CLINICAL RESEARCH STUDY

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History of Thyroid Disorders in Relation to Clinical Outcomes in Atrial Fibrillation

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ABSTRACT

BACKGROUND: Atrial fibrillation is the most common cardiac complication of hyperthyroidism. The association between history of hyperthyroidism and stroke remains unclear. We sought to determine whether history of thyroid dysfunction is a thromboembolic risk factor in patients with atrial fibrillation.

METHODS: Patients with atrial fibrillation seen in an academic institution between 2000 and 2010 were identified and followed-up. Clinical events (stroke/systemic embolism, bleeding, all-cause death) were recorded and related to thyroid status and disorders. Associations were examined in time-dependent models with adjustment for relevant confounders.

RESULTS: Among 8962 patients, 141 patients had a history of hyperthyroidism, 540 had a history of hypothyroidism, and 8271 had no thyroid dysfunction. Mean follow-up was 929 ± 1082 days. A total of 715 strokes/systemic embolism were recorded, with no significant difference in the rates of these events in patients with a history of thyroid dysfunction vs those without thyroid problems in either univariate or multivariable analysis (hazard ratio [HR] 0.85; 95% confidence interval [CI], 0.41-1.76 for hyperthyroidism; HR 0.98; 95% CI, 0.73-1.34 for hypothyroidism). There were 791 bleeding events; history of hypothyroidism was independently related to a higher rate of bleeding events (HR 1.35; 95% CI, 1.02-1.79). No significant difference among the 3 groups was observed for the incidence of death.

CONCLUSIONS: History of hyperthyroidism was not an independent risk factor for stroke/systemic embolism in atrial fibrillation, whereas hypothyroidism was associated with a higher risk of bleeding events. These data suggest no additional benefit from the inclusion of thyroid dysfunction in thromboembolic prediction models in atrial fibrillation.

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KEYWORDS: Atrial fibrillation; Hyperthyroidism; Hypothyroidism; Stroke

Hyperthyroidism is a common endocrine disorder, affecting between 0.5% and 2% of the general population.[1] Atrial fibrillation is the most common cardiac complication of hyperthyroidism, occurring in an estimated 10% to 25% of overtly hyperthyroid patients. In comparison, 1.5% to 2% of the general population has atrial fibrillation.[2-5] Although hyperthyroidism may have cardiovascular consequences, the association between the natural history of hyperthyroidism and ischemic stroke remains unclear in patients with atrial fibrillation. The Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category (female) stroke risk-prediction (CHA_2DS_2-VASc) score can be used to determine the optimal treatment strategy for stroke prevention. Hyperthyroidism is not among the thromboembolic risk factors included in the CHA_2DS_2-VASc score, and the use of anticoagulation to prevent thromboembolic complications of thyrotoxic atrial fibrillation is controversial.

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Furthermore, national guideline recommendations for use of anticoagulation in this population are inconsistent.[3-5] Guidelines from the American College of Chest Physicians[3] conclude that thyrotoxicosis does not appear to be a valid risk factor in stroke, and recommend antithrombotic therapy regardless of whether hyperthyroidism is present. Conversely, the American College of Cardiology/American Heart Association guidelines[5] state that anticoagulation is recommended in atrial fibrillation patients with hyperthyroidism, in the absence of a specific contraindication, at least until a euthyroid state has been restored. The aim of our study was to determine whether history of thyroid dysfunction, particularly hyperthyroidism, is a thromboembolic risk factor in patients with atrial fibrillation.

CLINICAL SIGNIFICANCE

- History of hyperthyroidism was not an independent risk factor for stroke/systemic embolism in patients with atrial fibrillation.
- These data suggest no additional benefit from the inclusion of thyroid dysfunction in thromboembolic prediction models in atrial fibrillation.
- By contrast, history of hypothyroidism was associated with a higher risk of bleeding events.

