Clinical outcomes of solitary atrial flutter patients using anticoagulation therapy: a national cohort study

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Aims	Anticoagulation therapy is indicated to prevent stroke in atrial flutter (AFL) and atrial fibrillation (AF) patients. However, the outcomes of solitary AFL patients may differ from those with AFL who develop AF during follow-up. This study aimed to investigate the differences in clinical outcomes: (i) among patients with solitary AFL, AF, and AFL developing AF thereafter and (ii) between solitary AFL patients with vs. without anticoagulation therapy.
Methods and results	This nationwide cohort study enrolled patients with solitary AFL, solitary AF, and AFL developing AF from a 12 years National Health Insurance Research Database in Taiwan. There were 230 367 patients without anticoagulation therapy in the solitary AF cohort, 8064 in the solitary AFL cohort, and 4495 in the AFL with AF cohort. The AFL with AF and solitary AF cohorts had higher incidences of ischaemic stroke and major bleeding than the solitary AFL cohort. Solitary AFL patients with anticoagulation therapy had a lower ischaemic stroke rate than those without ($P < 0.05$) at the level of a CHA_2DS_2-VASc score ≥ 3. Solitary AFL patients with anticoagulation therapy had a higher intracranial haemorrhage rate than those without ($P < 0.05$) at the level of a CHA_2DS_2-VASc score ≤ 3. Net clinical outcomes including ischaemic stroke, systemic embolization, and major bleeding favoured anticoagulation use in solitary AFL patients with a CHA_2DS_2-VASc score ≥ 4.
Conclusion	Solitary AFL patients without anticoagulation therapy had better clinical outcomes than AFL patients developing AF in this study. Anticoagulation therapy may offer the best net clinical outcome for solitary AFL patients with a CHA_2DS_2-VASc score ≥ 4.
Keywords	Atrial fibrillation • Atrial flutter • Stroke • Anticoagulation

Introduction

Atrial flutter (AFL) patients are recommended to be risk stratified and managed the same as atrial fibrillation (AF) patients in terms of preventing stroke and systemic embolization, according to clinical guidelines.[1] However, this recommendation is mainly based on experts' opinions and limited evidence.[1,2] Previous studies found that the prognoses differed between AFL and AF patients, with regard to

ischaemic stroke, heart failure, and mortality.[3,4] Therefore, the indication for stroke prevention and risk of anticoagulation use in AFL patients should be re-evaluated. In addition, AFL patients are at risk of developing AF clinically,[5] and one study[6] reported that AFL patients who developed AF had an incidence of stroke similar to AF patients. It would be interesting to elucidate whether AFL patients who developed AF had a similar incidence of stroke after stratification by using CHA_2DS_2-VASc score. Therefore, this study employed

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What's new?
- Solitary atrial flutter (AFL) patients without anticoagulation therapy had better clinical outcomes than those AFL patients developing atrial fibrillation.
- Solitary AFL patients with anticoagulation therapy had lower ischaemic stroke rate than those without at the level of CHA_2DS_2-VASc score $\geq$ 3.
- Anticoagulation therapy may offer the best net clinical outcome in solitary AFL patients with a CHA_2DS_2-VASc score $\geq$ 4.

two datasets to evaluate these two questions: First, we aimed to evaluate the difference in outcomes among patients with solitary AFL, solitary AF, and AFL with developing AF without anticoagulation therapy. Second, we aimed to evaluate the safety and efficacy of anticoagulation therapy in solitary AFL patients.

Methods

Data sources

This national cohort study employed data retrieved from the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes. Taiwan's National Health Insurance is a compulsory single-payer healthcare system featuring care coverage for more than 20 million Taiwanese, and contains health care information dating back to 1997. Briefly, the healthcare information in the database includes outpatient visits, hospitalization, drug prescriptions, diseases, and vital status. Diseases were registered using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. The identification numbers of all participants were encrypted to protect their privacy, but the encrypting procedure was consistent; therefore, the participants could be longitudinally followed. In this study, AF and AFL participants who were newly diagnosed with AF or AFL on or after 1 January 2001 were enrolled. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (201700865B0).

Study populations in two datasets

A total of 295 706 participants who were newly diagnosed with AF or AFL between 1 January 2001 and 31 December 2012 were identified for inclusion in this study. After excluding those who were <20 years of age and those with AF who had been diagnosed with AFL during this observation period, 281 396 participants were enrolled in the two datasets. Dataset 1 included three cohorts (solitary AF, solitary AFL, and AFL with developing AF) enrolled for outcomes assessment after the exclusion of participants with anticoagulation therapy (*Figure 1*). Solitary AF participants were those who were not diagnosed with AFL during the observation period, while solitary AFL participants were those who were not diagnosed with AF during the observation period. The AFL developing AF participants were those who were first diagnosed as having AFL and later diagnosed with AF between 1 January 2001 and 31 December 2012. With the exception of a few (<0.1%) demographic data (i.e. sex and age) that were missing and were excluded, there were no missing data in the database in terms of variables of primary interest (i.e. CHA_2DS_2-VASc and outcomes) that were identified based on the ICD-9 code diagnosis. The two cohorts enrolled in Dataset 2 were those with solitary AFL with or without anticoagulation treatment (*Figure 1*).

