Increased risk of ischemic stroke and systemic embolism in hyperthyroidism-related atrial fibrillation: A nationwide cohort study

Kyu Kim, MD a,b, Pil-Sung Yang, MD b,c, Eunsun Jang a, Hee Tae Yu, MD a, Tae-Hoon Kim, MD a, Jae-Sun Uhm, MD a, Jong-Youn Kim, MD a, Jung-Hoon Sung, MD b, Hui-Nam Pak, MD a, Moon-Hyoun Lee, MD a, Gregory Y.H. Lip, MD a,b,c,d, and Boyoung Joung, MD a† England, United Kingdom

Background We aimed to evaluate the long-term risk of ischemic stroke/systemic embolism of hyperthyroidism-related AF.

Methods This retrospective population-based cohort study included records of 1,034,099 atrial fibrillation patients between 2005 and 2016 from the Korean National Health Insurance Service database. After exclusion, we identified 615,724 oral anticoagulation-naïve patients aged ≥18 years with new-onset non-valvular atrial fibrillation, of whom 20,773 had hyperthyroidism-related atrial fibrillation. After 3:1 propensity score matching, ischemic stroke and systemic embolism occurrences were compared between hyperthyroidism-related and non-hyperthyroidism-related (“nonthyroidal”) atrial fibrillation patients.

Results After exclusion, we identified 615,724 oral anticoagulation-naïve AF patients of whom 20,773 had hyperthyroidism-related AF. Median follow-up duration was 5.9 years. Hyperthyroidism-related AF patients had significantly higher risks of ischemic stroke and systemic embolism than nonthyroidal AF patients (1.83 vs 1.62 per 100-person-year, hazard ratio[HR], 1.13; 95% confidence interval[CI], 1.07 to 1.19; P < 0.001). This risk was 36% higher in hyperthyroidism-related than in nonthyroidal AF patients within 1 year of atrial fibrillation diagnosis (3.65 vs 2.67 per 100-person-year, HR, 1.36; 95% CI, 1.24 – 1.50; P < 0.001). This difference was also observed in the CHA2DS2-VASc score subgroup analysis. The risk of ischemic stroke and systemic embolism significantly decreased in patients treated for hyperthyroidism (HR, 0.64; 95% CI, 0.58 to 0.70; P < 0.001).

Conclusions Hyperthyroidism-related AF patients have high risks of ischemic stroke and systemic embolism like nonthyroidal AF, especially when initially diagnosed. This risk is reduced by treating hyperthyroidism. (Am Heart J 2021;242:123–131.)

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia in patients with hyperthyroidism and is observed in 5%–15% of hyperthyroidism cases.1,2 Sub-clinical hyperthyroidism and overt thyrotoxicosis are important predisposing factors for AF.3 It is well known that AF is associated with an increased risk of ischemic stroke and systemic embolism (SSE) and that anticoagulation treatment reduces the risk of SSE.4–6 However, the risk of SSE in hyperthyroidism-related AF remains unclear.7–8

Previous observational studies with small populations have shown a high incidence of ischemic stroke in hyperthyroidism-related AF patients and claimed the need for anticoagulation treatment.9,10 However, in a previous large-scale nationwide cohort study, hyperthyroidism-related AF was not deemed an independent risk factor for stroke.11 Thus, previously published clinical guidelines regard hyperthyroidism as a weakly validated risk factor for ischemic stroke in AF patients.12,13 This discrepancy is derived from the nature of hyperthyroidism-related AF. Hyperthyroidism is a curable disease, and its treatment can result in the spontaneous restoration of sinus rhythm in a significant propor-
tion of patients with hyperthyroidism who present with new-onset AF. However, recent studies have shown an increased risk of stroke in “transient” and “resolved” AF patients with various conditions such as postoperative or secondary AF. In the absence of anticoagulation therapy, AF patients may be at a high risk of ischemic stroke. To clarify these uncertainties, we aimed to evaluate the risk of SBE in oral anticoagulation-naïve patients with hyperthyroidism-related AF, particularly in relation to time since AF diagnosis and treatment status.

