ORIGINAL INVESTIGATION

Hyperthyroidism and Risk of Atrial Fibrillation or Flutter

A Population-Based Study

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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 ±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, 3362 (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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ATRIAL FIBRILLATION IS associated with increased cardiovascular morbidity and mortality.[1-4] The risk of atrial fibrillation increases exponentially with age, and it has been estimated that the prevalence of atrial fibrillation after the age of 75 years is 7% to 8% in men and 2% to 6% in women.[5,6] The most important risk factors for atrial fibrillation are increasing age, male sex, hypertension, diabetes, myocardial infarction, and congestive heart failure.[7]

It is well recognized that hyperthyroidism is associated with risk of worsening of a preexisting heart disease, but hyperthyroidism can also, by itself, cause cardiac disease.[8,9] Atrial fibrillation is a common cardiac manifestation in hyperthyroidism, and the prevalence of atrial fibrillation has been reported to be in the range of 1% to 60% among patients with hyperthyroidism, depending on sex, age, and the presence of previous or concomitant cardiovascular diseases.[10-20] A review of published literature from 1916 to 1943 on risk of atrial fibrillation associated with hyperthyroidism can be found in the book *On Goitre and Allied Diseases* by Hertz.[21]

The relation between hyperthyroidism and atrial fibrillation has been analyzed in a limited number of mostly selected patients reported from single centers, and the strength of the association between hyperthyroidism and atrial fibrillation has so far not been estimated. We therefore examined the risk of atrial fibrillation among patients with hyperthyroidism diagnosed in Denmark during a 20-year period.

METHODS

The study was conducted from January 1, 1977, to December 31, 1999, in Denmark. During the study period, the population increased from approximately 5.1 million to 5.3 million inhabitants. The general health and hospital care systems in Denmark are no-charge and nonprofit systems that are financed through taxes.

Patients seen in Danish hospitals are offered a clinical examination at admission, and most patients are offered an electrocardio-

gram, especially in medical departments. Furthermore, an electrocardiogram will be recorded, when indicated. Patients newly diagnosed as having atrial fibrillation are, according to guidelines, screened for hyperthyroidism.

IDENTIFICATION OF PATIENTS WITH HYPERTHYROIDISM

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=11 737) 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 3-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 day 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 *International Classification of Diseases, Eighth Revision (ICD-8)* to *International Classification of Diseases, 10th 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.

Diagnosis	Code
Atrial fibrillation and atrial flutter	427.93, 427.94, I48
Hyperthyroidism	242, E05
Hypothyroidism	244, E00, E03
Hypertension	400-404, 410.09, 411.09, 412.09, 413.09, 414.09, 435.09, 437.00, 437.01, 437.08, 437.09, 438.09, I10-I15
Diabetes	249, 250, E10-E14
Ischemic heart disease	410-414, I20-I25
Congestive heart failure	425.99, 427.09, 427.10, 427.11, 427.19, 427.99, 428.99, I50
Mitral and/or aortic valve disease	394-396, I05, I06, I08, I34, I35

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-

Table 1. Demographic and Clinical Characteristics of 40 628 Patients Diagnosed in Danish Hospitals as Having Hyperthyroidism (January 1, 1980–December 31, 1999)

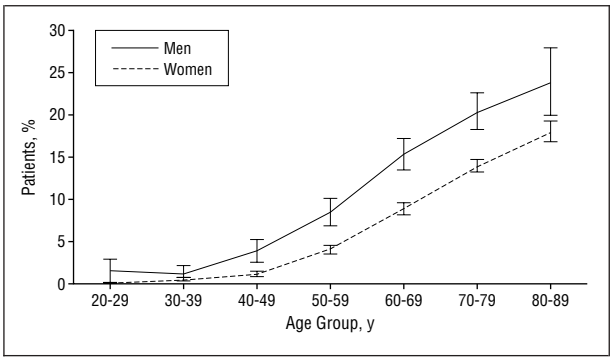
Characteristic	Patients, No. (%)
Sex	
Men	6115 (15.1)
Women	34 513 (84.9)
Age at diagnosis, y	
20-29	2590 (6.4)
30-39	4303 (10.6)
40-49	5621 (13.8)
50-59	7073 (17.4)
60-69	7922 (19.5)
70-79	8841 (21.8)
80-89	4278 (10.5)
Medical condition before or at diagnosis of hyperthyroidism	
Hypertension	1863 (4.6)
Diabetes	1770 (4.4)
Ischemic heart disease	2792 (6.9)
Congestive heart failure	1660 (4.1)
Aortic and/or mitral valve disease	276 (0.7)

Table 2. Frequency Distribution of 3362 Patients With Atrial Fibrillation Among 40 628 Patients With Hyperthyroidism in Denmark (January 1, 1980–December 31, 1999)

