Hyperthyroidism and Risk of Atrial Fibrillation or Flutter

A Population-Based Study

Lars Frost, MD, PhD; Peter Vestergaard, MD, PhD; Leif Mosekilde, MD, PhD

Background: Atrial fibrillation is a common cardiac manifestation of hyperthyroidism. The relation between hyperthyroidism and atrial fibrillation has so far been analyzed in a limited number of selected patients, and the strength of the association has not been estimated. We examined the risk of atrial fibrillation among patients aged 20 to 89 years with hyperthyroidism diagnosed in hospitals in Denmark during a 20-year period.

Methods: We identified all patients with an incident hospital diagnosis of hyperthyroidism during the study period in the Danish National Registry of Patients, and among those we identified patients with a diagnosis of atrial fibrillation or flutter that occurred within ±30 days from the date of the hospital diagnosis of hyperthyroidism. We used logistic regression analysis to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between sex, 10-year age group, cardiovascular diseases, and risk of atrial fibrillation or flutter.

Results: Among 40,628 patients diagnosed as having hyperthyroidism, 3,362 (8.3%) were diagnosed as having atrial fibrillation or flutter within ±30 days from the date of the diagnosis of hyperthyroidism. The following factors were associated with risk of atrial fibrillation or flutter: male sex (OR, 1.8; 95% CI, 1.6-1.9), age (OR, 1.7; 95% CI, 1.7-1.8) per 10-year increment, ischemic heart disease (OR, 1.8; 95% CI, 1.6-2.0), congestive heart failure (OR, 3.9; 95% CI, 3.5-4.4), and heart valve disease (OR, 2.6; 95% CI, 1.9-3.4).

Conclusion: Male sex, increasing age, ischemic heart disease, congestive heart failure, and heart valve disease are associated with an increased risk of atrial fibrillation or flutter in patients with hyperthyroidism.

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We identified all patients with a hospital discharge diagnosis of hyperthyroidism from January 1, 1977, through December 31, 1999, in the Danish National Registry of Patients.22 From January 1, 1995, through December 31, 1999, patients with an outpatient hospital clinic diagnosis of hyperthyroidism were also recorded in the Danish National Registry of Patients. These patients (n = 11737) were also included in our study. The date of admission was recorded together with sex and age at diagnosis. The validity of a diagnosis of hyperthyroidism is in general high in the Danish National Registry of Patients. A screening of case records of 900 patients revealed misclassification in less than 2% of patients.23

We excluded patients who were younger than 20 years or older than 89 years. We also excluded patients diagnosed as having hyperthyroidism in the 5-year period from January 1, 1977, through December 31, 1979, to reduce the risk of inclusion of prevalent cases of hyperthyroidism. Patients with a diagnosis of hypothyroidism that occurred before a diagnosis of hyperthyroidism were excluded, because overdosing treatment of hypothyroidism could cause this sequence of events. We also excluded patients who died or emigrated within 30 days from the date of diagnosis of hyperthyroidism.

IDENTIFICATION OF PATIENTS WITH ATRIAL FIBRILLATION OR FLUTTER

We identified all patients with a hospital discharge diagnosis of atrial fibrillation or flutter from January 1, 1977, through December 31, 1999, or with an outpatient hospital clinic diagnosis of atrial fibrillation or flutter from January 1, 1995, through December 31, 1999, in the Danish National Registry of Patients. A change in the codes from the International Classification of Diseases, Eighth Revision (ICD-8) to the International Classification of Diseases, Tenth Revision (ICD-10) occurred in Denmark in 1994. Atrial fibrillation and atrial flutter were coded separately in ICD-8 (codes 427.93 and 427.94), but in ICD-10 atrial fibrillation and flutter have the same ICD code (I48). Therefore, we had to include atrial flutter in our study. The ICD-8 and ICD-10 codes are given here.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Code</th>
</tr>
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<tbody>
<tr>
<td>Atrial fibrillation and</td>
<td>427.93,</td>
</tr>
<tr>
<td>atrial flutter</td>
<td>427.94, I48</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>242, E05</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>244, E00, E03</td>
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<tr>
<td>Hypertension</td>
<td>400-404, 410.09, 411.09, 412.09, 413.09, 414.09, 435.09, 437.00, 437.01, 437.08, 437.09, 438.09, 110-115</td>
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<tr>
<td>Diabetes</td>
<td>249, 250, E10-E14</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>410-414, I20-I25</td>
</tr>
<tr>
<td>Mitral and/or aortic valve</td>
<td>394-396, I05, I06, I08, I34, I35</td>
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</table>

We excluded patients with a diagnosis of atrial fibrillation or flutter that occurred more than 30 days before the diagnosis of hyperthyroidism to reduce the risk of inclusion of prevalent cases of atrial fibrillation or flutter in the study.