Methods
Study design and population
We performed this retrospective nationwide cohort study using the National Health Insurance Service (NHIS) data of Korea. The NHIS is mandatory for all Koreans and includes 97.1% of the Korean population as mandatory subscribers. This database contains information regarding personal data, medical and pharmaceutical records, inpatient and outpatient service usage, and mortality data. This study was approved by the Institutional Review Board of the Yonsei University Health System (Number 4-2016 - 0179). The need for informed consent was waived. There were 1,034,099 AF patients aged >18 years between January 1, 2005 and December 31, 2016. In order to include only newly diagnosed AF patients, we screened for patients who were not diagnosed with AF during a 3-year blanking period from January 2002 to December 2004. As a result, we identified 847,460 newly diagnosed AF patients. AF was defined by International Classification of Disease, Tenth Revision (ICD-10) code I48, as determined in hospitalization or outpatient visits. To evaluate the accuracy of our definition of AF, we conducted a validation study with 628 randomly chosen patients from hospitals who had ICD-10 code I48 and underwent electrocardiography. Their electrocardiograms were reviewed by two physicians. Patients were diagnosed with AF with a positive predictive value of 94.1%.

Hyperthyroidism was defined by ICD-10 code E05. In a validation study with 189 randomly chosen patients with ICD-10 code E05, hyperthyroidism diagnosis had a positive predictive value of 94.7%. Hyperthyroidism-related AF was defined as a hyperthyroidism diagnosis claim occurring 30 days before or after AF diagnosis. The index date was defined as the date of AF diagnosis. We excluded patients with valvular AF (including diagnosis of mitral stenosis or prosthetic heart valves, or insurance claims for valve replacement or valvuloplasty), patients with insurance claim occurred at the same date of AF diagnosis, and thyroid cancer and also those prescribed oral anticoagulants before cohort enrollment. After exclusion, there were 615,724 oral anticoagulation-naïve non-valvular AF patients, of whom 20,773 were classified as hyperthyroidism-related AF patients. The rest were assigned to the control group, which was defined as the nonthyroidal AF group. All study groups were matched via 1:3 propensity score matching. Details are presented in (Figure 1).

Covariates and outcome data
We obtained information on select comorbid conditions from inpatient and outpatient hospital diagnoses. Baseline comorbidities were defined using medical claims and prescription medication data prior to the index date. To ensure diagnostic accuracy, patients were considered to have comorbidities when the condition was a discharge diagnosis or was confirmed at least twice in an outpatient setting. This was similar to the methods reported in previous studies (Table 1).

Patients’ first ischemic stroke or systemic embolism was assessed. The definitions of clinical outcomes are presented in S1 Table. The accuracy of ischemic stroke diagnoses based on the NHIS claim data was previously validated. Patients were followed up from the index date until the occurrence of the study outcome, initiation of oral anticoagulant, or end of the follow-up pe-
iod, whichever occurred first. Each end point was analyzed independently of the others without being censored. We analyzed the risk of SSE and incidence rate difference between groups in different time periods (within 1 year of AF diagnosis and overall study periods). Additionally, we performed subgroup analyses based on patients’ covariates and hyperthyroidism treatment status. Treated hyperthyroidism was defined as hyperthyroidism treated with antithyroid drugs for at least 1 month since hyperthyroidism diagnosis. Treated intractable hyperthyroidism was defined as hyperthyroidism treated with radioactive iodine or thyroidectomy.

