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# Risk of ischaemic stroke in thyrotoxic atrial fibrillation

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## Abstract

**Objective:** Atrial fibrillation (AF) is the most common cardiac complication of thyrotoxicosis and is strongly implicated in thromboembolic events. However, the incidence of stroke in thyrotoxic AF remains unclear. Herein, we aimed to investigate the risks of mortality and ischaemic stroke between patients with thyrotoxic AF and nonthyrotoxic AF.

**Designs and Methods:** From Taiwan's National Health Insurance Research Database, 1868 patients with the concomitant diagnoses of AF and thyrotoxicosis identified between 2001 and 2010 were compared to 7472 patients with nonthyrotoxic AF using propensity score matching for age, sex and comorbidities.

**Results:** There was no significant difference in either $CHA_2DS_2$-VASc score or anticoagulant usage between the groups. Alternatively, the thyrotoxic group contained more β-blocker/digoxin users, whereas the nonthyrotoxic group contained more statin users. Patients with thyrotoxic AF exhibited lower risks of all-cause mortality (HR: 0.66, CI: 0.59-0.73, $P < .0001$) and ischaemic stroke (HR: 0.73, CI: 0.64-0.84, $P < .0001$) than those with nonthyrotoxic AF, especially thyrotoxic patients with $CHA_2DS_2$-VASc scores ≥1. Comorbidities, including diabetes, hyperlipidaemia, hypertension and coronary artery disease, contributed to all-cause mortality in patients with nonthyrotoxic AF; however, this effect was diminished in thyrotoxic AF.

**Conclusions:** Patients with thyrotoxicosis and AF have a lower risk of stroke than patients with nonthyrotoxic AF. Treatment for thyrotoxicosis is also crucial as the prescription of anticoagulants based on CHA2DS2-VASc scores.

KEYWORDS
Atrial fibrillation, stroke, thyrotoxicosis

## 1 | INTRODUCTION

Atrial fibrillation (AF) affects nearly 3% of adults and even greater numbers among the elderly and subjects with cardiovascular comorbidities such as hypertension, heart failure, coronary artery disease (CAD), diabetes mellitus and chronic kidney disease (CKD).[1-6] In addition to these risk factors, many potentially reversible causes of AF have been reported, such as electrolyte imbalance, and thyroid disorder.[2,3,7,8] Notably, an estimated 10%-25% of patients with thyrotoxicosis developed AF,[2,3,8] which is independently associated with a 2-fold higher risk of all-cause mortality, and approximately 20%-30% of ischaemic stroke patients have a previous AF diagnosis.[2,6] Although several factors contributing to a potential hypercoagulable state are observed in thyrotoxicosis, such as increased thrombin/fibrinogen activity, decreased fibrinolysis and endothelial dysfunction, the correlation between thromboembolic disease and thyrotoxicosis remains controversial.[9,10] Yuen and colleagues described a case series of 21 subjects with thyrotoxic AF in which 23% developed subsequent systemic emboli.[11] Moreover, thyrotoxicosis was found to enhance the hypercoagulable

  

state as evidenced by D-dimer levels as well as the risk of ischaemic stroke in patients with AF.[12] In contrast, another single-centre observational study reported that thyrotoxicosis did not confer additional risk of ischaemic stroke compared to nonthyrotoxic AF.[13] Despite some small-scale studies reporting elevated risk of thromboembolism in patients with thyrotoxic AF, current guidelines suggest that embolic risk is not necessarily increased independently of other stroke risk factors and that the usage of anticoagulants should be guided by CHA2DS2-VASc scoring.[2,3] However, the predictive value of CHA2DS2-VASc scores remains unclear in patients with thyrotoxic AF. Because the risks of thromboembolic events and bleeding share certain common characteristics and antithyrotoxic therapy may increase the liability of anticoagulants, understanding the risk of bleeding in patients with thyrotoxic AF is crucial.[12,14] Therefore, using a large population-based national cohort, we investigated the risks of mortality, ischaemic stroke and bleeding in patients with thyrotoxic AF compared to those with nonthyrotoxic AF.

## 2 | MATERIALS AND METHODS

### 2.1 | Database

The National Health Insurance Research Database (NHIRD) of Taiwan was used as the source for this study. The NHIRD is a claims database for the Taiwan National Health Insurance Programme, a single-payer healthcare insurance system that covers almost 100% of the Taiwan population. The NHIRD provided encrypted patient identification numbers, sex, date of birth, dates of hospital admission and discharge, the International Classification of Diseases codes (Ninth Revision), Clinical Modification (ICD-9-CM) codes of diagnoses and procedures, and details of prescriptions. Several previous studies have validated the accuracy of the NHIRD information on diagnosis, stroke and acute coronary syndrome.[15,16] The current study was approved by the Institutional Review Board of Chi-Mei Medical Center (CV code: 10406-E01). Informed consent from participants was waived since the data set consists of de-identified data. This waiver does not affect the rights and welfare of the participants.