Study design and outcome assessment

The clinical outcomes assessed in this study were ischaemic stroke, systemic embolization, intracranial haemorrhage (ICH), and major bleeding. The clinical outcomes were diagnosed according to the principle diagnosis at hospitalization.

We used two datasets to achieve the two aims of this study, i.e. examining incident major bleeding and stroke among patients with solitary AFL, AFL developing AF, and solitary AF in Dataset 1 and exploring the safety and efficacy of anticoagulation therapy among solitary AFL patients in Dataset 2. The clinical outcomes of ischaemic stroke, systemic embolization, ICH, and major bleeding were assessed in Datasets 1 and 2. Then, the net clinical outcomes in terms of stroke, systemic embolization, and major bleeding were compared between the solitary AFL with anticoagulation cohort and the solitary AFL without anticoagulation cohort in Dataset 2. In addition, the clinical outcomes in Datasets 1 and 2 were assessed across different CHA_2DS_2-VAS_C levels. The participants in Dataset 1 were stratified using CHA_2DS_2-VAS_C scores of 0, 1, 2, 3, 4, 5, 6, and 7–9, whereas those in Dataset 2 were stratified as 0, 1, 2, 3, 4, and 5–9 because of the smaller population. The CHA_2DS_2-VASc score was calculated using a point system in which two points were assigned for a history of stroke or transient ischaemic attack or age $\geq$75 years, and one point was assigned for age 65–74 years or a history of hypertension, diabetes, heart failure, or vascular disease (myocardial infarction and peripheral artery disease), or female sex.[7] The index date was the date when AF or AFL was first diagnosed in outpatient clinics (two consecutive clinical visits) or hospitalization for solitary AF and AFL participants, whereas the index date was the date when AFL was first diagnosed in outpatient clinics or at hospitalization for AFL developing AF participants. Events that occurred between the two outpatient clinical visits were also counted with the duration of the event measured since the first diagnosis. The observation period ended at the time of death or on 31 December 2012. Death was defined as a patient's withdrawal from the National Health Insurance (NHI) programme.[8]

Ascertainment of atrial fibrillation, atrial flutter, comorbidities, and clinical outcomes

Atrial fibrillation (ICD-9-CM: 427.31), AFL (ICD-9-CM: 427.32), and all comorbidities were defined as when the diagnosis was made at least once during hospitalization or on two consecutive clinical visits. The high accuracy of the AF diagnosis based on the ICD-9-CM in the NHIRD was confirmed previously.[9] A validation study for AFL was conducted previously and the positive predictive value was 97.5%.[4] The major comorbidities were validated and reported in the literature.[10] In addition, hypertension, diabetes, and dyslipidaemia were ascertained according to the ICD-9-CM, combined with medication use, to decrease the risk of misclassification. The diagnostic definitions and medications are listed in the Supplementary material online, *Tables S1 and S2*. Ischaemic stroke, systemic embolism, and ICH were defined according to the principle diagnosis on admission, based on the ICD-9-CM; a high-positive predictive value for this was noted in a previous study.[4] Systemic embolism was defined as an acute vascular occlusion of an extremity or organ. Major bleeding was defined according to the diagnosis on admission, based on the ICD-9-CM, which included haemorrhagic stroke and subdural or subarachnoid haemorrhage, symptomatic bleeding at critical areas or organs, and those bleeding events at which blood transfusions of at least 2 units of blood were given.