Statistical analyses

Data are presented as median (interquartile range [IQR]) for continuous variables and number (percentage) for categorical variables. We constructed a 3:1 propensity score model based on multiple logistic regression analysis that included the following variables: age; sex; components of the CHA2DS2-VASc score (hypertension, diabetes mellitus, heart failure, prior ischemic stroke or transient ischemic attack [TIA] events, and vascular disease); patients’ dyslipidemia, chronic obstructive pulmonary disease, chronic kidney disease, and liver disease status; history of major bleeding; previous cancer diagnoses; and prescribed medication at enrollment. Matching was performed using the nearest-neighbor matching method, in which patients were matched on the logit of the propensity score using a-caliper width of 0.1 of the standard deviation. Standardized mean differences were estimated to assess pre- and post-match balance. We used Aalen-Johansen analysis to construct cumulative incidence curves with competing risk as death. Poisson distribution to calculate SSE incidence rates and incidence rate difference (IRD) with 95% confidence intervals (CIs) and, and Cox regression to calculate hazard ratios (HRs) with 95% CIs. We analyzed clinical outcomes within 1 year of enrollment and overall study periods. We computed time-dependent hazard rates and HRs using generalized survival models which were created using the stpm2 function in the “stpm2” R package. We identified sufficient overlaps of propensity scores between groups,
which represents the existence of equipoise between the 2 groups (eFigure 1).21 We also performed the following sensitivity analyses to make our study findings more robust. 1) We used a Cox multivariable regression model to analyze clinical outcomes of subjects before propensity score matching. This model contained all the variables listed in (Table 1 – II 2) We also used the inverse probability of treatment weighting method for analyzing clinical outcomes. 3) We assessed the risk of SSE without censoring at the date of oral anticoagulant initiation. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA) and R version 3.3.2 (The R foundation, www.R-project.org).

Results

Baseline characteristics

Patients’ baseline characteristics are presented in (Table 1). Of the 615,724 oral anticoagulation-naïve non-valvular AF patients, 20,773 (3.4%) had hyperthyroidism-related AF. After 3:1 propensity score matching, all groups had well-balanced baseline characteristics (Table 1). The median age and CHA2DS2-VASc score of the study subjects were 61.0 (IQR, 48.0 – 72.0) and 2.0 (IQR, 1.0 – 4.0), respectively (Table 1). The median follow-up duration was 5.9 years. During follow-up periods, 30.7% patients were prescribed oral anticoagulants and censored.

Risk of ischemic SSE

During the study period, 1,806 and 4,980 SSE events occurred in the hyperthyroidism-related AF and nonthyroidal AF groups, respectively. The incidence rate of SSE events was 1.83 per 100 person-years (95% CI, 1.75 to 1.92) in the hyperthyroidism-related AF group and 1.62 per 100 person-years (95% CI, 1.57 to 1.66) in the nonthyroidal AF group (Table II ). Additionally, the hyperthyroidism-related AF group had a significantly higher cumulative SSE incidence rate than the nonthyroidal AF group (log-rank, P < 0.001) (Figure 2). The hyperthyroidism-related AF group also had a significantly higher risk of SSE than the nonthyroidal AF group (HR, 1.13; 95% CI, 1.07 to 1.19; P < 0.001) (Table II ).

Time-dependent changes in the risk of SSE

There were higher incidences of SSE within 1 year of AF diagnosis in both study groups. We observed 633 (35.0%) SSE events in the hyperthyroidism-related AF group and 1,489 (29.9%) SSE events in the nonthyroidal AF group. The risk of SSE was 36% higher in the hyperthyroidism-related AF group than in the nonthyroidal AF group within 1 year of AF diagnosis (HR, 1.36; 95% CI, 1.24 to 1.50, IRD, 0.99; 95% CI, 0.67 to 1.30; P < 0.001), but IRD decreased over time (IRD, 0.22; 95% CI 0.12 to 0.31) (Table II, Figure 2).

The time-dependent hazard rates of SSE are presented in (Figure 3A). Within 1 year of AF diagnosis, SSE hazard rates were higher in the hyperthyroidism-related AF than in the nonthyroidal AF group. Among the 1,806 SSE events that occurred in the hyperthyroidism-related AF group, 633 (35.0%) occurred within 1 year of AF diagnosis. Beyond 1 year of AF diagnosis, the difference in hazards became statistically insignificant between the two groups. The time-dependent HRs are shown in (Figure 3B).