### 2.2 | Study design

This was a retrospective, case-cohort study. We selected all patients newly diagnosed with AF (ICD-9 code 427.31) with a principal diagnosis of thyrotoxicosis (ICD-9-CM code 242, thyrotoxicosis with or without goitre) from 1 January 2001 to 31 December 2012 as the study cohort. To ensure the accuracy of diagnosis, we defined patients with AF only when it was a discharge diagnosis or confirmed more than twice in the outpatient department. The diagnostic accuracy of AF and thyrotoxicosis in NHIRD using this definition has been previously validated.[17] We excluded patients who had thyrotoxicosis

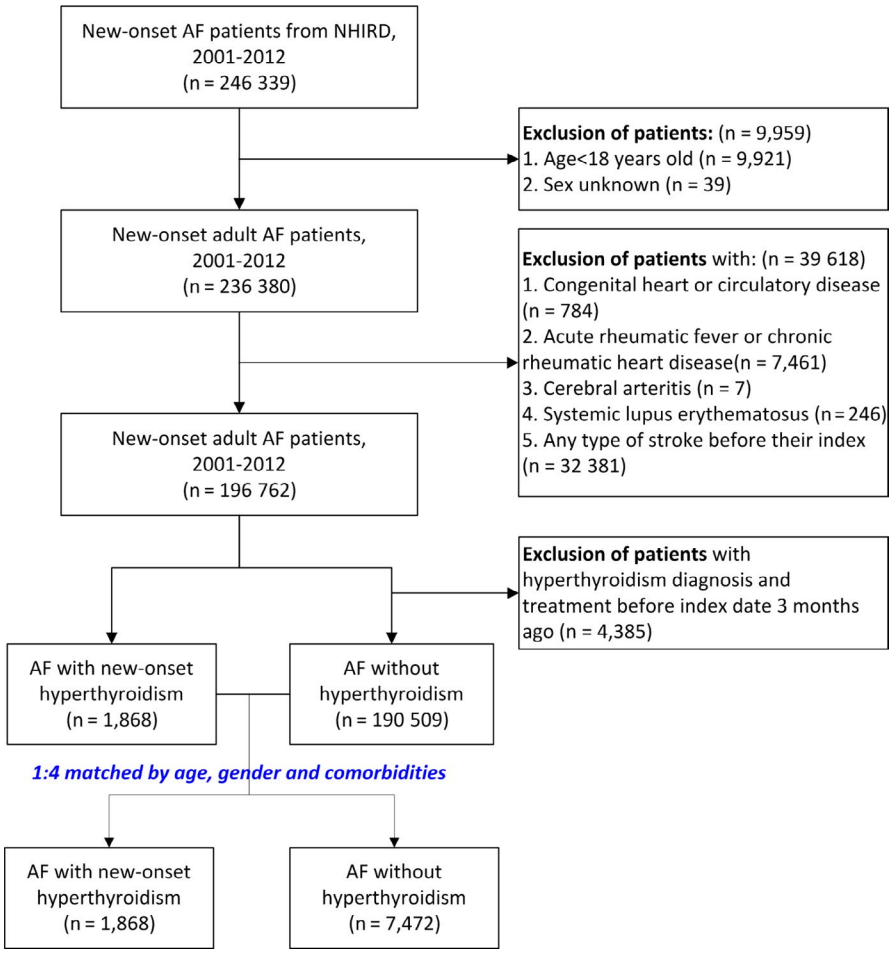


**FIGURE 1** The summary of patient enrolment in this study

diagnosed before 1998 to increase the likelihood of identifying only new thyrotoxicosis cases. In this study, we assigned their first visit for the treatment of thyrotoxicosis as the index ambulatory care visit. Additionally, we also excluded patients aged <18 years to limit our study sample to the adult population. Furthermore, to avoid mistaken diagnoses, we only selected patients who had at least two consensus-diagnosed episodes of thyrotoxicosis during the study period and who had been prescribed antithyroid drugs. To exclude other causes of ischaemic stroke, we eliminated patients with congenital heart or circulatory disease (ICD-9-CM 745-747), acute rheumatic fever or chronic rheumatic heart disease (ICD-9-CM codes 390-398), other forms of heart disease (ICD-9-CM codes 420-429), or arterial dissection (ICD-9-CM code 443.2). Moreover, we excluded patients who had any type of stroke (ICD-9-CM codes 430-438) before their index ambulatory care visit. As a result, 1868 thyrotoxicosis patients were included as the study cohort and were compared to 7472 age-, sex- and comorbidity-matched control patients with nonthyrotoxic AF. A flow chart of the study enrolment is shown in Figure 1.

Age at the time of participation in this study was separated into five subgroups: 18-49, 50-64, 65-74 and over 75 years. In addition to age and sex, we gathered information on chronic cardiovascular risk factors, including hypertension (ICD-9-CM codes 401-405), diabetes (ICD-9-CM code 250), hyperlipidaemia (ICD-9-CM code 272) and coronary artery disease (CAD; ICD-9-CM: 410-414). Based on this information, CHA2 DS2-VASc score was calculated by assigning 1 point each for age between 65 and 74 years, history of hypertension, diabetes mellitus, heart failure, vascular disease (coronary and peripheral artery disease), and female sex, and two points each for a history of stroke, transient ischaemic attack, and age ≥75 years. In addition, history of medications such as aspirin, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB), β-blockers, digoxin, statin and anticoagulants including novel oral anticoagulants (NOACs) and warfarin was recorded.

Propensity scores were estimated using the multivariable logistic regression model with the aforementioned potential risk factors as dependent variables among patients with thyrotoxic AF and nonthyrotoxic AF. The independent variables were age, sex, hypertension, diabetes, hyperlipidaemia and CAD. The propensity score matching approach was used to reduce selection bias because it can group many confounding covariates that may be present in an observational study. The SAS (SAS Institute) macro, "%OneToManyMTCH", was used to match cases and controls from 1-to-1 to 1-to-N using propensity score.[18] This macro based on the algorithm of nearest neighbour to make study subjects was matched by the best propensity score first and the second best propensity score next. The process was repeated until all subjects were matched. The minimum calliper distance was set for the matches distance with matching ratio of one case to four controls in this study.

