
<td>1334 (11.3)</td>
</tr>
<tr>
<td>Coumarins</td>
<td>124 (3.6)</td>
<td>329 (2.8)</td>
</tr>
</tbody>
</table>

N indicates number

*aHospitalizations and medication use ≤ 90 days and ≥ 1 day prior to index date
Thyroid disease and risk of pulmonary embolism

A total of 35 (1.0%) case patients and 69 (0.6%) control subjects were identified as new users of thyreomimetic agents during the study period (Table 3). No individuals were hospitalized for hypothyroidism during this period.

### Table 2. Risk of pulmonary embolism associated with new use of antithyroid agents or hospitalization for thyrotoxicosis

<table>
<thead>
<tr>
<th>Case</th>
<th>N=3479 (%)</th>
<th>Control</th>
<th>N=11830 (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No thyroid disease</td>
<td>3303 (94.9)</td>
<td>11391 (96.3)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Start of antithyroid agents before the index dateb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 90 days</td>
<td>1 (0.0)</td>
<td>3 (0.0)</td>
<td>0.90 (0.09-8.68)</td>
<td>0.89 (0.09-8.59)</td>
<td></td>
</tr>
<tr>
<td>≤ 180 days</td>
<td>3 (0.1)</td>
<td>5 (0.0)</td>
<td>1.74 (0.41-7.34)</td>
<td>1.60 (0.38-6.82)</td>
<td></td>
</tr>
<tr>
<td>≤ 365 days</td>
<td>4 (0.1)</td>
<td>11 (0.1)</td>
<td>1.11 (0.35-3.52)</td>
<td>0.94 (0.28-3.17)</td>
<td></td>
</tr>
<tr>
<td>Start of antithyroid agents after the index datec</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 90 days</td>
<td>3 (0.1)</td>
<td>2 (0.0)</td>
<td>3.46 (0.57-21.10)</td>
<td>3.57 (0.58-21.83)</td>
<td></td>
</tr>
<tr>
<td>≤ 180 days</td>
<td>7 (0.2)</td>
<td>8 (0.1)</td>
<td>2.74 (0.98-7.05)</td>
<td>3.22 (1.12-9.22)</td>
<td></td>
</tr>
<tr>
<td>≤ 365 days</td>
<td>9 (0.3)</td>
<td>15 (0.1)</td>
<td>1.75 (0.75-4.07)</td>
<td>1.81 (0.75-4.35)</td>
<td></td>
</tr>
</tbody>
</table>

N indicates number; OR, odds ratio; and CI, confidence interval

aAdjusted for hospitalizations (for malignancy, trauma, surgery, pregnancy or heart failure) and use of anticoagulants within 90 days prior to the index date.

bNo individuals were hospitalized for thyrotoxicosis in the year before the index date.

cOne case patient was hospitalized for thyrotoxicosis 118 days after the index date; the three control subjects were hospitalized 42, 97, and 292 days after the index date.

### New use of thyreomimetic agents or hospitalization for hypothyroidism

A total of 35 (1.0%) case patients and 69 (0.6%) control subjects were identified as new users of thyreomimetic agents during the study period (Table 3). No individuals were hospitalized for hypothyroidism during this period.

### Table 3. Risk of pulmonary embolism associated with new use of thyreomimetic agentsa

<table>
<thead>
<tr>
<th>Case</th>
<th>N=3479 (%)</th>
<th>Control</th>
<th>N=11830 (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted ORb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No thyroid disease</td>
<td>3303 (94.9)</td>
<td>11391 (96.3)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Start of thyreomimetic agents before the index datea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 90 days</td>
<td>6 (0.2)</td>
<td>4 (0.0)</td>
<td>4.98 (1.39-17.82)</td>
<td>4.58 (1.28-16.43)</td>
<td></td>
</tr>
<tr>
<td>≤ 180 days</td>
<td>10 (0.3)</td>
<td>14 (0.1)</td>
<td>2.62 (1.14-5.99)</td>
<td>2.57 (1.10-6.01)</td>
<td></td>
</tr>
<tr>
<td>≤ 365 days</td>
<td>17 (0.5)</td>
<td>28 (0.2)</td>
<td>2.05 (1.11-3.78)</td>
<td>2.07 (1.11-3.85)</td>
<td></td>
</tr>
<tr>
<td>Start of thyreomimetic agents after the index dateb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 90 days</td>
<td>4 (0.1)</td>
<td>14 (0.1)</td>
<td>0.87 (0.28-2.70)</td>
<td>0.95 (0.30-2.96)</td>
<td></td>
</tr>
<tr>
<td>≤ 180 days</td>
<td>10 (0.3)</td>
<td>19 (0.2)</td>
<td>1.68 (0.77-3.66)</td>
<td>1.81 (0.83-3.97)</td>
<td></td>
</tr>
<tr>
<td>≤ 365 days</td>
<td>18 (0.5)</td>
<td>41 (0.3)</td>
<td>1.41 (0.80-2.48)</td>
<td>1.54 (0.86-2.75)</td>
<td></td>
</tr>
</tbody>
</table>