Statistical analysis

Clinical characteristics (i.e. age, sex, baseline characteristics, and medications) of participants in the three study cohorts (solitary AF, solitary AFL, and AFL developing AF) without anticoagulant treatment were compared using one-way analysis of variance for continuous variables or the χ^2 test
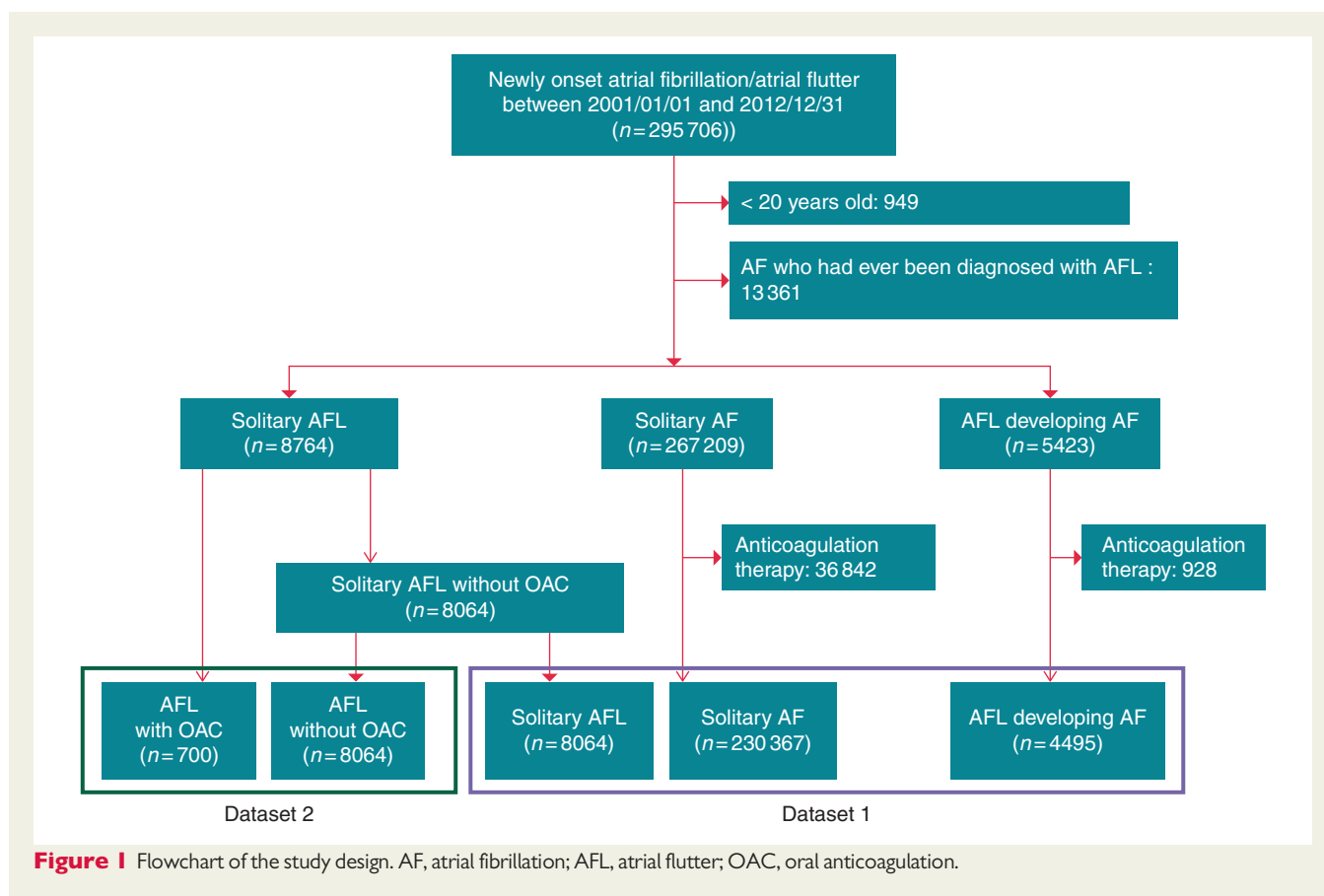
Figure I Flowchart of the study design. AF, atrial fibrillation; AFL, atrial flutter; OAC, oral anticoagulation.

for categorical variables. Pairwise *post hoc* multiple comparisons between any two study groups were made using the Bonferroni adjustment. The risk of clinical outcomes (ischaemic stroke, ICH, systemic embolization, and major bleeding) was expressed as incidence density (ID; event numbers per 100 person-years). We compared the risk of clinical outcomes among the three study cohorts without anticoagulant treatment using a Cox proportional hazard model in which the CHA_2DS_2-VASc score was treated as a stratum variable (as our primary analysis). A similar analysis was done when comparing the risk of clinical outcomes in solitary AFL patients between those who received oral anticoagulation (OAC) therapy and those who did not. In addition to stratifying the CHA_2DS_2-VASc score, we performed a sensitivity analysis, comparing outcomes of the AFL population between those with anticoagulation therapy and those without, using propensity score matching. Levels of statistical significance were set as 0.05 and no adjustment of multiple testing (multiplicity) was done in this study. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of solitary atrial fibrillation, solitary atrial flutter, and atrial flutter developing atrial fibrillation patients in the Dataset 1

There were 230 367 patients in the solitary AF cohort, 8064 patients in the solitary AFL cohort, and 4495 patients in the AFL developing

AF cohort in Dataset 1. During a mean follow-up duration of 2.88 years (standard deviation = 2.92 years), a total of 133 356 patients (54.7%) were withdrawn from the NHI system. The differences in baseline characteristics among the three cohorts are shown (*Table 1* and Supplementary material online, *Table S3*). Briefly, solitary AF patients were the oldest and solitary AFL patients were the youngest. The proportion of female patients was highest in the solitary AF cohort and lowest in the AFL developing AF group. Comorbidities (except peripheral artery disease), event history, and medications were significantly different among the three groups. Solitary AF and AFL developing AF participants had hypertension, ischaemic heart disease, and gout more frequently. The solitary AF cohort had heart failure and chronic obstructive pulmonary disease more frequently, and the AFL developing AF cohort had heart failure and chronic obstructive pulmonary disease less frequently than the solitary AFL patients. When we compared baseline characteristics among the three groups after dividing them by gender, the differences tended to be broadly similar in the male and female populations (Supplementary material online, *Tables S4 and S5*). We also evaluated the potential risk of AFL patients developing AF and found that older age, male, hypertension, heart failure, and ischaemic stroke/systemic embolism were potential risks of developing AF (Supplementary material online, *Table S6*). The solitary AF and solitary AFL cohorts had more patients with chronic kidney disease than the AFL developing AF cohort. The prevalence of ischaemic stroke was highest in the solitary AF participants and lowest in the solitary AFL patients.