COMORBIDITY

We obtained data on diagnoses of diabetes and cardiovascular diseases (hypertension, ischemic heart disease, congestive heart failure, and heart valve disease) from the Danish National Registry of Patients from 1977 to the end of 1999.

FOLLOW-UP AND OUTCOME

Patients were followed up in the Danish National Registry of Patients and in the Central Person Registry (vital status and emigration status). A diagnosis of atrial fibrillation that occurred in the Danish National Registry of Patients ±30 days from the date of diagnosis of hyperthyroidism was considered as the association of interest (ie, the outcome was a hospital diagnosis of atrial fibrillation that occurred ±30 days from date of the hospital diagnosis of hyperthyroidism). The short interval of 30 days was chosen to increase the probability of a causal association between hyperthyroidism and atrial fibrillation or flutter.

RECORD LINKAGE

We linked the records from different registries by use of the civil registration number, a unique 10-digit code given to each individual having had an address in Denmark since April 1968.

STATISTICAL ANALYSIS

We used logistic regression analysis to calculate odds ratios for the association between sex, age, diabetes, cardiovascular diseases, and atrial fibrillation. We assessed the potentials for interactions (ie, effect modification) by stratified analyses. We used the statistical software package from SPSS, version 11.0 (SPSS Inc, Chicago, Ill).

Our study was approved by the Danish Data Protection Agency.

RESULTS

We identified 40,628 patients with a hospital diagnosis of hyperthyroidism (Table 1). Most patients with hyperthyroidism were women (84.9%), and approximately one third of the patients were older than 70 years. Diabetes and cardiovascular diseases were seen in a few patients (Table 1). Among patients with hyperthyroidism, 3362 (8.3%) were diagnosed as having atrial fibrillation within ±30 days from the date of the diagnosis of hyperthyroidism (Table 2). The proportion with atrial fibrillation was higher among men than women (12.1% vs 7.6%). Less than 1% of patients younger than 40 years had atrial fibrillation, whereas 10% to 20% of patients older than 60 years had atrial fibrillation. The Figure shows that the proportion of patients with atrial fibrillation was higher among men than women in all 10-year age groups and that the proportion of patients with atrial fibrillation increased by age in both sexes. Twenty to forty percent of patients with ischemic heart disease, congestive heart failure, or heart valve disease had atrial fibrillation (Table 2). The adjusted odds ratio of atrial fibrillation was almost doubled in men, and the odds ratio of atrial fibrillation increased by 1.7 per 10-year increment in age (Table 3). In the presence of ischemic heart disease, congestive heart failure, or heart valve disease, the odds ratios for atrial fibrillation increased 1.8-fold, 3.9-fold, and 2.6-fold (Table 3). Stratified analysis by sex did not show any clinically relevant effect modifica-
tion by age (data not shown). We observed a less pronounced effect of an increasing age in patients with a history of ischemic heart disease or congestive heart failure. In patients with ischemic heart disease, the odds ratio for atrial fibrillation of a 10-year increment in age was 1.4 (vs 1.7 in the overall estimate), and in patients with congestive heart failure, the odds ratio of a 10-year increment in age was 1.1 (vs 1.7 in the overall estimate).

The risk of atrial fibrillation or flutter in hyperthyroidism was higher in men than in women, and the risk of atrial fibrillation in hyperthyroidism increased by increasing age during the age range of 20 to 89 years. The presence of ischemic heart disease, congestive heart failure, and heart valve disease was also associated with an increased risk of atrial fibrillation.