N indicates number; OR, odds ratio; and CI, confidence interval

aNo individuals were hospitalized for hypothyroidism during the study period.

bAdjusted for hospitalizations (for malignancy, trauma, surgery or pregnancy) and use of anticoagulants within 90 days prior to the index date.
New use of thyreomimetic agents before the index date was associated with pulmonary embolism, in a time-dependent fashion. The risk of pulmonary embolism was highest for treatment onset within 3 months before the index date (crude OR 4.98, 95 CI 1.39-17.82), and gradually decreased when the time interval between the date of treatment onset and the index date increased. No clear association was found between pulmonary embolism and new use of thyreomimetic agents after the index date, but the risk was below unity in the analysis of treatment onset within the first 3 months after the index date. Adjustment for potential confounding factors slightly altered the crude odds ratios.

DISCUSSION

In this nested case-control population-based study, consisting of over 15000 individuals, we found that new use of antithyroid agents or hospitalization for thyrotoxicosis after the index date (i.e. untreated hyperthyroidism) was associated with an increased risk of pulmonary embolism, in a time-dependent manner. In addition, a significant association between pulmonary embolism and new use of thyreomimetic agents in the 12 months before the index date was found. The risk was highest for treatment onset within three months prior to the index date, again indicating a time-dependent relationship.

Our finding of an association between pulmonary embolism and new use of antithyroid agents, or hospitalization for thyrotoxicosis, after the index date, i.e. untreated hyperthyroidism at the index date, is in line with our previous report on the relation between high levels of FT4 (mostly within reference range) and venous thrombosis as well as studies describing a hypercoagulable and hypofibrinolytic state in hyperthyroid patients. This association only reached statistical significance when it concerned treatment onset or hospitalization within 6 months after the index date. However, the time-dependent relationship is indicative of hyperthyroidism as risk factor for venous thromboembolism, considering that those individuals identified as new users of antithyroid agents or hospitalized for thyrotoxicosis within the first months after the index date were most likely to have experienced hyperthyroidism at the index date. Also, this association was not present for patients who were already treated for hyperthyroidism at the index date, which strengthens the hypothesis that treatment with antithyroid agents may rapidly reduce the risk of venous thromboembolism in hyperthyroid patients.

As for hypothyroidism, our findings confirm that patients suffering from this condition are at increased risk for venous thromboembolism, but only after institution of thyroid hormone substitution therapy. Several studies have described an increase in coagulation factor levels after treatment with thyreomimetic agents in hypothyroid patients. Moreover, thyreomimetic agents have been reported to induce prothrombotic changes in euthyroid subjects. Taken together with the fact that almost one fifth of the hypothyroid patients is given an excessive amount of
medication, it is conceivable that these haemostatic changes may result in an increased risk of venous thromboembolism.

In general, three major causes of thrombosis have been identified: changes in the vessel wall, changes in the blood flow, and changes in the blood composition. Weight gain or obesity, hypertension, and altered lipid metabolism are present in prolonged thyroid hormone deficiency; all affect one or more of these components of thrombosis risk. Overweight and obesity have been reported to increase the risk of venous thrombosis by 1.7- to 2.4-fold. It is, therefore, most likely that the combination of both weight gain and a transition in coagulation factors is responsible for the increased risk of venous thromboembolism in hypothyroid patients in the first months of thyroid hormone substitution therapy.

Some methodological aspects of this study require comments. This study concerns a large sample size of a well-defined population, with precise documentation of drug prescription. The study design has also some obvious limitations, inherent to all population based cohort studies. For example, some concern could be raised with regards to the accuracy of diagnosis of pulmonary embolism, given that diagnosis was derived from ICD-codes rather than hospital records. However, verification of a 10% random sample of the cases showed that pulmonary embolism was nearly always confirmed by objective diagnostic tests. Also, since this analysis was performed using drug prescription and hospitalization data as indicators for the presence of thyroid disease, no information was available on the exact thyroid status at the index date. Treatment onset or hospitalization after the index date could not ensure that thyroid disease was already present at the time of the index date, and diagnosis of thyroid disease may also have been delayed until after the study period causing misclassification. However, these biases have probably equally affected both cases and controls. Last, the small number of individuals identified as new users of thyroid medication or hospitalized for thyroid disease limits the robustness of our findings. With the incidence of hyperthyroidism in the general population being so low, even in this large registry study there was insufficient power to efficiently report on this topic. Nevertheless, the present observations consistently point towards an increased risk of pulmonary embolism for increasing levels of thyroid hormone and therefore provide valuable insights in the relation between thyroid disease, antithyroid or thyreomimetic agents, and pulmonary embolism. Although this study only concerned pulmonary embolism and not deep venous thrombosis of the lower extremities (as this usually does not lead to hospital admission), we believe the association applies for both manifestations of venous thrombosis.

Overall, our findings suggest that both patients with untreated hyperthyroidism and patients who have recently started with thyreomimetic agents for hypothyroidism are at increased risk of pulmonary embolism. Physicians should be aware of this relationship, and adequately assess the presence of additional risk factors for venous thromboembolism when prescribing thyreomimetic agents.
REFERENCES