Risk of SSE according to CHA2DS2-VASc score

SSE incidence rates based on CHA2DS2-VASc scores are presented in (Figure 4). During the study period, the annual incidence of SSE exceeded 2 per 100 person-years in hyperthyroidism-related AF patients with a CHA2DS2-VASc score ≥ 3. Moreover, the hyperthyroidism-related
AF group had higher SSE incidence rates than the nonthyroidal AF group with respect to patients with a CHA$_2$DS$_2$-VASc score > 5. Within 1 year of AF diagnosis, the incidence of SSE exceeded 2 per 100 person-year in hyperthyroidism-related AF patients with a CHA$_2$DS$_2$-VASc score ≥2. In patients with hyperthyroidism-related AF group and lower SSE risk (CHA$_2$DS$_2$-VASc score <2), SSE incidence was 0.69 (95% CI, 0.62 to 0.77) per 100 person-year.

**Subgroup analysis**

The hyperthyroidism-related AF group had a higher risk of SSE than the nonthyroidal AF group in our subgroup analyses regarding age, comorbidities (hypertension and heart failure status), sex, prior ischemic stroke or TIA events, and CHA$_2$DS$_2$-VASc score subgroups (all $P$ for interaction > 0.05) (Figure 5). The risk of SSE in the treated hyperthyroidism (HR, 0.64; 95% CI, 0.58 to 0.70; $P$ for interaction < 0.001) and treated intractable hyperthyroidism subgroups (HR, 0.45; 95% CI, 0.28 to 0.73; $P$ for interaction < 0.001) was significantly lower than that in the nonthyroidal AF group. The risk of SSE decreased in the treated hyperthyroidism subgroup within 1 year of hyperthyroidism diagnosis. The untreated hyperthyroidism subgroup had a significantly higher risk of SSE than the nonthyroidal AF group (HR, 1.46; 95% CI, 1.35 to 1.55) (Figure 5).
Incidence rate of SSE in AF patients with and without hyperthyroidism stratified by CHA2DS2-VASc score. A, overall follow-up duration; B, within 1 year from AF diagnosis. *P < 0.05

**Figure 4**

**Figure 5**

<table>
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<th>No. of Patients</th>
<th>Overall SSE Hazard ratio (95% CI)</th>
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<th>Within 1-year SSE Hazard ratio (95% CI)</th>
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<td>1.46 (1.30-1.65)</td>
<td></td>
<td>1.75 (1.56-1.96)</td>
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</table>

Hazard ratios of ischemic stroke and systemic embolism in different subgroups.

**Table II**

**Sensitivity analysis**

For all subjects, before propensity score matching, hyperthyroidism was significantly associated with the increased risk of SSE, as determined based on the following adjusted HRs: 1.13 (95% CI, 1.08 to 1.18; P < 0.001) during the whole study period, 1.36 (95% CI, 1.26 to 1.48; P < 0.001) within 1 year of AF diagnosis, and 1.04 (95% CI, 0.98 to 1.10; P = 0.205) beyond 1 year of AF diagnosis. In the inverse probability of treatment-weighted cohort, the results were still similar to the main result. The assessed SSE risk without censoring at the date of oral anticoagulant initiation was consistent with primary findings (Table II).

**Discussion**

In this large-scale retrospective cohort study, hyperthyroidism-related AF patients showed a higher incidence of SSE than nonthyroidal AF patients within 1 year of AF diagnosis, but incidence of SSE became similar to that of nonthyroidal AF over time. This trend remained consistent in all ranges of CHA2DS2-VASc scores. After hyperthyroidism treatment, the incidence rate of SSE significantly decreased and was lower in hyperthyroidism-related AF patients than in nonthyroidal AF patients. Our findings suggest that hyperthyroidism-related AF patients might have higher risks of ischemic stroke and systemic embolism, especially when initially
diagnosed. This risk might be reduced by treating hyperthyroidism. However, further prospective study would be needed.