### 2.3 | Outcomes

The primary outcome was ischaemic stroke (ICD-9-CM codes 433-437), and the secondary outcomes were mortality and bleeding. Bleeding included major bleeding of haemorrhagic stroke (ICD-9-CM codes 430-432) and minor gastrointestinal bleeding (ICD-9-CM codes 530-537, 562, 569, 578) as well as bleeding during re-operation (procedure codes 35.21-35.24). Cases ending in mortality were identified using the "in-hospital death" code at discharge. However, many Taiwanese choose to "die at home"; therefore, the in-hospital death code would underestimate the true mortality rate. As enrolment in the NHI programme is mandatory for everyone in Taiwan and registration must be withdrawn within 30 days after death, patients who were withdrawn within 30 days after discharge were presumed to have died. All patients were followed from the index date to either death, loss to follow-up or 31 December 2013.

In supplementary analysis, we compared outcomes in patients with thyrotoxicosis and AF to outcomes in [1] patients with thyrotoxicosis without AF and [2] the general population without thyrotoxicosis or AF. For this analysis, we used the same propensity matching scheme as the primary analysis, that is one patient with thyrotoxicosis and AF was matched to four patients with thyrotoxicosis without AF and to four control subjects without thyrotoxicosis or AF.

### 2.4 | Statistical analysis

Categorical variables are presented as frequency (percentage), and patients with thyrotoxicosis were compared to matched cohorts using Pearson's chi-square test. Continuous variables (time to events) were first tested for normality and, based on results, are reported as the median with interquartile range. Values were compared between patients with thyrotoxicosis and matched cohorts by Wilcoxon's rank sum test. Cumulative incidences of events are plotted using the Kaplan-Meier method and compared between patients with AF and thyrotoxicosis and matched cohorts by log-rank test. The adjusted hazard ratios (HRs) for ischaemic stroke, mortality and bleeding were estimated using a Cox proportional hazard regression model including the potential confounding factors listed in Table 1. SAS software version 9.4 (SAS Institute) was used for all analyses. The Kaplan-Meier curves were plotted using STATA (version 12; Stata Corp.). Significance was set at 0.05 (two-tailed) for all tests.

## 3 | RESULTS

### 3.1 | Characteristics of the study population

After excluding patients with structural heart disease and hypercoagulable state, the enrolled patients with AF were generally in middle age (50-64 years old) with female predominance (Table 1). About one-fifth of both patients with thyrotoxic and those with nonthyrotoxic AF presented with $CHA_2DS_2$-VASc score of 0, while the majority scored 1. Notably, only around quarter of patients in both thyrotoxic and nonthyrotoxic AF groups received anticoagulants (NOACs or warfarin). Only a small percentage of patients

**TABLE 1** Baseline characteristics and outcome of study subjects and matched cohort (n = 9340)

| Characteristic | Total (n = 9340) N (%) | AF with hyperthyroidism (n = 1868) N (%) | AF without hyperthyroidism (n = 7472) N (%) | *P* |
|---|---|---|---|---|
| Age (y, mean ± SD) | | | | |
| 18-49 | 2305 (24.68) | 461 (24.68) | 1844 (24.68) | 1.0000 |
| 50-64 | 3280 (35.12) | 656 (35.12) | 2624 (35.12) | |
| 65-74 | 1995 (21.36) | 399 (21.36) | 1596 (21.36) | |
| ≥75 | 1760 (18.84) | 352 (18.84) | 1408 (18.84) | |
| Gender | | | | |
| Female | 6180 (66.17) | 1236 (66.17) | 4944 (66.17) | 1.0000 |
| Male | 3160 (33.83) | 632 (33.83) | 2528 (33.83) | |
| Comorbidities | | | | |
| DM | 1125 (12.04) | 225 (12.04) | 900 (12.04) | 1.0000 |
| Hyperlipidaemia | 540 (5.78) | 108 (5.78) | 432 (5.78) | 1.0000 |
| Hypertension | 2510 (26.87) | 502 (26.87) | 2008 (26.87) | 1.0000 |
| CAD | 915 (9.80) | 183 (9.80) | 732 (9.80) | 1.0000 |
| $CHA_2DS_2$-VASc score | | | | |
| 0 | 1804 (19.31) | 367 (19.65) | 1437 (19.23) | .7513 |
| 1 | 3099 (33.18) | 633 (33.89) | 2466 (33.00) | |
| 2 | 1798 (19.25) | 346 (18.52) | 1452 (19.43) | |
| ≥3 | 2639 (28.25) | 522 (27.94) | 2117 (28.33) | |
| Comedications | | | | |
| NOACs[a] | 27 (0.29) | 6 (0.32) | 21 (0.28) | .7725 |
| Warfarin | 2196 (23.51) | 450 (24.09) | 1746 (23.37) | .5100 |
| Anticoagulants (NOACs or warfarin) | 2207 (23.63) | 452 (24.20) | 1755 (23.49) | .5186 |
| Aspirin | 5550 (59.42) | 1163 (62.26) | 4387 (58.71) | .0052 |
| ACEI/ARB | 5106 (54.67) | 1066 (57.07) | 4040 (54.07) | .0199 |
| Beta-blocker | 5980 (64.03) | 1649 (88.28) | 4331 (57.96) | <.0001 |
| Digoxin | 4583 (49.07) | 1178 (63.06) | 3405 (45.57) | <.0001 |
| Statin | 1334 (14.28) | 185 (9.90) | 1149 (15.38) | <.0001 |
| Outcome | | | | |
| All-cause mortality | 2956 (31.65) | 453 (24.25) | 2503 (33.50) | <.0001 |
| Time to mortality (years, median (IQR)) | 2.3 (0.6-5.0) | 2.8 (0.9-6.0) | 2.3 (0.5-4.9) | <.0001[a] |
| Ischaemic stroke | 1506 (16.12) | 260 (13.92) | 1246 (16.68) | .0038 |
| Time to stroke (y, median [IQR]) | 3.0 (1.1-5.9) | 3.3 (1.0-6.6) | 2.9 (1.1-5.8) | <.0001[a] |
| Bleeding | 953 (10.20) | 194 (10.39) | 759 (10.16) | .7714 |
| Haemorrhagic stroke | 252 (2.70) | 43 (2.30) | 209 (2.80) | .2374 |
| UGIB | 656 (7.02) | 144 (7.71) | 512 (6.85) | .1951 |
| LGIB | 94 (1.01) | 20 (1.07) | 74 (0.99) | .7558 |
| Time to bleeding (y, median (IQR)) | 2.6 (0.8-5.5) | 2.2 (0.8-5.8) | 2.7 (0.9-5.5) | <.0001[a] |