Table I Baseline characteristics of real-world solitary AFL, solitary AF, and AFL developing AF population without anticoagulation treatment

Variables	Solitary AFL (n = 8064)	Solitary AF (n = 230 367)	AFL developing AF (n = 4495)	P-value
Age (years), mean ± SD	67.7 ± 16.5	73.3 ± 13.5[a]	69.8 ± 12.8[a,b]	<0.001
Age group (years)				<0.001
<65	2949 (36.6)	52 575 (22.8)[a]	1415 (31.5)[a,b]	
65–74	1902 (23.6)	54 335 (23.6)	1281 (28.5)[b]	
≥75	3213 (39.8)	123 457 (53.6)[a]	1799 (40.0)[b]	
Sex				<0.001
Male	4875 (60.5)	125 486 (54.5)[a]	2811 (62.5)[b]	
Female	3189 (39.5)	104 881 (45.5)[a]	1684 (37.5)[b]	
Comorbidities				
Hypertension	4235 (52.5)	130 488 (56.6)[a]	2550 (56.7)[a]	<0.001
Diabetes mellitus	1530 (19.0)	42 596 (18.5)	745 (16.6)[b]	0.002
Ischaemic heart disease	2793 (34.6)	86 901 (37.7)[a]	1747 (38.9)[a]	<0.001
Heart failure	1084 (13.4)	33 582 (14.6)[a]	481 (10.7)[a,b]	<0.001
Dyslipidaemia	935 (11.6)	23 229 (10.1)[a]	429 (9.5)[a]	<0.001
Gout	758 (9.4)	23 013 (10.0)[a]	484 (10.8)[a]	0.046
Chronic obstructive pulmonary disease	1602 (19.9)	52 231 (22.7)[a]	762 (17.0)[a,b]	<0.001
Peripheral artery disease	209 (2.6)	6140 (2.7)	108 (2.4)	0.518
Chronic kidney disease	1267 (15.7)	34 805 (15.1)[a]	518 (11.5)[a,b]	<0.001
Event history				
Ischaemic stroke	1035 (12.8)	40 493 (17.6)[a]	655 (14.6)[a,b]	<0.001
Systemic embolization	145 (1.8)	4984 (2.2)	80 (1.8)	0.020
Intracranial haemorrhage	195 (2.4)	5740 (2.5)	71 (1.6)[a,b]	<0.001
Major bleeding	854 (10.6)	26 264 (11.4)	322 (7.2)[a,b]	<0.001
Risk score				
CHA_2DS_2-VASc	2.9 ± 1.9	3.4 ± 1.9[a]	3.0 ± 1.8[a,b]	<0.001
HAS-BLED	2.1 ± 1.2	2.3 ± 1.1[a]	2.3 ± 1.1[a]	<0.001

AF, atrial fibrillation; AFL, atrial flutter; SD, standard deviation.
[a]$P < 0.05$ vs. solitary AFL.
[b]$P < 0.05$ vs. solitary AF.

Intracranial haemorrhage and major bleeding were more common in the solitary AFL and solitary AF cohorts than in the AFL developing AF cohort.

The average CHA_2DS_2-VASc score was highest in the solitary AF cohort, followed by the AFL developing AF and solitary AFL cohorts ($P < 0.001$). The HAS-BLED scores were higher in the solitary AF and AFL developing AF cohorts than in the solitary AFL cohort ($P < 0.001$).

Clinical outcomes among the three cohorts in Dataset 1 stratified by CHA_2DS_2-VASc scores

