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CLINICAL RESEARCH

Association between antithrombotic therapy after stroke in patients with atrial fibrillation and the risk of net clinical outcome: an observational cohort study

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Aims

Data on the optimal use of antithrombotic drugs and associated clinical outcomes in patients with atrial fibrillation (AF) and acute ischaemic stroke (IS) are limited. We investigated the prescription patterns of antithrombotics in community practice and long-term clinical prognosis according to early post-stroke antithrombotic therapy in patients with AF and acute IS.

Methods and results

Patients with AF who were admitted for acute IS at a single tertiary hospital in 2010–2020 were retrospectively reviewed. Clinical profiles including the aetiology of stroke and prescription patterns of antithrombotics were identified. The net clinical outcome (NCO)—the composite of recurrent stroke, any bleeding, hospitalization or emergency department visits for cardiovascular (CV) events, and death—was compared according to the antithrombotic therapy at the first outpatient clinic visit [oral anticoagulation (OAC) alone vs. antiplatelet (APT) alone vs. OAC/APT(s)] following discharge. A total of 918 patients with AF and acute IS (mean age, 72.6 years; male, 59.3%; mean CHA_2DS_2-VASc score 3.3) were analysed. One-third (33.9%, $n = 310$) of patients were simultaneously diagnosed with AF and IS. The most common aetiology of IS was cardioembolism (71.2%), followed by undetermined aetiology (19.8%) and large artery atherosclerosis (6.0%). OAC, APT(s), and concomitant OAC and APT(s) were prescribed in 33.4%, 11.1%, and 53.4% of patients during admission that changed to 67.0%, 9.1%, and 21.7% at the first outpatient clinic, and were mostly continued up to one year after IS. Non-prescription of OAC was observed in 11.3% of post-stroke patients with AF. During a median follow-up of 2.1 years, the overall incidence rate of NCO per 100 patient-year (PY) was 20.14. APT(s) monotherapy presented the highest cumulative risk of NCO (adjusted hazard ratio 1.47, 95% confidence interval 1.08–2.00, $P = 0.015$; with reference to OAC monotherapy) mainly driven by the highest rates of recurrent stroke and any bleeding. OAC/APT(s) combination therapy was associated with a 1.62-fold significantly higher risk of recurrent stroke ($P = 0.040$) and marginally higher risk of any bleeding than OAC monotherapy.

Conclusion

Approximately one-third of acute IS in AF have a distinctive mechanism from cardioembolism. Although APT was frequently prescribed in post-stroke patients with AF, no additive clinical benefit was observed. Adherence to OAC treatment is essential to prevent further CV adverse events in patients with AF and IS.

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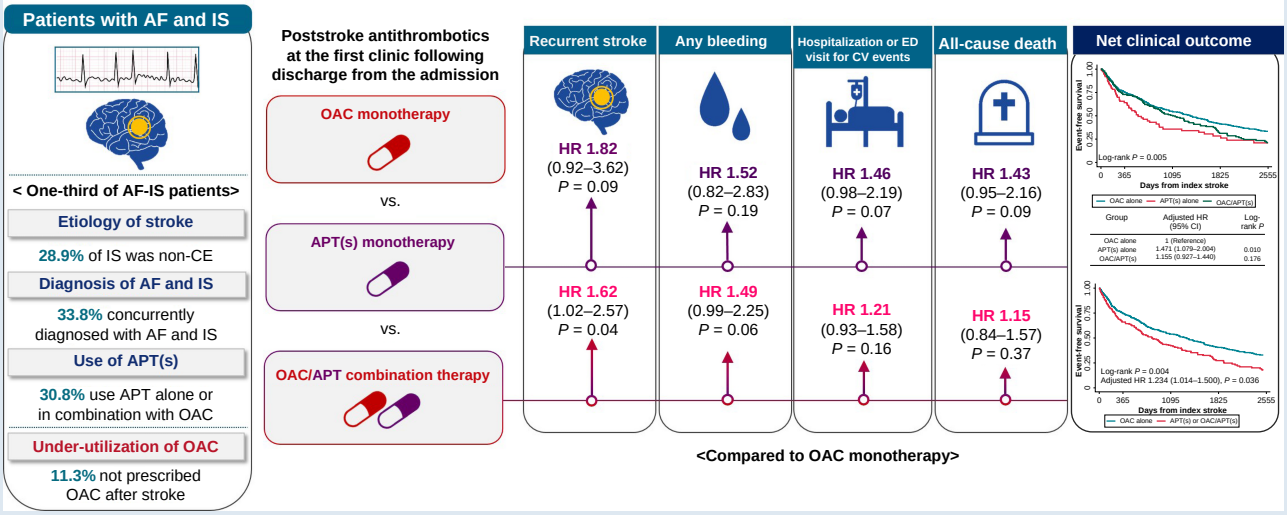
Graphical Abstract