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CAD, coronary artery disease; DM, diabetes mellitus; LGIB, lower gastrointestinal bleeding; NOAC, novel oral anticoagulants; UGIB, upper gastrointestinal bleeding.
[a]Wilcoxon signed rank test. Including dabigatran and rivaroxaban.

received dabigatran or rivaroxaban as these NOACs were just entering the market in Taiwan during the study period. Most patients were prescribed aspirin instead. β-blockers and digoxin were prescribed more frequently to patients with thyrotoxic AF, whereas statins were prescribed to a higher proportion of patients with non-thyrotoxic AF.

### 3.2 | Risk of all-cause mortality

Compared to patients with nonthyrotoxic AF, those with thyrotoxic AF demonstrated a lower risk of all-cause mortality (HR: 0.66, CI: 0.59-0.73, $P < .0001$; Table 2). This risk reduction covered all age subgroups and both sexes. Notably, relatively young patients with thyrotoxic AF (18-49 years ago) demonstrated a markedly lower risk of mortality compared to patients with nonthyrotoxic AF. Comorbidities including diabetes, hyperlipidaemia, hypertension and coronary artery disease contributed to all-cause mortality in patients with nonthyrotoxic AF but this effect was diminished in patients with thyrotoxic AF. In patients with $CHA_2DS_2$-VASc score ≥1, thyrotoxic AF was associated with a significantly reduced risk of mortality compared to nonthyrotoxic AF. Patients with thyrotoxic AF showed better survival than those with nonthyrotoxic AF according to Kaplan-Meier analysis (Figure 2A).

### 3.3 | Risk of ischaemic stroke and bleeding

In addition to lower all-cause mortality risk, patients with thyrotoxic AF demonstrated lower risks of ischaemic stroke than those with nonthyrotoxic AF (HR: 0.73, CI: 0.64-0.84, $P < .0001$) regardless of sex (Table 2). In contrast to all-cause mortality, however, which favoured younger patients with thyrotoxic AF, the risk of ischaemic stroke was especially lower in older patients with thyrotoxic AF (above 65 years). Concomitant cardiovascular risk factors did not show differential effects on ischaemic stroke risk between patients with nonthyrotoxic AF and those with thyrotoxic AF. Moreover, thyrotoxicosis reduced ischaemic stroke risk among patients with AF and $CHA_2DS_2$-VASc score ≥1. The risk of bleeding was similar between patients with thyrotoxic AF and nonthyrotoxic AF, and cardiovascular disease risk factors did not change the risk of bleeding. Among patients with $CHA_2DS_2$-VASc score of 0, those with thyrotoxic AF exhibited a reduced risk of bleeding compared to patients with nonthyrotoxic AF. Additionally, patients with thyrotoxic AF demonstrated a significantly greater probability of remaining ischaemic stroke-free than those with nonthyrotoxic AF (Figure 2B). There was no significant difference in the probability of bleeding between groups (Figure 2C). Regarding the effect of medications, given that the duration of prescriptions and PT (INR) varied, we analysed the risks of mortality, ischaemic stroke and bleeding within the first year, during the first to the third year, during the third to the fifth year and longer than 5 years after medications (Table S1). Interestingly, the use of β-blocker instead of anticoagulants represented significant lower risks of mortality and ischaemic stroke in patients with thyrotoxic AF compared with those in AF patients without thyrotoxicosis. The benefit of risk reduction started since the initial use and persisted to more than 5 years. Also, aspirin might attenuate the risk of mortality and ischaemic stroke after the use of longer than 1 year but it increased the risk of bleeding at the first moment. The prescription of ACEI/ARB, digoxin and statin reduced the risk of mortality and ischaemic stroke in a certain degree but were not consistent.