The three cohorts were individually stratified according to CHA_2DS_2-VASc scores. The annual incidence of ischaemic stroke and the combined endpoints of ischaemic stroke and systemic embolization were higher in the AFL developing AF and solitary AF cohorts than in the solitary AFL cohort across CHA_2DS_2-VASc scores of 0–9 (*Figure 2A* and *B*). Although, AFL developing AF seemed to present a risk of developing ischaemic stroke, there were no significant differences between the AFL developing AF and solitary AF cohorts across CHA_2DS_2-VASc scores of 0–6. In terms of bleeding events, the annual incidence of major bleeding was higher in the AFL developing AF and solitary AF cohorts than in the solitary AFL cohort across CHA_2DS_2-VASc scores of 0–9 (*Figure 2D*), while the annual incidence of ICH among the three groups did not reflect this phenomenon (*Figure 2C*). In general, the annual incidence of ICH was higher in the solitary AF cohort than in the solitary AFL cohort [stratified hazard ratio (SHR), 1.29; 95% confidence interval (CI), 1.08–1.55; $P = 0.005$) (*Figure 2C*). The detailed event numbers and ID among the three groups are shown (Supplementary material online, *Tables 7–10*). We performed an additional analysis of major bleeding by adjusting for HAS-BLED scores, since the HAS-BLED score is an index scoring system to predict bleeding events. The major bleeding results were similar after additional adjustment of HAS-BLED scores, in terms of which, the solitary AF cohort had a higher risk than the solitary AFL cohort (SHR, 1.23; 95% CI, 1.13–1.33; $P < 0.001$), and the AFL developing AF cohort had higher risks than the solitary AFL cohort (SHR, 1.14; 95% CI, 1.01–1.28; $P = 0.036$) (data not shown).
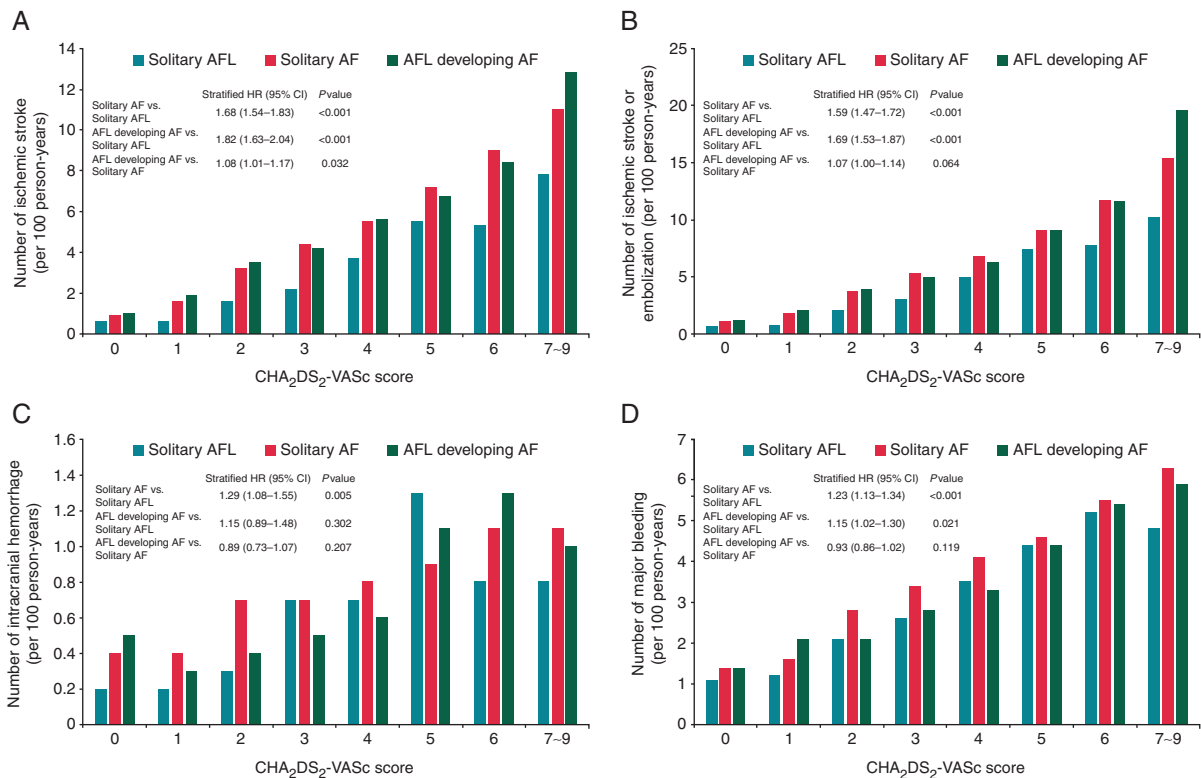
Figure 2 Incidence density of (*A*) ischaemic stroke, (*B*) ischaemic stroke/systemic embolization, (*C*) intracranial haemorrhage, and (*D*) major bleeding, in each study group stratified by CHA_2DS_2-VASc score. AF, atrial fibrillation; AFL, atrial flutter; CI, confidence interval; HR, hazard ratio.

In pairwise comparisons, the solitary AF and AFL developing AF cohorts were seen to have a significantly higher ID of ischaemic stroke, a composite of ischaemic stroke and systemic embolization, and major bleeding than the solitary AFL cohort across all levels of CHA_2DS_2-VAS$_C$ scores (*Figure 2A, B,* and *D*). The ID of ischaemic stroke was even higher in the AFL developing AF cohort than in the solitary AF cohort in pairwise comparisons (SHR, 1.08; 95% CI, 1.01–1.17; $P = 0.032$) (*Figure 2A*). Finally, we evaluated the differences in risks of clinical outcomes between the three groups after separation by gender, and the trends among males and females were similar to those of the whole population (*Table 2*).

Clinical outcomes between solitary atrial flutter participants with and without anticoagulation in Dataset 2

A total of 700 participants with solitary AFL received anticoagulation therapy, whereas the other 8064 did not. The ID of ischaemic stroke and systemic embolization among the solitary AFL participants that received anticoagulation and those that did not are shown in Supplementary material online, *Tables S11 and S12*, and the ID increased with the level of CHA_2DS_2-VASc scores in the solitary AFL participants without anticoagulation. With regard to the effect of anticoagulation therapy on preventing stroke or systemic embolization, a significant benefit appeared with a CHA_2DS_2-VASc score of ≥3, in terms of both ischaemic stroke (SHR, 0.58; 95% CI, 0.38–0.88;