Increased risk of SSE in hyperthyroidism-related AF

Hyperthyroidism is a common endocrinologic disorder that can exacerbate pre-existing cardiac disease and cause de novo cardiovascular abnormalities, including AF, heart failure, and cardiovascular disease. Despite the close associations between AF and hyperthyroidism and ischemic stroke, whether hyperthyroidism-related AF results in a higher risk of ischemic stroke than nonthyroidal AF remains controversial. Therefore, hyperthyroidism-related AF is not regarded as a major risk factor for ischemic stroke in current guidelines. Only Canadian Cardiovascular Society guidelines suggested anticoagulation during thyrotoxic state with low quality evidence. Prior observational studies have reported that the risk of SSE was higher in hyperthyroidism-related AF patients than in nonthyroidal AF patients. Moreover, a prospective observational study of 480 patients by Siu et al. revealed that hyperthyroidism-related AF patients had a higher risk of stroke than nonthyroidal AF patients. Alternatively, a retrospective cohort study using Swedish nationwide cohort data reported that thyroid disease was not an independent risk factor for stroke (HR, 0.96; 95% CI, 0.73 to 1.25). However, while this study analyzed 182,678 AF patients without oral anticoagulation, only 55 ischemic stroke events occurred in hyperthyroidism-related AF patients. Moreover, the number of such patients was not presented.

In our study, we analyzed 615,724 oral anticoagulation-naïve non-valvular AF patients, which included 20,773 patients with hyperthyroidism. To our knowledge, our study is the largest study that investigates the risk of stroke in hyperthyroidism-related AF.

The mechanism(s) for an increased risk of thromboembolism associated with new-onset AF in patients with hyperthyroidism remains unclear. The high risk of stroke in hyperthyroidism-related AF may be derived from hemostatic changes in thyroid disease. Hypothyroid and hyperthyroid statuses are associated with abnormal hemostasis, whereby the coagulation factor turnover rate and fibrinogen levels increase. Hypercoagulability in new-onset non-valvular AF patients may also play a role in this abnormal hemostasis. Moreover, hyperthyroidism is associated with hypercoagulability. Therefore, the presence of both AF and hyperthyroidism may synergistically increase thromboembolic risk.

Increased risk of SSE within 1 year of AF diagnosis and reduced risk after treatment

Our study shows an increased risk of SSE within 1 year of AF diagnosis, concurring with results of the study of GARFIELD-AF data that showed that the highest number of clinical events occurred during the first 4 months of follow-up, results reported by Siu et al. where the majority of ischemic strokes (>70%) occurred within the first 30 days of presentation, and results reported by Dekkers et al. who showed an increased risk of death and cardiovascular events in the initial months of hyperthyroidism diagnosis. Half of our hyperthyroidism-related AF patients did not receive hyperthyroidism treatment, possibly because some had subclinical hyperthyroidism, which is also classified as ICD code E05. There have been several studies on the association between subclinical hyperthyroidism and AF. Despite this, patients treated for hyperthyroidism had a significantly lower risk of SSE than nonthyroidal AF patients, even in intractable cases. Insufficient hyperthyroidism treatment has also been associated with an increased cardiovascular risk. Unfortunately, the rate of sinus conversion was not available in this study. However, there was a data about spontaneous conversion to sinus rhythm after hyperthyroidism treatment can result in decreased AF burden and a lower risk of SSE. In this study, there was a residual SSE risk during entire follow-up duration. In this study, there was a residual SSE risk during entire follow-up duration. However, the incidence rate of SSE was not significant in subgroup with low CHA2DS2-VASc score under 2, who do not need for anticoagulation in current guidelines. These finding suggest anticoagulation might be not required in patients with hyperthyroidism related AF and CHA2DS2-VASc score under 2.

When the study population was classified according to the CHA2DS2-VASc score, SSE incidence rates were around 2 per 100 person-years in patients whose CHA2DS2-VASc score was ≥2. Our results are consistent with those of our previous study, which investigated risk factors for stroke and the application of the CHA2DS2-VASc score in the Korean AF population.