### 3.4 | Risks among patients with thyrotoxic AF

Within the thyrotoxic AF group, the crude HR of CHA2DS2-VASc score indicated that the higher score had higher risk (Table S2). However, as adjusted by age, gender, comorbidities and drugs, the risk of mortality presented as nonsignificant effects is shown in Table 3. Furthermore, all-cause mortality and ischaemic stroke risk increased with age (Table 3), while risk of bleeding did not differ among age groups. Comorbid diabetes increased the risk of ischaemic stroke in patients with thyrotoxic AF but conversely, other common cardiovascular risks and diseases including hypertension, hyperlipidaemia and CAD failed to influence the subsequent occurrence of ischaemic stroke in this group. Most importantly, even though current guidelines still recommend that risk of ischaemic stroke in AF be evaluated using $CHA_2DS_2$-VASc scoring, the $CHA_2DS_2$-VASc score showed little prognostic value for thyrotoxic AF. Specifically, risk of ischaemic stroke did not rise in parallel with $CHA_2DS_2$-VASc score in patients with thyrotoxic AF. Among AF patients with thyrotoxicosis, the use of anticoagulants attenuated the risk of mortality (HR: 0.47, CI: 0.27-0.83, $P = .009$) at the first year but the benefit disappeared thereafter (Table S3). Conversely, patients who received β-blocker (HR: 0.46, CI: 0.28-0.78, $P = .0039$) had a lower risk of mortality during the first to the third year. Nevertheless, regarding ischaemic stroke, only β-blocker showed a risk reduction effect after the prescription for more than 5 years (HR: 0.54, CI: 0.32-0.92, $P = .0233$).

### 3.5 | Risk between thyrotoxic patients with and without AF

Compared with thyrotoxic patients without AF, those with both thyrotoxicosis and AF presented similar risks of all-cause mortality and bleeding, but a higher risk of ischaemic stroke (HR: 1.26, CI: 1.03-1.56, $P = .0252$; Table S4 and S5). In another perspective, compared with general population, there were significant higher risks of ischaemic stroke (HR: 2.93, CI: 2.3-3.74, $P < .0001$) and bleeding (HR: 1.29, CI: 1.02-1.63, $P = .0373$) in thyrotoxic patients with AF, while the all-cause mortality was similar (Table S5 and S6).

## 4 | DISCUSSION

It is well established that patients with thyrotoxicosis are at significant risk of AF.[7,8] However, stroke risk among patients with thyrotoxic AF remains controversial. Based on our clinical observations that the risk of ischaemic stroke in patients with reversible thyrotoxicosis is not as high as in patients with nonthyrotoxic AF, we conducted this nationwide study directly comparing matched samples of these two patient groups. Patients with thyrotoxic AF presented lower risks of all-cause mortality and ischaemic stroke than those with nonthyrotoxic AF, especially among patients with comorbidities such as diabetes, hyperlipidaemia, hypertension and coronary artery disease. Second, whether the widely applied *$CHA_2DS_2$-VASc* scoring

**TABLE 2** Specific subgroup analysis for study outcomes in subjects with hyperthyroidism compared with the ones without hyperthyroidism (n = 9340)

| | | All-cause mortality | | | | Ischaemic stroke | | | | Bleeding | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| htf | Total | Event (%) | AHR[a] | (95% CI) | *P* | Event (%) | AHR[a] | (95% CI) | *P* | Event (%) | AHR[a] | (95% CI) | *P* |
| Overall | 9340 | 2956 (31.65) | 0.66 | (0.59-0.73) | <.0001 | 1506 (16.12) | 0.73 | (0.64-0.84) | <.0001 | 953 (10.20) | 0.90 | (0.77-1.07) | .2314 |
| Age (y) | | | | | | | | | | | | | |
| 18-49 | 2305 | 332 (14.40) | 0.53 | (0.38-0.75) | .0004 | 195 (8.46) | 0.81 | (0.55-1.21) | .3047 | 163 (7.07) | 0.70 | (0.45-1.09) | .1098 |
| 50-64 | 3280 | 704 (21.46) | 0.64 | (0.52-0.80) | <.0001 | 510 (15.55) | 0.84 | (0.66-1.06) | .1401 | 350 (10.67) | 0.78 | (0.58-1.04) | .0902 |
| 65-74 | 1995 | 784 (39.30) | 0.60 | (0.49-0.74) | <.0001 | 444 (22.26) | 0.69 | (0.54-0.89) | .0045 | 238 (11.93) | 1.04 | (0.76-1.42) | .8271 |
| ≥75 | 1760 | 1136 (64.55) | 0.75 | (0.64-0.89) | .0006 | 357 (20.28) | 0.64 | (0.48-0.86) | .0028 | 202 (11.48) | 1.12 | (0.80-1.56) | .5014 |
| Gender | | | | | | | | | | | | | |
| Female | 6180 | 1999 (32.35) | 0.67 | (0.59-0.76) | <.0001 | 1068 (17.28) | 0.71 | (0.60-0.83) | <.0001 | 622 (10.06) | 1.00 | (0.81-1.22) | .9931 |
| Male | 3160 | 957 (30.28) | 0.63 | (0.52-0.75) | <.0001 | 438 (13.86) | 0.81 | (0.63-1.04) | .1034 | 331 (10.47) | 0.74 | (0.56-1.00) | .0488 |
| Comorbidities | | | | | | | | | | | | | |
| DM | 1125 | 507 (45.07) | 0.48 | (0.37-0.62) | <.0001 | 224 (19.91) | 1.10 | (0.80-1.51) | .5496 | 131 (11.64) | 1.02 | (0.68-1.54) | .9240 |
| Hyperlipidaemia | 540 | 177 (32.78) | 0.47 | (0.29-0.74) | .0013 | 93 (17.22) | 1.19 | (0.72-1.98) | .5051 | 59 (10.93) | 1.47 | (0.79-2.74) | .2213 |
| Hypertension | 2510 | 997 (39.72) | 0.62 | (0.52-0.74) | <.0001 | 507 (20.20) | 0.81 | (0.64-1.01) | .0603 | 307 (12.23) | 1.06 | (0.81-1.40) | .6616 |
| CAD | 915 | 387 (42.30) | 0.62 | (0.46-0.82) | .0008 | 171 (18.69) | 1.00 | (0.68-1.47) | .9911 | 120 (13.11) | 0.96 | (0.61-1.51) | .8586 |
| $CHA_2DS_2$-VASc score | | | | | | | | | | | | | |
| 0 | 1804 | 316 (17.52) | 0.73 | (0.54-1.01) | .0565 | 194 (10.75) | 1.11 | (0.76-1.61) | .5904 | 155 (8.59) | 0.59 | (0.37-0.93) | 0.0229 |
| 1 | 3099 | 603 (19.46) | 0.66 | (0.52-0.83) | .0005 | 409 (13.20) | 0.61 | (0.46-0.82) | .0010 | 279 (9.00) | 0.76 | (0.55-1.07) | 0.1129 |
| 2 | 1798 | 635 (35.32) | 0.61 | (0.48-0.76) | <.0001 | 342 (19.02) | 0.72 | (0.54-0.97) | .0277 | 217 (12.07) | 1.00 | (0.72-1.40) | 0.9832 |
| ≥3 | 2639 | 1402 (53.13) | 0.67 | (0.58-0.77) | <.0001 | 561 (21.26) | 0.74 | (0.59-0.92) | .0073 | 302 (11.44) | 1.16 | (0.88-1.52) | 0.2955 |