MATERIALS AND METHODS

Study Population

We included all patients with a diagnosis of atrial fibrillation or atrial flutter seen in our institution between January 2000 and December 2010. The patients' characteristics were obtained from computerized medical records held in our institution. Extensive information was collected, including dates of admission and discharge, clinical presentation, diagnosis, presence of comorbid conditions, medication use, and subsequent hospitalization. The patients' CHA_2DS_2-VASc score and Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly (HAS-BLED) score were calculated retrospectively.[4]

Patients with a thyroid disorder at the time of entry into the registry (ie, at baseline for a given patient when atrial fibrillation was diagnosed) were identified using the computerized codification system completed for each patient using the International Classification of Diseases, 10th Revision of the World Health Organization, with codes E00 to E07, and by screening clinical reports. On the basis of this information, the following were determined: history of hyperthyroidism or hypothyroidism, thyroid status at baseline (when atrial fibrillation was diagnosed), and amiodarone-induced thyroid dysfunction. Patients were divided into 3 groups: patients with no thyroid dysfunction, patients with a history of hyperthyroidism, and patients with a history of hypothyroidism. Hospitalization reports were screened to collect data on medication use at discharge from hospital.

Patients were followed-up to collect data on stroke/systemic embolism, bleeding events, and all-cause death. Information was also obtained from the computerized database in our institution, which provides specialist services across 4 sites, and covers a catchment area of around 4000 km^2 with a population of approximately 400,000.[6] In addition, deaths were identified using an online search tool dedicated to local news, covering an area of 35,000 km^2.[7]

The study was approved by the institutional review board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital on December 7, 2010 and registered as a clinical audit. Ethical review was therefore not required. Patient consent was not sought. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care.

Statistical Analysis

The characteristics of the patients are given as counts and percentages or means ± SDs. The chi-squared test was used to compare categorical variables, and Student's t test or the nonparametric Kruskal-Wallis test, where appropriate, to compare continuous variables. Multivariable analysis with a proportional hazards model was used to investigate the association between thyroid dysfunction and outcomes. We also compared the rates of thromboembolic events in the 3 groups according to the Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke [Doubled] ($CHADS_2$) score, with additional adjustment on anticoagulant use based on the assumption that vitamin K antagonist (VKA) medication reduces the risk of thromboembolic events by 64% in patients who received this therapy within each stratum of risk.[3] A P value $< .05$ was considered to be statistically significant. Statistical analysis was carried out with Statview 5.0 software (Abacus Concepts, Berkeley, CA, USA).

RESULTS

A total of 8962 patients with atrial fibrillation were included in this study between 2000 and 2010: 8281 (92%) patients had normal thyroid function, 141 (2%) had a history of hyperthyroidism, and 540 (6%) had a history of hypothyroidism. Patient characteristics are presented in **Table 1**. Amiodarone-induced thyroid dysfunction was present in 42 (30%) patients with a history of hyperthyroidism and in 76 (14%) patients with a history of hypothyroidism. Thyroid-stimulating hormone values measured in the previous 6 months were available for 109 patients with a thyroid disorder; mean concentrations were significantly lower in patients with a history of hyperthyroidism than in those with hypothyroidism (1.0 ± 3.1 vs 12.3 ± 20.1 mIU/L, $P = .0002$).

Table 1 Characteristics of Patients with Atrial Fibrillation According to History of Thyroid Dysfunction