$P = 0.010$) (*Figure 3A*) and a composite of ischaemic stroke and systemic embolization (SHR, 0.60; 95% CI, 0.42–0.86; $P = 0.005$) (*Figure 3B*), but there was no significant benefit for AFL patients with a CHA_2DS_2-VASc score of <3 (*Figure 3A and B*). The ID of ICH and major bleeding between solitary AFL patients who received anticoagulation and those who did not are shown (Supplementary material online, *Tables S13 and S14*); the ID of those who did not receive anticoagulation showed an obvious increase with increases in the CHA_2DS_2-VASc score. With respect to risk of bleeding, the annual incidence of ICH generally was higher in solitary AFL participants who received anticoagulation therapy than in those who did not (SHR, 1.81; 95% CI, 1.13–2.87; $P = 0.013$), especially in those with a CHA_2DS_2-VASc score of ≤3 (SHR, 2.48; 95% CI, 1.39–4.42; $P = 0.002$) (*Figure 3C*). On the other hand, the incidence of major bleeding did not differ between solitary AFL participants receiving anticoagulation therapy and those who did not, across all CHA_2DS_2-VASc scores (*Figure 3D*). Of note, when focusing on the net clinical outcomes of stroke, systemic embolization, and major bleeding, even though their incidence increased with increases in the CHA_2DS_2-VASc scores (Supplementary material online, *Table S15*), AFL participants who received anticoagulation therapy had better net clinical outcomes than solitary AFL participants without anticoagulation therapy when the CHA_2DS_2-VASc score was ≥4 (SHR, 0.68; 95% CI, 0.50–0.93; $P = 0.014$) (*Figure 3E*). The details of pairwise comparisons between AFL participants receiving anticoagulation therapy and those who did not in different re-groupings based on the

Table 2 The differences of individual clinical outcomes in separated gender among solitary AF, solitary AFL, and AFL developing AF cohorts

Outcome/contrast	Male		Female	
	Stratified HR (95% CI)	*P*-value	Stratified HR (95% CI)	*P*-value
Ischaemic stroke				
Solitary AF vs. solitary AFL	1.55 (1.38–1.73)	<0.001	1.84 (1.60–2.12)	<0.001
AFL developing AF vs. solitary AFL	1.69 (1.46–1.95)	<0.001	1.91 (1.59–2.28)	<0.001
AFL developing AF vs. solitary AF	1.09 (0.99–1.20)	0.071	1.04 (0.92–1.16)	0.557
Ischaemic stroke/systemic embolization				
Solitary AF vs. solitary AFL	1.47 (1.34–1.63)	<0.001	1.73 (1.53–1.96)	<0.001
AFL developing AF vs. solitary AFL	1.58 (1.38–1.79)	<0.001	1.76 (1.50–2.07)	<0.001
AFL developing AF vs. solitary AF	1.07 (0.98–1.17)	0.133	1.02 (0.92–1.13)	0.747
Intracranial haemorrhage				
Solitary AF vs. solitary AFL	1.20 (0.96–1.48)	0.106	1.43 (1.04–1.97)	0.027
AFL developing AF vs. solitary AFL	0.99 (0.72–1.36)	0.944	1.34 (0.86–2.07)	0.196
AFL developing AF vs. solitary AF	0.83 (0.65–1.05)	0.118	0.93 (0.68–1.27)	0.659
Major bleeding				
Solitary AF vs. solitary AFL	1.20 (1.08–1.33)	<0.001	1.27 (1.10–1.47)	0.001
AFL developing AF vs. solitary AFL	1.04 (0.90–1.20)	0.613	1.25 (1.02–1.53)	0.035
AFL developing AF vs. solitary AF	0.87 (0.78–0.96)	0.009	0.98 (0.84–1.13)	0.760

Solitary AFL patients without anticoagulation therapy had better clinical outcomes than those developing atrial fibrillation. Anticoagulation lowered the risk of ischaemic stroke in solitary AFL patients with CHA_2DS_2-VASc score ≥3 and may offer the best net clinical outcome in those patients with a score ≥4.
AF, atrial fibrillation; AFL, atrial flutter; CI, confidence interval; HR, hazard ratio.

CHA_2DS_2-VASc score are listed (Supplementary material online, *Table S16*). Furthermore, because of significant differences in high levels of the CHA_2DS_2-VASc score, we did subgroup analysis in the male population with CHA_2DS_2-VASc ≥3 and female population with CHA_2DS_2-VASc ≥4 (Supplementary material online, *Table S17*). In general, the trends of differences among groups of the separate genders were similar to our main analysis. The Kaplan-Meier survival curves of composite endpoints (with weights of 1.5 for ICH and 1.0 for ischaemic stroke) stratified by CHA_2DS_2-VASc ≤3 and ≥4 are illustrated in Supplementary material online, *Figure S1A* (score ≤3) and *S1B* (score ≥4), and the result of comparing AFL with/without anticoagulation was the same as in our main analysis above (Supplementary material online, *Figure S1A and B*). Finally, sensitivity analyses comparing AFL populations with and without OAC were done by using propensity score matching, and the results were generally similar to those of our primary analysis (Supplementary material online, *Tables S18 and S19*).

Discussion

There are several important findings in this study. First, the solitary AF patients and AFL developing AF patients had higher ischaemic stroke, systemic embolization, and major bleeding rates than the solitary AFL patients. Second, solitary AFL patients with a CHA_2DS_2-VASc score ≥3 who received anticoagulation therapy had lower rates of ischaemic stroke and/or systemic embolization than those who did not receive anticoagulation therapy. Third, solitary AFL patients received anticoagulation therapy had better net clinical outcomes of stroke, systemic embolization, and major bleeding

than those without anticoagulation therapy at a CHA_2DS_2-VASc score ≥4.