Characteristic	Proportion With Atrial Fibrillation or Flutter	Percent With Atrial Fibrillation or Flutter (95% CI)
Total	3362/40 628	8.3 (8.0-8.5)
Sex		
Men	741/6115	12.1 (11.3-13.0)
Women	2621/34 513	7.6 (7.3-7.9)
Age at diagnosis of hyperthyroidism, y		
20-29	7/2590	0.3 (0.1-0.5)
30-39	24/4303	0.6 (0.4-0.8)
40-49	87/5621	1.5 (1.3-1.9)
50-59	337/7073	4.8 (4.3-5.3)
60-69	795/7922	10.0 (9.4-10.7)
70-79	1316/8841	14.9 (14.2-15.6)
80-89	796/4278	18.6 (17.5-19.8)
Medical condition before or at diagnosis of hyperthyroidism		
Hypertension	233/1863	12.5 (11.1-14.1)
Diabetes	225/1770	12.7 (11.2-14.3)
Ischemic heart disease	635/2792	22.7 (21.2-24.3)
Congestive heart failure	619/1660	37.3 (35.0-39.6)
Aortic and/or mitral valve disease	90/276	32.6 (27.3-38.3)

Abbreviation: CI, confidence interval.

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).



Proportion of men and women by 10-year age groups with atrial fibrillation or flutter among patients with hyperthyroidism. Error bars indicate 95% confidence intervals.

Table 3. Risk Factors for Atrial Fibrillation Among 40 628 Patients With Hyperthyroidism in Denmark (January 1, 1980–December 31, 1999)

Characteristic	Adjusted OR (95% CI)*
Men (reference women)	1.8 (1.6-1.9)
Age at diagnosis of hyperthyroidism (risk per 10-year increment)	1.7 (1.7-1.8)
Medical condition before or at diagnosis of hyperthyroidism†	
Hypertension	1.1 (0.9-1.3)
Diabetes	1.0 (0.8-1.2)
Ischemic heart disease	1.8 (1.6-2.0)
Congestive heart failure	3.9 (3.5-4.4)
Aortic and/or mitral valve disease	2.6 (1.9-3.4)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Risk estimates are adjusted for the other characteristics in the table.
†Relative risk to no disease.

COMMENT

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.[24] 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[17] 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[25] 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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Correction

Error in Tables. In the Original Investigation titled "Hyperthyroidism and Risk of Atrial Fibrillation or Flutter: A Population-Based Study" by Frost et al published in the August 9/23 issue of the ARCHIVES (2004;164:1675-1678), there were errors in the tables. The errors do not change any major conclusions of the study.

The section in Table 1 ("Demographic and Clinical Characteristics of 40 628 Patients Diagnosed in Danish Hospitals as Having Hyperthyroidism [January 1, 1980–December 31, 1999]") published with incorrect data is reprinted here as a tabulation with the correct data.

Characteristic	Patients, No. (%)
Medical condition before or at diagnosis of hyperthyroidism	
Hypertension	3176 (7.8)
Diabetes	2198 (5.4)
Ischemic heart disease	4521 (11.1)
Congestive heart failure	2475 (6.1)
Aortic and/or mitral valve disease	458 (1.1)

The section in Table 2 ("Frequency Distribution of 3362 Patients With Atrial Fibrillation Among 40 628 Patients With Hyperthyroidism in Denmark [January 1, 1980–December 31, 1999]") published with incorrect data is reprinted here as a tabulation with the correct data.

Characteristic	Proportion With Atrial Fibrillation or Flutter	Percent With Atrial Fibrillation or Flutter (95% CI)
Medical condition before or at diagnosis of hyperthyroidism		
Hypertension	358/3176	11.3 (10.2-12.4)
Diabetes	254/2198	11.6 (10.3-13.0)
Ischemic heart disease	817/4521	18.1 (17.0-19.2)
Congestive heart failure	727/2475	29.4 (27.6-31.2)
Aortic and/or mitral valve disease	115/458	25.1 (21.4-29.3)

Abbreviation: CI, confidence interval.

Table 3 is reprinted here with the correct data.

Table 3. Risk Factors for Atrial Fibrillation Among 40 628 Patients With Hyperthyroidism in Denmark (January 1, 1980–December 31, 1999)

Characteristic	Adjusted OR (95% CI)*
Men (reference, women)	1.7 (1.6-1.9)
Age at diagnosis of hyperthyroidism (risk per 10-y increment)	1.7 (1.7-1.8)
Medical condition before or at diagnosis of hyperthyroidism†	
Hypertension	0.9 (0.8-1.0)
Diabetes	0.9 (0.8-1.1)
Ischemic heart disease	1.3 (1.2-1.4)
Congestive heart failure	2.8 (2.6-3.1)
Aortic and/or mitral valve disease	1.9 (1.5-2.4)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Risk estimates are adjusted for the other characteristics in the table.
†Relative risk to no disease.