[a]Adjusted hazard ratio, adjusted for the patients' age, gender, comorbidities, $CHA_2DS_2$-VASc score and comedications.

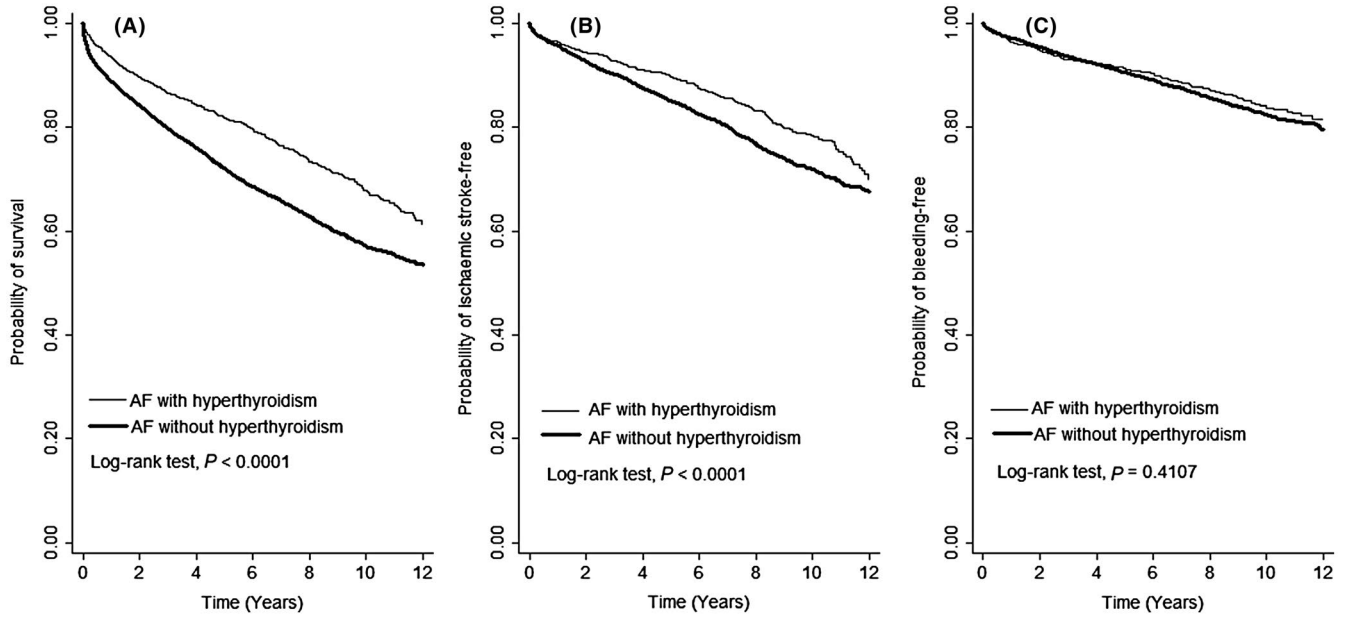


**FIGURE 2** Cumulative survival curve stratified by thyrotoxicosis, A, all-cause mortality, B, ischaemic stroke, C, bleeding

system is ideal in predicting the development of ischaemic stroke in patients with thyrotoxic AF requires more evidences. However, patients with thyrotoxicosis and AF still had a higher risk of ischaemic stroke compared to patients with thyrotoxicosis without AF implying that there could still be a case for more aggressive treatment of AF in patients with thyrotoxicosis.