Variable	Atrial Fibrillation and No Thyroid Dysfunction (n = 8281, 92%)	Atrial Fibrillation and History of Hyperthyroidism (n = 141, 2%)	Atrial Fibrillation and History of Hypothyroidism (n = 540, 6%)	*P* Value among the 3 Groups
Age (y) (mean ± SD)	71 ± 14	68 ± 13	74 ± 12	<.0001
Women, n (%)	3044 (37)	69 (49)	354 (66)	<.0001
Heart failure, n (%)	4470 (54)	83 (59)	359 (66)	<.0001
Hypertension, n (%)	3412 (41)	58 (41)	273 (51)	.0001
Diabetes mellitus, n (%)	1265 (15)	19 (13)	102 (19)	.06
Previous ischemic stroke	678 (8)	12 (9)	48 (9)	.84
Coronary artery disease, n (%)	2484 (30)	35 (25)	99 (37)	.001
Previous myocardial infarction, n (%)	1176 (14)	22 (16)	100 (19)	.02
Valve disease, n (%)	1842 (22)	38 (27)	159 (29)	.003
$CHADS_2$ score (mean ± SD)	1.7 ± 1.3	1.6 ± 1.3	2.1 ± 1.3	<.0001
CHA_2DS_2-VASc score (mean ± SD)	3.1 ± 1.8	3.1 ± 1.8	4.0 ± 1.7	<.0001
HAS-BLED score (mean ± SD)	1.6 ± 1.1	1.5 ± 1.2	1.9 ± 1.1	<.0001
Renal insufficiency, n (%)	713 (9)	12 (9)	83 (15)	<.0001
Chronic obstructive pulmonary disease, n (%)	838 (10)	21 (15)	92 (17)	<.0001
Hyperlipidemia, n (%)	1594 (19)	24 (17)	146 (27)	<.0001
Permanent atrial fibrillation, n (%)	3228 (39)	61 (43)	206 (38)	.54
Pacemaker or implantable cardioverter defibrillator, n (%)	1360 (16)	27 (19)	117 (22)	.005
Left ventricular ejection fraction (mean ± SD) (n = 1934)	47 ± 16	45 ± 18	46 ± 17	.63
Euthyroid clinical status at the time of atrial fibrillation diagnosis, n (%)	8281 (100)	91 (65)	488 (90)	<.0001
Hyperthyroidism at the time of atrial fibrillation diagnosis, n (%)	0 (0)	50 (35)	9 (2)	<.0001
Hypothyroidism at the time of atrial fibrillation diagnosis, n (%)	0 (0)	0 (0%)	43 (8)	<.0001
Amiodarone-induced thyroid dysfunction, n (%)	0 (0)	42 (30)	76 (14)	<.0001
Medication during follow-up				
Oral anticoagulation (n = 8120), n (%)	4246/7487 (57)	98/134 (73)	293/499 (59)	.0005
Antiplatelet agent (n = 7951), n (%)	2534/7330 (35)	32/131 (24)	196/490 (40)	.002
ACE or ARB (n = 4938), n (%)	1805/4530 (40)	31/97 (32)	139/311 (45)	.06
Beta-blocker (n = 4938), n (%)	1984/4530 (44)	51/97 (53)	139/311 (45)	.22
Diuretic (n = 4476), n (%)	1906/4085 (47)	36/89 (40)	183/302 (61)	<.0001
Class III antiarrhythmic agent (n = 5101), n (%)	1590/4687 (34)	29/100 (29)	118/314 (38)	.23

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category (female) stroke risk-prediction; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol.

The average CHA_2DS_2-VASc and HAS-BLED scores were higher in patients with a history of hypothyroidism than in those without thyroid dysfunction and those with a history of hyperthyroidism. Several patient characteristics, most prominently older age, hypertension, history of congestive heart failure, coronary artery disease, and renal insufficiency, were significantly associated with a history of hypothyroidism (all $P \leq .0001$; Table 1). By contrast, history of stroke had a homogeneous distribution in each group. During follow-up of 929 ± 1082 days, an oral anticoagulant was given in 57% of patients without thyroid dysfunction, in 73% of patients with a history of hyperthyroidism, and in 59% of patients with history of hypothyroidism ($P = .0005$).

Follow-up Events

Stroke/Systemic Embolism. The event rates for stroke/systemic embolism are shown in Table 2. Patients on a VKA at discharge had a lower risk of stroke/systemic embolism compared with patients not taking this medication (hazard ratio [HR] 0.84; 95% confidence interval [CI], 0.72-0.99; $P = .03$). There were no significant differences in the rates of stroke/systemic embolism in patients with a history of hyperthyroidism or hypothyroidism compared with patients without thyroid dysfunction (Figure 1).

Table 2 presents the univariate and multivariable analyses for prediction of stroke/systemic embolism. History of hyperthyroidism, hypothyroidism, and amiodarone-induced thyroid dysfunction were not independent risk factors for

Table 2 Cox Regression Analysis for Prediction of Stroke/Systemic Thromboembolism and Bleeding Events