Keywords Atrial fibrillation • Ischaemic stroke • Oral anticoagulation • Antiplatelet • Antithrombotics

What's new?

- In this observational cohort study of patients with atrial fibrillation (AF) ($n = 918$) who were admitted for an acute ischaemic stroke (IS), 33.8% of patients were concurrently diagnosed with AF and IS.
- Among patients with AF and IS, 71.1% of IS had an aetiology as cardioembolism (CE), while remained 28.9% of IS was non-CE.
- Nearly one-third of patients with AF and IS utilized antithrombotic therapy including antiplatelet (APT), either APT(s) alone or in combination with oral anticoagulant (OAC).
- Compared to OAC monotherapy, patients with APT(s) monotherapy from the early post-stroke period presented a 47% higher risk of net clinical outcome, and patients with OAC/APT(s) combination therapy was related to 62% significantly higher risk of recurrent stroke and marginally higher risk of any bleeding than OAC monotherapy.

Introduction

Atrial fibrillation (AF) contributes to 20–30% of ischaemic stroke (IS) and is associated with five-fold increased risk of stroke.[1,2] Oral anticoagulation (OAC) is a pivotal drug for the primary and secondary prevention of IS in patients with AF, but optimal antithrombotic strategies and the timing of initiation largely depend on expert consensus.[2–6] Indeed, combination with antiplatelet (APT) agents remains common in clinical practice, and even APT(s) monotherapy, which is discouraged by guidelines, is prescribed in a substantial portion of patients with AF.[7]

The gap between guideline recommendations and real-world clinical practice might be partly explained by the possible coexistence of alternative stroke mechanisms in patients with AF, such as large artery atherosclerosis (LAA) or small-vessel occlusion (SVO).[8,9] Meanwhile, the recent guidelines for secondary stroke prevention emphasize the need to define the aetiology of IS to identify treatment targets.[3] Given that some patients with AF of acute IS often have vascular risk factors that necessitate APT therapy,[10] the optimal antithrombotic drug regimen in these patients has been subject to debate.[9] Concurrently, little information is known about the real-world clinical practice of the prescription pattern of antithrombotics for patients with AF during acute IS, early post-stroke, and long-term maintenance period, as well as the accompanying clinical outcomes.

In this study, we aimed to investigate (1) the detailed characteristics, including the aetiology of stroke, (2) the antithrombotic therapy treatment pattern, and (3) long-term clinical outcomes in patients with AF and acute IS according to early post-stroke phase antithrombotic therapy, especially by OAC alone vs. APT(s) alone vs. OAC/APT(s).

Methods

Ethics approval and consent to participate

The institutional review board at Seoul National University Hospital (H-2105-165-1221) authorized this study. Written informed consent was waived since all the information was anonymized and de-identified. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (see Supplementary material online, Supplementary file 1).