A study by Sheu et al suggested that thyrotoxic patients free from AF are at a 1.44-fold increased risk of ischaemic stroke compared to euthyroid individuals.[19] This could be due to thyrotoxicosis-associated cardiovascular effects such as hypertension, tachycardia-mediated cardiomyopathy and (or) increased intima-media stiffness and thickness.[2,20] In addition, thyrotoxicosis itself causes hypercoagulable status through activation of thrombin and fibrinogen.[9] However, in contrast to our study, these authors did not address whether the risk of ischaemic stroke is mediated by the development of AF. Moreover, they focused only on young adults.[19] Alternatively, the Swedish Atrial Fibrillation cohort study of 182 678 patients with AF found that thyrotoxicosis was not independently predictive of stroke according to multivariate analysis.[21] Another observational study conducted in China indicated that the overall stroke risk was lower in thyrotoxic AF compared to patients with nonthyrotoxic AF [13] in accord with our results.

Although there appear to be links between ischaemic stroke and thyrotoxicosis, there are no specific recommendations regarding anticoagulation therapy for these patients. Moreover, current guidelines do not include thyrotoxicosis as a risk factor for ischaemic stroke.[2,3] In fact, thyrotoxicosis in not included in the most widely used risk evaluation metric, the CHA2DS2-VASc score.[2,3] Notably, whether anticoagulation therapy should be included for patients with thyrotoxic AF remains unclear. Only some experts suggest that patients with hyperthyroid AF may benefit from anticoagulation until sinus rhythm and stable euthyroid state are restored.[2,22] Currently, the only suggested guidance for anticoagulation in patients with thyrotoxic AF still refers to the CHA2DS2-VASc risk factors, but there is a lack of evidence.[2] In particular, post-treatment hypothyroidism is associated with a diminished response to warfarin, likely owing to decreased catabolism of vitamin K-dependent clotting factors.[1,14] Given the potential drug-drug interactions between antithyroid therapies and the potential risk of bleeding, some physicians are hesitant to prescribe anticoagulants and prescribe aspirin instead, which is not effective for stroke prevention. Indeed, less than a quarter of patients with thyrotoxic AF or those with nonthyrotoxic AF in the present study received anticoagulants while most were taking aspirin. Despite the attenuated risk of mortality and ischaemic stroke after aspirin use for longer than one year, it increased the risk of bleeding at the first place. Instead, β-blocker but not anticoagulants represented persistent lower risks of mortality and ischaemic stroke in patients with thyrotoxic AF compared with those in AF patients without thyrotoxicosis. It could be a residual confounding factor, while there was a higher incidence of β-blocker use in patients with thyrotoxicosis. Again, our findings reflected the potential importance of thyrotoxicosis treatment such as β-blocker in addition to the prescription of aspirin or anticoagulants. Correspondingly, Okosieme and colleagues reported that early and effective control of thyrotoxicosis among patients with Graves' disease is associated with better survival compared with less effective control.[23] Nevertheless, there was indeed a higher risk of ischaemic stroke in patients with thyrotoxic AF compared with thyrotoxic patients without AF. Thus, it remains worthwhile for an adequate treatment of AF in patients with thyrotoxicosis, while it shares several risk factors for bleeding and ischaemic stroke with AF, including diabetes, hypertension and old age. Therefore, we further studied the bleeding risk and observed that there were no specific differences between patients with thyrotoxic AF and nonthyrotoxic AF and that the bleeding risk was relatively low (10%), especially major bleeding (2%).

**TABLE 3** Multivariable analysis for study outcomes in AF patients with hyperthyroidism (n = 1868)

| | | All-cause mortality | | | | Ischaemic stroke | | | | Bleeding | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variables** | **Total** | **Event (%)** | **AHR[a]** | **(95% CI)** | ***P*** | **Event (%)** | **AHR[a]** | **(95% CI)** | ***P*** | **Event (%)** | **AHR[a]** | **(95% CI)** | ***P*** |
| Age (y) | | | | | | | | | | | | | |
| 18-49 | 461 | 40 (8.68%) | 1.00 | (Reference) | - | 34 (7.38%) | 1.00 | (Reference) | - | 26 (5.64%) | 1.00 | (Reference) | - |
| 50-64 | 656 | 104 (15.85%) | 2.09 | (1.43-3.06) | .0001 | 90 (13.72%) | 1.82 | (1.20-2.77) | .0052 | 61 (9.30%) | 1.50 | (0.92-2.44) | .1056 |
| 65-74 | 399 | 121 (30.33%) | 4.73 | (2.85-7.87) | <.0001 | 77 (19.30%) | 2.81 | (1.56-5.08) | .0006 | 58 (14.54%) | 1.73 | (0.88-3.39) | .1107 |
| ≥75 | 352 | 188 (53.41%) | 12.55 | (6.69-23.53) | <.0001 | 59 (16.76%) | 3.86 | (1.83-8.14) | .0004 | 49 (13.92%) | 2.26 | (0.94-5.42) | .0677 |
| Gender | | | | | | | | | | | | | |
| Female | 1236 | 304 (24.60%) | 1.00 | (Reference) | - | 180 (14.56%) | 1.00 | (Reference) | - | 133 (10.76%) | 1.00 | (Reference) | - |
| Male | 632 | 149 (23.58%) | 1.22 | (0.90-1.65) | .2004 | 80 (12.66%) | 0.81 | (0.53-1.25) | .3395 | 61 (9.65%) | 1.36 | (0.85-2.19) | .2045 |
| Comorbidities | | | | | | | | | | | | | |
| DM | 225 | 70 (31.11%) | 1.20 | (0.88-1.63) | .2523 | 55 (24.44%) | 1.82 | (1.24-2.68) | .0023 | 33 (14.67%) | 1.09 | (0.68-1.75) | .7240 |
| Hyperlipidaemia | 108 | 21 (19.44%) | 0.82 | (0.51-1.32) | .4098 | 21 (19.44%) | 1.13 | (0.69-1.86) | .6198 | 15 (13.89%) | 1.25 | (0.69-2.25) | .4565 |
| Hypertension | 502 | 151 (30.08%) | 0.95 | (0.72-1.26) | .7399 | 100 (19.92%) | 1.44 | (0.97-2.15) | .0689 | 72 (14.34%) | 1.16 | (0.73-1.84) | .5216 |
| CAD | 183 | 60 (32.79%) | 1.05 | (0.79-1.39) | .7514 | 36 (19.67%) | 1.21 | (0.83-1.75) | .3248 | 26 (14.21%) | 1.10 | (0.71-1.70) | .6798 |
| $CHA_2DS_2$-VASc score | | | | | | | | | | | | | |
| 0 | 367 | 52 (14.17%) | 1.00 | (Reference) | - | 42 (11.44%) | 1.00 | (Reference) | - | 24 (6.54%) | 1.00 | (Reference) | - |
| 1 | 633 | 93 (14.69%) | 0.87 | (0.56-1.36) | .5474 | 58 (9.16%) | **0.52** | (0.30-0.90) | .0197 | 47 (7.42%) | 1.29 | (0.67-2.49) | .4533 |
| 2 | 346 | 89 (25.72%) | 0.71 | (0.38-1.33) | .2807 | 58 (16.76%) | 0.57 | (0.27-1.24) | .1563 | 48 (13.87%) | 2.13 | (0.85-5.31) | .1051 |
| ≥3 | 522 | 219 (41.95%) | 0.78 | (0.33-1.82) | .5593 | 102 (19.54%) | 0.46 | (0.15-1.38) | .1647 | 75 (14.37%) | 2.32 | (0.64-8.43) | .2028 |