	Univariate Analysis		Multivariable Analysis	
Variable	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Stroke/systemic thromboembolism				
Age (per 1-year increase)	1.05 (1.04-1.05)	<.0001	1.02 (1.01-1.03)	<.0001
Female sex	0.80 (0.69-0.93)	.004	0.86 (0.81-1.14)	.62
CHA_2DS_2-VASc score (per unit increase)	0.72 (0.69-0.75)	<.0001	1.34 (1.23-1.45)	<.0001
HAS-BLED score (per unit increase)	0.69 (0.65-0.73)	<.0001	0.93 (0.83-1.05)	.23
Valve disease	1.27 (1.08-1.49)	.004	1.09 (0.91-1.29)	.35
History of hyperthyroidism	0.70 (0.37-1.31)	.25	0.85 (0.41-1.76)	.66
History of hypothyroidism	1.11 (0.84-1.48)	.43	0.98 (0.73-1.34)	.92
Current hyperthyroidism	0.70 (0.26-1.88)	.48	0.64 (0.18-2.24)	.49
Current hypothyroidism	0.60 (0.19-1.85)	.37	0.48 (0.15-1.53)	.22
Amiodarone-induced thyroid dysfunction	1.00 (0.65-1.55)	.99	1.23 (0.77-1.97)	.39
Atrial flutter and no documented atrial fibrillation	0.41 (0.24-0.68)	.0005	0.48 (0.28-0.84)	.01
Atrial flutter with documented atrial fibrillation	0.50 (0.30-0.84)	.01	0.76 (0.44-1.29)	.31
Permanent atrial fibrillation	1.26 (1.09-1.47)	.002	1.12 (0.95-1.31)	.19
Vitamin K antagonist at discharge	0.84 (0.72-0.99)	.03	0.93 (0.77-1.11)	.42
Antiplatelet agent at discharge	1.53 (1.30-1.79)	<.0001	1.21 (1.00-1.47)	.05
Bleeding events				
Age (per 1-year increase)	1.02 (1.02-1.03)	<.0001	1.01 (1.00-1.02)	.002
Female sex	1.23 (1.06-1.42)	.01	0.68 (0.57-0.82)	<.0001
CHA_2DS_2-VASc score (per unit increase)	0.85 (0.81-0.88)	<.0001	1.05 (0.97-1.13)	.27
HAS-BLED score (per unit increase)	0.74 (0.70-0.79)	<.0001	1.18 (1.06-1.31)	.002
Valve disease	1.73 (1.49-2.00)	<.0001	1.53 (1.30-1.79)	<.0001
History of hyperthyroidism	0.96 (0.57-1.59)	.86	1.26 (0.70-2.24)	.44
History of hypothyroidism	1.31 (1.01-1.69)	.04	1.35 (1.02-1.79)	.03
Current hyperthyroidism	0.62 (0.23-1.66)	.34	0.51 (0.17-1.51)	.22
Current hypothyroidism	0.92 (0.38-2.22)	.86	0.53 (0.19-1.44)	.21
Amiodarone-induced thyroid dysfunction	1.21 (0.82-1.77)	.34	1.25 (0.83-1.88)	.29
Atrial flutter and no documented atrial fibrillation	0.70 (0.48-1.02)	.06	0.72 (0.49-1.07)	.11
Atrial flutter with documented atrial fibrillation	0.58 (0.37-0.91)	.01	0.70 (0.44-1.11)	.12
Permanent atrial fibrillation	1.41 (1.23-1.62)	<.0001	1.30 (1.12-1.52)	.0001
Vitamin K antagonist at discharge	1.22 (1.04-1.42)	.01	1.14 (0.96-1.36)	.14
Antiplatelet agent at discharge	1.20 (1.03-1.40)	.02	1.05 (0.87-1.26)	.59

CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category (female) stroke risk-prediction; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol.

stroke/systemic embolism, whereas increasing age and CHA_2DS_2-VASc score were risk factors.

Table 3 shows the rates of use of VKA and the observed and estimated rates (in the absence of therapy with VKA) of stroke/systemic embolism according to $CHADS_2$ score. The rate of stroke/systemic embolism in patients without thyroid dysfunction was similar to that in patients with a history of hypothyroidism or hyperthyroidism.

Bleeding Events. During follow-up, 791 bleeding events were recorded, with an annual rate of 3.7%. History of hypothyroidism was associated with a higher rate of bleeding events compared with patients without thyroid dysfunction (Table 2, Figure 2). Multivariable analyses for predicting bleeding events confirmed this result. Other factors associated with a higher bleeding risk are in Table 2.

All-Cause Death. There were 1155 deaths during follow-up. The death rate was 5.1% per year, with no difference in incidence in patients with a history of hyperthyroidism (HR 0.80; 95% CI, 0.50-1.28; $P = .35$) or hypothyroidism (HR 1.19; 95% CI, 0.96-1.48; $P = .11$) vs patients without thyroid dysfunction.