Real-world characteristics and outcomes of solitary atrial fibrillation, solitary atrial flutter, and atrial flutter developing atrial fibrillation participants

According to clinical guidelines, anticoagulation should be used with AFL patients and AF patients. However, there may be differences in pathophysiology and clinical outcome.[1,6,10] Several prospective or retrospective studies have compared the stroke event rates among AFL patients, non-AFL/AF subjects, and AF patients.[3,6,11,12] Most of these prospective or retrospective studies enrolled very few AFL patients (<150) and revealed heterogeneous results.[3,11,12] However, one retrospective study enrolled 17 413 AFL patients and showed that they were at greater risk of stroke than the controls (relative risk, 1.4; 95% CI, 1.35–1.46), but had a lower stroke risk than AF patients.[6] In our previous study, we found that the incidence of ischaemic stroke was also higher in the AF cohort than in the AFL cohort (2.2 vs. 1.4 events per 100 person-years; hazard ratio, 1.52; 95% CI, 1.36–1.69).[4] Some studies reported no significant difference in stroke risk between AFL and AF patients.[3,12] However, those studies did not analyse the differences between solitary AFL patients and AFL developing AF patients. Some AFL patients may develop AF clinically during follow-up, whereas other patients may not.[3] The clinical outcomes might differ between patients with solitary AFL and those with AFL developing AF during follow-up. The present study showed that AFL developing AF patients might have worse outcomes in terms of ischaemic stroke, systemic embolization, and major bleeding
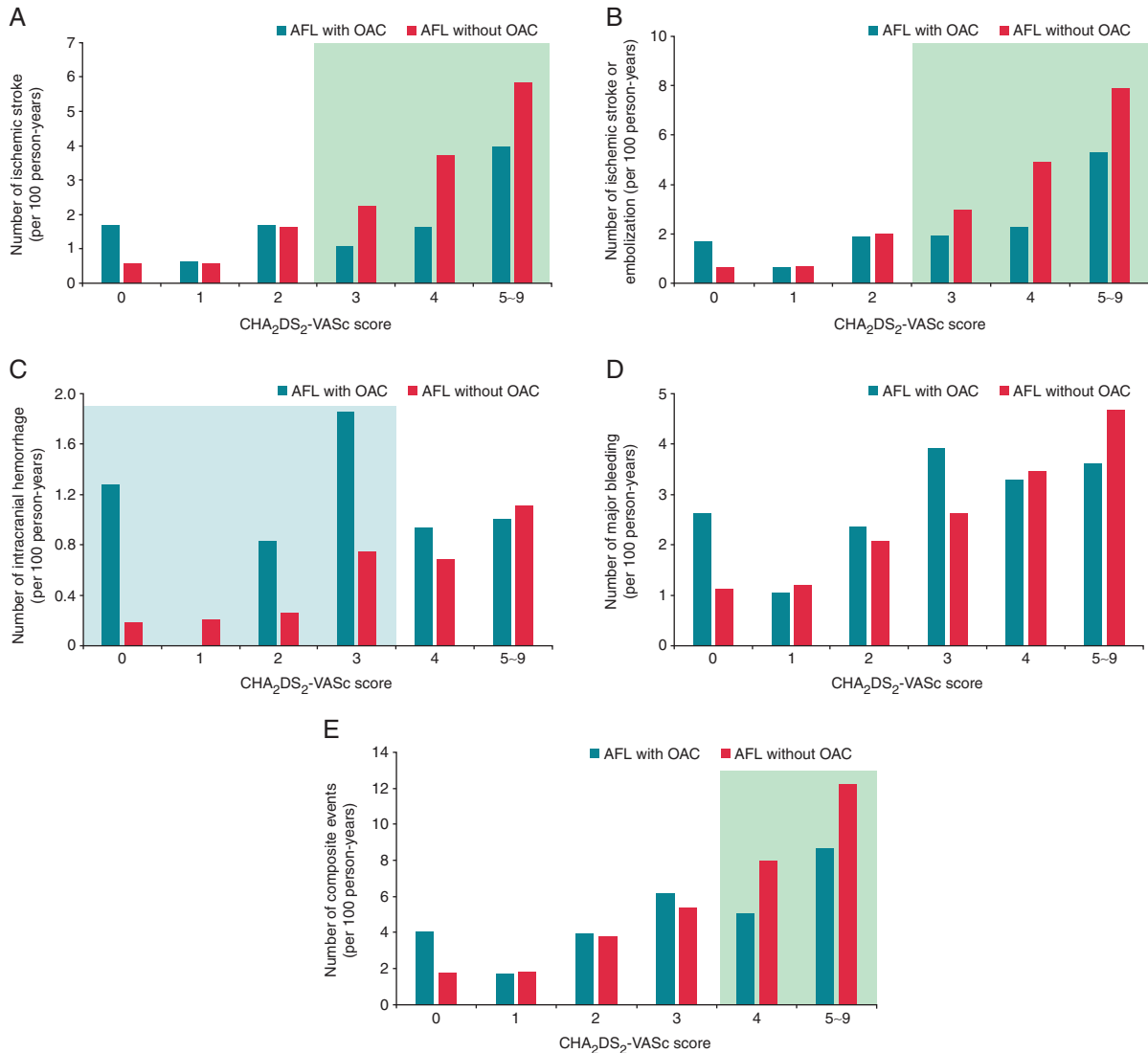
Figure 3 Impact of anticoagulation therapy status on the risk of (*A*) ischaemic stroke, (*B*) ischaemic stroke/systemic embolization, (*C*) intracranial haemorrhage, (*D*) major bleeding, and (*E*) composite events, which included major bleeding or ischaemic stroke/systemic embolization, in solitary AFL patients stratified by CHA_2DS_2-VASc score. Anticoagulation therapy has a good impact on solitary AFL participants with a CHA_2DS_2-VASc score in the slash area, but has a bad impact on those with a CHA_2DS_2-VASc score in the dot-area. AFL, atrial flutter; OAC, oral anticoagulation.