Study design and population

This is a single-centre retrospective cohort study including hospitalized patients who were admitted for IS or transient ischaemic attack (TIA) (hereafter, index stroke) and subsequently underwent evaluation through brain magnetic resonance imaging (MRI) at a tertiary referral hospital (Seoul National University Hospital) from January 2010 to December 2020. Among them, only those with a prior or concurrent diagnosis of AF were included. Patients were initially identified based on the International Classification of Diseases (ICD)-10 codes—I63, I64, and G459 for index stroke and I48 for AF, which presented 82–97% positive predictive value (PPV) for IS/TIA and 98% PPV for AF[11–13]—from the electrical medical record. Individual cases were comprehensively evaluated by two cardiologists (H.-J.A. and S.-R.L.). Misclassified patients labelled as having AF based on diagnostic code (preliminary diagnosis) but were later confirmed to have AF after the index admission period or those admitted for other medical reasons such as seizure, neuropathy, or supportive care were excluded during the thorough review process.

Covariates, information on index stroke, and antithrombotic regimens

Demographic data, anthropometric measurements, comorbidities, laboratory examination results, medication history, and smoking/drinking status

investigated at the index admission were retrospectively reviewed. We collected echocardiographic data closest to the index stroke, with a maximum range of six months before and after the occurrence of the index stroke. The utilization of antithrombotic drugs at four distinct time points was assessed: before admission for the index stroke, during the admission period, at the first clinic visit following discharge from the index admission, and one year after the occurrence of the index stroke.

We evaluated detailed information on AF, including type, date of diagnosis, and the chronological relationship with the index stroke (whether AF is diagnosed precedingly or simultaneously). The aetiology of stroke was determined based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[14] by the agreement of neurologists who were primarily responsible for the peri-stroke care as one of the five categories: LAA, cardioembolism (CE), SVO, stroke of other determined aetiology (OD), and stroke of undetermined aetiology (UD). We also explored the concomitant presence of microbleeds or haemorrhagic transformation on brain MRI, which was performed as an initial evaluation of the index stroke.

The use of OAC, APT, and subtype of each drug category at four time points was investigated. We assessed how the prescription pattern of antithrombotic drugs changed at designated time intervals. Also, we evaluated clinical factors associated with the exclusive use of OAC—which is recommended for secondary stroke prevention in AF[15,16]—at the first clinic visit with the assumption that this treatment would be continued in the subsequent acute stroke period.

Study outcomes and follow-up

The primary outcome was the net clinical outcome (NCO), defined as the composite of recurrent stroke, any bleeding, hospitalization or emergency department (ED) visits for cardiovascular (CV) events, and death. The secondary outcomes were the individual components of the primary outcome. The outcomes were consecutively retrieved based on the medical records of the healthcare utilization at the study centre or individuals' self-report. The death records of the included patients were queried and retrieved from the National Statistical Information Service. The occurrence of the outcomes was followed up from the date of index stroke to 31 December 2021.

The risks of primary and secondary outcomes were compared according to the antithrombotics regimen at the first clinic following discharge: OAC alone vs. APT(s) alone vs. OAC/APT(s). The outcomes were also evaluated according to OAC monotherapy and the others: Group A (OAC alone) vs. Group B [APT(s) alone or OAC/APT(s)]. We defined the blanking period as the duration between the discharge date and the first clinic period to evaluate primary and secondary outcomes that occurred only after the first clinic visit. To evaluate the primary and secondary outcomes according to the antithrombotic drug regimen at the first clinic, we excluded patients lost to follow-up after discharge and those who were not prescribed any antithrombotic drugs to reduce the potential confounding effect of underlying medical conditions that precluded the use of antithrombotic medications.

Statistical analysis

Continuous variables are described as mean ± standard deviation or median (interquartile range), and categorical variables are presented as numbers (%). Student's *t*-test or Mann–Whitney test was performed to compare any differences in variables between study groups for continuous variables, and Pearson's χ^2 test or Fisher's exact test was applied for categorical variables as required. Clinical variables associated with an exclusive OAC use at the first clinic were evaluated by a multivariable logistic regression model and presented as odds ratio (OR) with 95% confidence intervals (CIs). The variables were chosen based on discrepancies in baseline clinical features between Group A and Group B while also taking into account their clinical significance. The risk of the primary and secondary outcomes according to the antithrombotic drug regimen at the first clinic was estimated using Cox proportional hazards regression models and reported as hazard ratios (HRs) with 95% CI. Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was adjusted by age, sex, hypertension, diabetes mellitus, stroke aetiology, and type of AF (paroxysmal AF vs. non-paroxysmal AF), of which are clinically important variables to be considered to decide antithrombotic drug regimen after stroke in AF. The cumulative risks of the primary and secondary outcomes stratified by the antithrombotics regimen at the first clinic were visualized by the Kaplan–Meier survival method with a log-rank test or the Breslow test.