DISCUSSION

Hyperthyroidism is a common metabolic disorder that can exacerbate preexisting cardiac disease or cause de novo

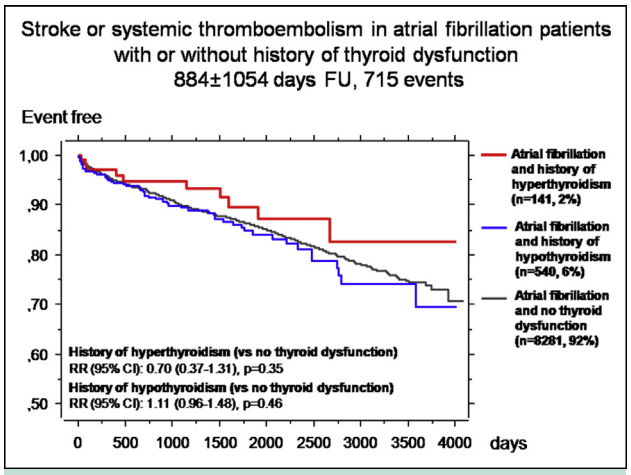

Figure 1 Stroke or systemic embolism in patients with atrial fibrillation according to history of thyroid dysfunction.

cardiovascular abnormalities including atrial fibrillation and heart failure.[8] Despite the close links between hyperthyroidism and atrial fibrillation, and between atrial fibrillation and stroke or thromboembolism, whether hyperthyroidism-induced atrial fibrillation per se is a risk factor for stroke remains controversial. In our large cohort study with a relatively long follow-up, we found that history of hyperthyroidism was not a significant risk factor for thromboembolism; neither was history of hypothyroidism or amiodarone-induced thyroid dysfunction. Furthermore, our data suggest that history of hypothyroidism is associated with a higher risk of bleeding events, in addition to the HAS-BLED score.

Most of the patients with thyroid dysfunction were euthyroid at the time of atrial fibrillation diagnosis, which may suggest that thyroid dysfunction was often a complication of established atrial fibrillation rather than an important etiological factor. Amiodarone-induced thyroid dysfunction was indeed the commonest cause identified in this cohort of patients with atrial fibrillation. The time course of diagnosis of thyroid problems presents a significant issue in this type of analysis. A patient who is euthyroid or hypothyroid may develop hyperthyroidism at a later stage, due to over-replacement or amiodarone use. Our analysis included both history of hypo- or hyperthyroidism and thyroid status at baseline, in order to deal with this time-dependent covariate. In addition, the approach mirrored that taken by a clinician, in which the patient's individual risk level is assessed at baseline (ie, without the knowledge of future events) in order to choose the appropriate treatment — in most cases, long-term antithrombotic therapy.

Clinical evidence for anticoagulation of thyrotoxic patients with atrial fibrillation comes predominantly from retrospective cohort trials or case series, conducted before 1990, with relatively small numbers of patients. Coagulation abnormalities, such as shortened activated partial thromboplastin time, increased fibrinogen levels, and

Table 3 Prevalence by CHA_2DS_2-VASc Score and Rates of Stroke/Systemic Embolism in Patients with Atrial Fibrillation According to History of Thyroid Dysfunction

	Atrial Fibrillation and No Thyroid Dysfunction (n = 8281, 92%)			Atrial Fibrillation and History of Hyperthyroidism (n = 141, 2%)			Atrial Fibrillation and History of Hypothyroidism (n = 540, 6%)			
CHA_2DS_2-VASc Score	Therapy with OAC (%)	Observed Rate of Events (%/y)	Estimated Rate of Events with No OAC (%/y)	Therapy with OAC (%)	Observed Rate of Events (%/y)	Estimated Rate of Events with No OAC (%/y)	Odds Ratio (95%CI) vs Group 1	Therapy with OAC (%)	Observed Rate of Events (%/y)	Estimated Rate of Events with No OAC (%/y)	Odds Ratio (95% CI) vs Group 1
0-1	51	0.96	1.26	70	0.00	0.00	–	41	1.25	1.54	1.82 (0.53-6.31)
2-3	61	2.73	3.60	78	1.16	1.67*	0.57 (0.18-1.76)	66	1.52	2.09*	0.69 (0.39-1.23)
4-5	56	4.32	5.70	68	4.98	6.86	1.58 (0.86-2.93)	61	4.56	6.13	1.12 (0.81-1.56)
≥6	52	8.89	11.73	79	3.74	5.39	0.87 (0.30-2.47)	48	8.75	11.57	1.04 (0.70-1.54)

CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category (female) stroke risk-prediction; CI = confidence interval; OAC = oral anticoagulant.