Hyperthyroidism in elderly patients is often associated with discrete and vague symptoms, so the hyperthyroid state may have had a longer duration before a diagnosis of hyperthyroidism is obtained. This could be one explanation for the increased proportion of patients with atrial fibrillation among the elderly population. Another explanation could be a shortening in the repolarization phase of the intracellular potential in the atrium induced by the hyperthyroidism. This may cause atrial fibrillation in those who are already at risk for atrial fibrillation (ie, elderly patients and patients with preexisting heart disease). Furthermore, Iwasaki and coworkers have reported that the hyperthyroidism was biochemically more severe (higher serum thyroxin and triiodothyronine levels) in those who had atrial fibrillation. However, we did not have biochemical data on the severity of hyperthyroidism in the present study.
In patients with preexisting heart disease, the increased workload caused by the induction of a hyperdynamic circulation caused by hyperthyroidism may further impair heart function, leading to heart failure, angina, and atrial fibrillation. Conversely, tachyarrhythmia caused by a combination of hyperthyroidism and atrial fibrillation may also lead to heart failure due to tachycardia-induced cardiomyopathy.

The major advantages of our study derive from the population-based design, the uniformly organized health care system, the sampling of incident cases, and the large number of outcomes. The risk of inclusion of amiodarone-induced thyrotoxicosis was minimized by the short interval of ±30 days from the date of the diagnosis of hyperthyroidism to the date of atrial fibrillation.

We did not have information on patients with hyperthyroidism who were not seen in the hospital. However, patients with hyperthyroidism are, according to tradition, almost always submitted for evaluation in hospital clinics in Denmark. Limitations may arise from errors in coding of discharge diagnoses. Misclassification of atrial fibrillation, hyperthyroidism, and comorbidity may have occurred, and we do not have clinical details, such as severity of the hyperthyroidism. The true proportion of patients with atrial fibrillation among patients with hyperthyroidism is surely higher than in the present study, because some cases of atrial fibrillation may not have been coded into the Danish National Registry of Patients. A systematic monitoring of the heart rhythm in patients with hyperthyroidism would have inflated the proportion of patients with atrial fibrillation. However, coding of patients with short episodes of self-limiting atrial fibrillation of minor clinical significance, like patients with atrial fibrillation in the Danish National Registry of Patients, would not have had any impact on the estimates of relative risk for atrial fibrillation among patients with hyperthyroidism, provided that this misclassification was independent of patient age, sex, and cardiovascular disease status. Some cases of hyperthyroidism complicated by atrial fibrillation may have been diagnosed among patients who were hospitalized primarily for cardiovascular diseases. A screening for hyperthyroidism among these patients would lead us to overestimate the risk for atrial fibrillation in patients with hyperthyroidism and preexisting cardiovascular disease. We could not differentiate atrial fibrillation from atrial flutter, because atrial fibrillation and atrial flutter had the same ICD-10 code. However, from evaluation of case records of patients participating in the Danish Diet, Cancer and Health Study and recorded in the Danish National Registry of Patients with an incident diagnosis of atrial fibrillation or flutter, we know that approximately 5% of the recorded cases have pure atrial flutter. If hyperthyroidism is not associated with risk of atrial flutter, inclusion of atrial flutter in the present study may have biased the risk estimates. However, given the low proportion of patients with atrial flutter, this bias would be modest.

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REFERENCES


Correction

Table 3 is reprinted here with the correct data.

Table 3. Risk Factors for Atrial Fibrillation Among 40628 Patients With Hyperthyroidism in Denmark (January 1, 1980–December 31, 1999)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted OR (95% CI)*</th>
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</thead>
<tbody>
<tr>
<td>Men (reference, women)</td>
<td>1.7 (1.6-1.9)</td>
</tr>
<tr>
<td>Age at diagnosis of hyperthyroidism (risk per 10-y increment)</td>
<td>1.7 (1.7-1.8)</td>
</tr>
<tr>
<td>Medical condition before or at diagnosis of hyperthyroidism†</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.9 (0.8-1.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.9 (0.8-1.1)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.3 (1.2-1.4)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2.6 (2.6-3.1)</td>
</tr>
<tr>
<td>Aortic and/or mitral valve disease</td>
<td>1.9 (1.5-2.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

*Risk estimates are adjusted for the other characteristics in the table.

†Relative risk to no disease.