Clinical implications

In contrast to current guidelines, we demonstrated the increased risk of SSE in hyperthyroidism-related AF patients compared with that in nonthyroidal AF patients, especially within the first year of AF diagnosis. The risk became similar to that of nonthyroidal AF patients over time. Therefore, stroke prevention via oral anticoagulation may be required in hyperthyroidism-related AF patients. Furthermore, hyperthyroidism treatment may reduce such patients’ risk of stroke.

Study limitations

Our study had several limitations. First, AF diagnoses and adverse events were based on the ICD-10 codes registered by the physicians responsible for patient care. However, the accuracy of AF and adverse event diagnoses in the Korean NHIS database were previously validated. Second, data on different AF types (paroxysmal and nonparoxysmal) were not available. Third, our study was based on Korean NHIS data, and we had
no information about thyroid function tests (TSH, T3, T4), autoimmunity status (TRAb, anti-TPO, anti-Tg), UL and scintigraph findings. We also did not have data for hyperthyroidism causes (offending drug such as amiodarone, glucocorticoids, or oral contraceptives), and the exact incidence of subclinical hyperthyroidism. So, we were not able to clarify the treatment response for hyperthyroidism. Fourth, definition of intractable hyperthyroidism was ambiguous. Some patients might be received radiiodine or thyroidectomy because of contraindication for antithyroid drug. Fifth, we did not have exact data of returning sinus rhythm after hyperthyroidism treatment. Sixth, as the present study included only OAC naive patients, we were not able to prove the benefit of anticoagulation in this population. Seventh, the definition of comorbidities in this study might ensure a high positive predictive value, but there were concerns for low sensitivity. Finally, we may have missed confounders that affected clinical events such as obesity, smoking or alcohol consumption. Despite these limitations, this study included evaluated longitudinal data from almost the entire Korean adult population, and to our knowledge, our study is the largest study to investigate the risk of stroke in hyperthyroidism-related AF patients.

Conclusion

The risk of SSE was similar in hyperthyroidism-related AF and nonthyroidal AF group. Within 1 year of AF diagnosis, the risk of SSE was much higher in hyperthyroidism-related AF group than nonthyroidal AF group. This risk was seemed to be reduced by treating hyperthyroidism. Hyperthyroidism-related AF patients have a high risk of stroke when initially diagnosed with AF and thus require regular follow-ups with appropriate anticoagulation strategy and prompt treatment for hyperthyroidism.

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Conflict of interest

Dr. Gregory Y.H. Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees were directly received personally. Dr. Boyoung Joung has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo, and has received research funding from Medtronic and Abbott. No fees were directly received personally. The other authors have no conflict of interest.

Author contributions

Conceptualization: Pil-Sung Yang, Boyoung Joung, Gregory Y.H. Lip.

Data curation: Pil-Sung Yang, Eunsun Jang, Hee Tae Yu.

Formal analysis: Kyu Kim, Boyoung Joung.

Funding acquisition: Boyoung Joung, Gregory Y.H. Lip.

Investigation: Jae-Sun Uhm, Jong-Youm Kim, Jung-Hoon Sung, Hui-Nam Pak, Moon-Hyoung Lee.

Methodology: Kyu Kim, Pil-Sung Yang, Boyoung Joung, Gregory Y.H. Lip.

Visualization: Kyu Kim.

Validation: Kyu Kim, Pil-Sung Yang.

Writing – original draft: Kyu Kim, Pil-Sung Yang, Boyoung Joung.

Writing – review & editing: Kyu Kim, Pil-Sung Yang, Hee Tae Yu, Tae-Hoon Kim, Jae-Sun Uhm, Jong-Youm Kim, Jung-Hoon Sung, Hui-Nam Pak, Moon-Hyoung Lee, Gregory Y.H. Lip, Boyoung Joung.

Additional information

The e-Figures can be found in the Supplemental Materials section of the online article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.08.018.

References