*Based on a 64% reduction in thromboembolic events for the percentage of patients treated with a vitamin K antagonist in each stratum of risk.

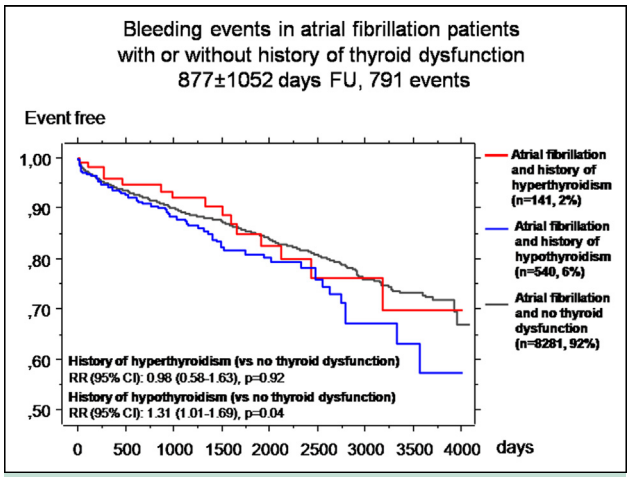

Figure 2 Major bleeding in patients with atrial fibrillation according to history of thyroid dysfunction.

increased factor VIII and factor X activity, are seen frequently in patients in sinus rhythm with thyrotoxicosis.[9,10] Previous short-term observational studies have reported a high incidence of systemic embolism in patients with hyperthyroidism-induced atrial fibrillation (8% to 24%).[11-15] However, a retrospective cohort trial analyzing data from 610 patients with thyrotoxicosis (of whom 91 had atrial fibrillation) concluded that age, rather than atrial fibrillation, was the only risk factor for stroke among patients with hyperthyroidism-induced atrial fibrillation.[2] The lack of an age-matched control group, or a control group in sinus rhythm, may account for the disparate results in previous studies.[11,14] A study comparing "lone" atrial fibrillation with thyrotoxic atrial fibrillation would be beneficial in exploring the independent thromboembolic risk of hyperthyroidism.[13]

A previous review of clinical studies suggested an increased rate of thromboembolic events in atrial fibrillation patients with thyrotoxicosis.[16] Most of the clinically evident emboli affected the central nervous system, with potentially devastating consequences. The authors concluded that, in the absence of clinical evidence, anticoagulation should be given on an individualized basis, taking into account the patient's age, bleeding risk, and associated cardiac disease. A 5-year follow-up study sought to estimate the risk for ischemic stroke among 3176 patients aged 18 to 44 years with hyperthyroidism, only 6 (0.2%) of whom had atrial fibrillation.[17] Hyperthyroidism was associated with an increased risk of ischemic stroke among young adults. The prospective Swedish cohort study investigated risk factors for stroke and bleeding in 182,678 patients with atrial fibrillation.[18] Several risk factors, including myocardial infarction, vascular disease, and renal failure, independently predicted ischemic stroke or thromboembolic events in atrial fibrillation, but thyroid disease (the prevalence of which was not indicated) did not emerge as an independent risk factor for stroke. In 160 patients with hyperthyroid disease who presented with new-onset atrial fibrillation, Siu et al[8] found an increased risk of ischemic stroke, clustering during the initial phase of presentation. To the best of our knowledge, our analysis is thus one of the largest in patients with both atrial fibrillation and a history of thyroid disorder, with improved antithrombotic management of atrial fibrillation and with a relatively long follow-up, and which included both stroke/systemic embolism events and bleeding outcomes.

Guidelines from the American College of Chest Physicians[3] suggested that currently available studies do not confirm that thyrotoxic atrial fibrillation is a more potent risk factor for stroke than other causes of atrial fibrillation. Because the incidence of thromboembolic events in patients with thyrotoxic atrial fibrillation appears similar to that of other atrial fibrillation patients, antithrombotic therapies should be chosen according to the presence of validated stroke risk factors.[4] Our results seem to confirm this general point of view. Despite the lack of specific evidence, oral anticoagulant therapy is recommended for the prevention of systemic embolism, in the presence of risk factors for stroke. It remains controversial whether patients with atrial fibrillation associated with previous (treated) thyrotoxicosis are at increased risk of thromboembolism, in the absence of risk factors.[4] By contrast, the American College of Cardiology in association with the American Heart Association[5] state that in patients with atrial fibrillation associated with thyrotoxicosis, oral anticoagulation (international normalized ratio [INR] range 2.0 to 3.0) is recommended to prevent thromboembolism, as recommended for atrial fibrillation patients with other risk factors for stroke. Once a euthyroid state has been restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism.