*Note:* Abbreviations as given in Table 1.

[a]Adjusted hazard ratio, adjusted for the patients' age, gender, comorbidities, $CHA_2DS_2$-VASc score and comedication.

$CHA_2DS_2$-VASc score is currently the most recommended risk stratification scheme for prediction of stroke in nonvalvular AF.[2,3] Nevertheless, the predictive value of CHA2DS2-VASc scores for thyrotoxic AF is not well studied. Among patients with thyrotoxic AF, we found that increasing $CHA_2DS_2$-VASc score may not be optimal to predict the development of stroke and so is suboptimal for predicting clinical events, especially ischaemic stroke. Certain risk factors such as age and female sex are not as strongly associated with ischaemic stroke in thyrotoxic AF as in nonthyrotoxic AF. In particular, patients with thyrotoxicosis were mainly female. Despite a lower age-adjusted prevalence of AF in women, the risk of death in women with AF is higher than in men with AF. Therefore, even warfarin-treated female patients with AF are at a greater risk of ischaemic stroke than male patients with AF. The exact mechanism by which sex affects the predisposition to stroke is still unclear, although possible explanations include sex difference in vascular physiology, endothelial function and hormonal influences.[24] Likewise, in our study, the incidence of thyrotoxicosis was higher in women. However, compared to patients with nonthyrotoxic AF, the power of female sex to predict ischaemic stroke was weaker in patients with thyrotoxic AF. Among patients with thyrotoxic AF, there was no significant difference in stroke risk between males and females.

This study has several limitations. First, AF, ischaemic stroke and thyrotoxicosis were diagnosed according to code registry by the attending physician. The accuracy of AF and ischaemic stroke diagnosis in Taiwan's NHIRD has been validated. However, it failed to differentiate the underlying cause of the thyrotoxicosis. Likewise, given that the aetiologies of AF are complex, it is difficult to define whether AF is contributed by old age, hypertension, coronary artery disease, etc Second, whether the recorded AF was paroxysmal or nonparoxysmal was not available in this nationwide database. However, the risk of stroke did not differ between patients with paroxysmal or nonparoxysmal AF, and current guidelines do not consider AF type as a determinant for anticoagulant use. Third, lifestyle factors such as smoking, alcohol consumption and body mass index, as well as family history of stroke, were not available. Fourth, although patients have been matched for major comorbidities including hypertension, dyslipidaemia, coronary artery disease and diabetes mellitus, the possibility that this matching could still have missed cases should be considered. Finally, since we excluded patients diagnosed of ischaemic stroke prior to the index date, our study is focusing on a primary prevention. This may explain the reason that less than one-fourth of patients received anticoagulants. Given that few NOACs were available in Taiwan during the study period, only a small number of patients were under dabigatran and rivaroxaban treatment and most of the patients with AF were prescribed aspirin instead of warfarin. Also, the duration of warfarin use and PT (INR) varied. Though we analysed the risks of ischaemic stroke separately according to the interval after the use of anticoagulants, it is still difficult to reflect the actual effects of anticoagulants on stroke prevention between AF patients with and without thyrotoxicosis.

## 5 | CONCLUSIONS

Collectively, our study showed that although patients with thyrotoxicosis and AF have a higher stroke risk than the general population, this risk is still not as high as that seen in patients with AF without thyrotoxicosis. Additionally, treatment for thyrotoxicosis should be conducted prior to the prescription of anticoagulants based on CHA2DS2-VASc scores. Until more definitive evidence is presented, patients with thyrotoxic AF should be treated individually with the major goal of restoring sinus rhythm and stabilizing cardiac and thyroid functions.

## CONFLICT OF INTEREST

Nothing to declare.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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