than solitary AFL patients, and annual event rates comparable to those of solitary AF patients. In our study, about 37% of AFL patients developed AF during the following 12 year observation period, and the clinical outcomes between patients with solitary AFL and those with AFL developing AF were totally different. However, we did not evaluate the association between clinical events and the duration between the dates of diagnosis of AFL and AF. Such a study design might lead to a bias of over-estimated adverse events in the solitary AFL group and under-estimated adverse events in the AFL developing AF group, because AFL patients who died before they developed AF might be included in the analysis of the solitary AFL group rather than in the AFL developing AF group. Despite this limitation, we thought this would have only limited influence on our results and

observations in this study, because the event rates were already significantly higher in the AFL developing AF group than in the solitary AFL group. Thus, further studies to investigate the predictors of future development of AF in AFL patients might be important for risk stratification and clinical management.

Different impacts of anticoagulation on patients with solitary atrial flutter using CHA_2DS_2-VASc scores

The CHA_2DS_2-VASc scoring system is the stratification system most commonly recommended in clinical guidelines and is widely used to predict the annual incidence of ischaemic stroke in AF and AFL patients.[13] The clinical guidelines also recommend using the

CHA_2DS_2-VASc scoring system in decision-making with AF and AFL patients on anticoagulation use.[1] However, the recommendation was based on studies that enrolled a small percentage of AFL patients.[14–17] Moreover, our previous study showed that the risk of stroke in AF patients was quite different from that in solitary AFL patients. According to the present study, the use of anticoagulation may decrease the risk of ischaemic stroke in solitary AFL patients with a CHA_2DS_2-VASc score ≥3. However, the use of anticoagulation may increase the risk of ICH in solitary AFL patients with a CHA_2DS_2-VASc score ≤3. Considering the net clinical outcome, including stroke, systemic embolization, and major bleeding, anticoagulation use in solitary AFL patients might be considered in solitary AFL patients with a CHA_2DS_2-VASc score ≥4. According to our study findings, the decision for or against anticoagulation use in solitary AFL patients must be individualized based on the benefits and risks.

Limitations

This retrospective insurance database cohort study has several limitations. First, the different AF patterns (paroxysmal, persistent, and permanent) and AFL types (typical and atypical) were not recorded in the NHIRD. However, the impact of AF pattern on the risk of ischaemic stroke and systemic embolization remains under debate.[18–21] Therefore, further studies regarding the impact of different classifications of AF and AFL on clinical outcome should be conducted. In addition, we did not analyse whether patients with AFL were treated with ablation or not. According to a previous study, patients with typical AFL who received cavotricuspid isthmus ablation may have a lower risk of stroke and/or thromboembolic events.[22] However, patients with atypical AFL may receive various combinations of drugs and ablation. This may play a role in the subsequent risk of adverse events. Second, we did not have access to prothrombin time-international normalized ratio data or the target therapeutic range for AFL patients who received warfarin therapy. Clearly, warfarin use within the therapeutic range would influence the outcome. Third, the outcome data in Dataset 2 of this study were mainly obtained in the warfarin era [only one patient in Dataset 2 received non-vitamin K oral anticoagulant (NOAC)]. It has been shown that using anticoagulation with NOAC may lead to a lowering of the stroke risk threshold with anticoagulation use to a rate of 0.9% per year.[23] This finding could result in being able to treat solitary AFL patients with a lower CHA_2DS_2-VASc score. Therefore, the recommendation for NOAC use in solitary AFL patients across different CHA_2DS_2-VASc scores should be evaluated in the future. Finally, there might be a potential bias to evaluate more thoroughly in the search for arrhythmias in those with adverse clinical events, compared with those without adverse clinical events, particularly stroke. Therefore, under diagnosis may have occurred in our study, especially in the no complications group. Another selection bias might have been made in the grouping of those patients with concomitant AF and AFL, and they might have been misclassified as solitary AFL or AF because some physicians may not routinely use two codes for patients with mixed AF and AFL. However, the prevalence and ratio of AF, AFL, and AFL developing AF in our study population were similar to a previous report, indicating that our data should be reasonable.[6]

Conclusions

This national cohort study showed that the risk of stroke, systemic embolization, and major bleeding in solitary AFL patients without anticoagulation therapy was significantly lower than that in patients with AFL developing AF or solitary AF. Anticoagulation use reduced the risk of ischaemic stroke or systemic embolization in solitary AFL patients with a higher CHA_2DS_2-VASc score (≥3). Solitary AFL patients with a CHA_2DS_2-VASc score ≥4 may have better net clinical outcomes of ischaemic stroke, systemic embolization, and major bleeding when receiving anticoagulation therapy.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.

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