One should prompt early use of anticoagulation therapy in hyperthyroid patients with atrial fibrillation.[8] In light of our results, it seems better to maintain a therapeutic approach in atrial fibrillation patients with a thyrotoxic history as is usually proposed for patients with nonvalvular atrial fibrillation. CHA_2DS_2-VASc does not include thyroid dysfunction among the risk factors, and this score seems to be an appropriate way in which to evaluate risk of stroke or thromboembolism in these individuals. Consequently, patients with a history of thyroid dysfunction judged to be at low risk of stroke based on the CHA_2DS_2-VASc score might not benefit from long-term oral anticoagulant therapy, particularly when a euthyroid state is obtained.

Interestingly, in our study, history of hypothyroidism was independently associated with an increased risk of bleeding events. A common opinion is that hyperthyroidism intensifies the anticoagulation effect of VKA therapy, whereas hypothyroidism has the opposite effect, which appears to contrast with our observations. Hypothyroidism is linked to a low level of free thyroxin (FT4), and FT4 can exert its effect on the coagulation system in 2 ways. First, FT4 is directly related to levels of factor VIII and von Willebrand factor, with lower levels of FT4 associated with lower levels of these factors.[19-22] This could explain the

higher bleeding risk with lower levels of FT4 found in our study. Second, the patients with a history of hypothyroidism in our study were frequently treated with VKAs. FT4 affects the pharmacodynamics of these drugs, with different levels of FT4 resulting in different INR values.[23,24] However, the fact that the VKA dose was adapted continuously to stay within the therapeutic range should have mitigated any effect of FT4 on INR levels.

Study Limitations

All data were obtained retrospectively from our hospital discharge records, with limitations of diagnostic coding and case ascertainment. This was a single-center study and our results should be interpreted with caution in the context of the general population or in primary care. Patients were identified from hospitalizations, which represent a selected fraction of patients with atrial fibrillation, and our results may not therefore apply to all patients with atrial fibrillation. The study population may have limited racial/ethnic diversity and this may affect the generalizability to other populations worldwide. While several parameters of cardiac function were available, left atrial size was not, and we were unable to evaluate a difference among groups with regard to left atrial size. Patients with primary thyroid disorders were mixed with those with thyroid disorders resulting from the treatment of atrial fibrillation with amiodarone. Despite adjustment for several risk factors, the nonrandomized design leaves a risk of residual confounding factors, but, as already stated, most randomized trials to date in patients with atrial fibrillation excluded analyses of the effect of thyroid disorders. If a resident moved away from the area, or died or had a stroke diagnosed elsewhere, information on the event was not available. However, the relatively high number of deaths in our study suggests a high proportion of ascertainment of events. The data for VKA use related only to baseline therapy and do not reflect any changes in prescribed therapy or in adherence. Although we had information on major episodes of labile INR for some patients, data regarding a precise time in therapeutic range were are not available, which is a limitation for the analysis of bleeding risk. The patient's thyroid status at the time of a stroke (or other event) was unknown. Finally, the number of individuals with atrial fibrillation and a thyroid disorder was relatively small (although it is the largest in the literature with concurrent atrial fibrillation and thyroid dysfunction) and therefore, the statistical power of analysis in this group may be limited. This underscores the difficulty in gathering a relevant cohort of such patients in order to derive sensible recommendations about bleeding risk and thromboprophylaxis.

CONCLUSIONS

In this large series of patients with atrial fibrillation, history of thyroid dysfunction, especially hyperthyroidism, was not an independent risk factor for stroke/systemic embolism. In contrast, history of hypothyroidism was independently associated with a higher risk of bleeding events. Our results suggest that the inclusion of thyroid dysfunction would not provide additional benefit in existing stroke risk scores. The CHA_2DS_2-VASc score remains the optimal tool for stratifying atrial fibrillation patients with a history of thyrotoxicosis according to their stroke risk and need for anticoagulation.

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