Sensitivity and subgroup analyses

We performed sensitivity analysis on the risk of NCO according to antithrombotic drug regimen at the first clinic in two ways: (1) by adjusting all covariates that presented differences in the baseline characteristics between groups ($P < 0.01$) and (2) by excluding patients who admitted in COVID-19 era (from January 2020 to December 2020).

Subgroup analyses were performed stratified by sex (male vs. female), age (age < 75 years vs. ≥75 years), history of stroke (no vs. yes), aetiology of stroke (non-CE vs. CE), and simultaneous diagnosis of AF and stroke (no vs. yes) for the outcomes that demonstrated significant differences according to the antithrombotic drug regimen at the first clinic (Group A vs. Group B). All analyses were performed using Stata (version 17, StataCorp LLC, College Station, TX, USA). A value of two-sided $P < 0.05$ was considered statistically significant.

Results

Study population and baseline characteristics

We identified 1173 patients admitted for IS or TIA with a prior history of AF or simultaneous diagnosis of AF and had brain MRI for the initial assessment between January 2010 and December 2020. Among them, 215 patients were excluded due to their preliminary diagnosis of AF, which was confirmed later after the index admission period. We also excluded 40 patients who were ascertained to be admitted for non-stroke medical reasons, and diagnostic code of IS or TIA was registered based on the past medical history (seizure, $n = 8$; encephalopathy or peripheral neuropathy, $n = 5$; supportive care, $n = 4$; dizziness or headache, $n = 4$; and others, $n = 17$). Finally, 918 patients with index stroke events with confirmation of brain MRI and previous/simultaneous diagnosis of AF upon admission were included for the analysis of clinical characteristics of patients with AF and stroke. Among them, patients lost to follow-up after discharge ($n = 116$) and those who were not prescribed any antithrombotic drugs ($n = 18$) were excluded. Ultimately, 784 patients with AF and stroke were analysed for the evaluation of clinical outcomes according to antithrombotic drug regimen at the first clinic following discharge (*Figure 1*).

The baseline characteristics of the total population are described in *Table 1*. The mean age was 72.6 ± 10.0 years, and 59.3% ($n = 544$) were male. The most common comorbidities were hypertension (64.1%) and diabetes mellitus (28.3%). Approximately one-fifth (21.6%) of the participants had a prior history of stroke. The pre-stroke mean CHA_2DS_2-VASc score was 3.3 ± 1.7 and HAS-BLED score was 2.5 ± 1.1. The left atrium of the overall population was dilated with a mean anteroposterior diameter of 50.1 ± 8.6 mm.

Half of the included patients had paroxysmal AF (50.7%). Of total index stroke cases, 33.8% ($n = 310$) were simultaneously diagnosed with AF. The median time from AF diagnosis to index stroke was 110.0 (0.0–1036.0) days. With respect to the aetiology of stroke, the most frequent cause was CE (71.1%), followed by UD (19.8%; 58 of 182 patients are suspected to have both CE and LAA) and LAA (6.0%). On brain MRI, 38.4% ($n = 334$) of patients presented concurrent microbleeds or haemorrhagic transformation. The median duration of admission was 8.0 (5.0–16.0) days, and the median time from discharge to the first clinic visit was 20.0 (14.0–27.0) days.

Peri-stroke prescription pattern of antithrombotics

The prescription pattern of antithrombotic drugs at four distinct time points is summarized in *Figure 2*. Prior to the occurrence of the index

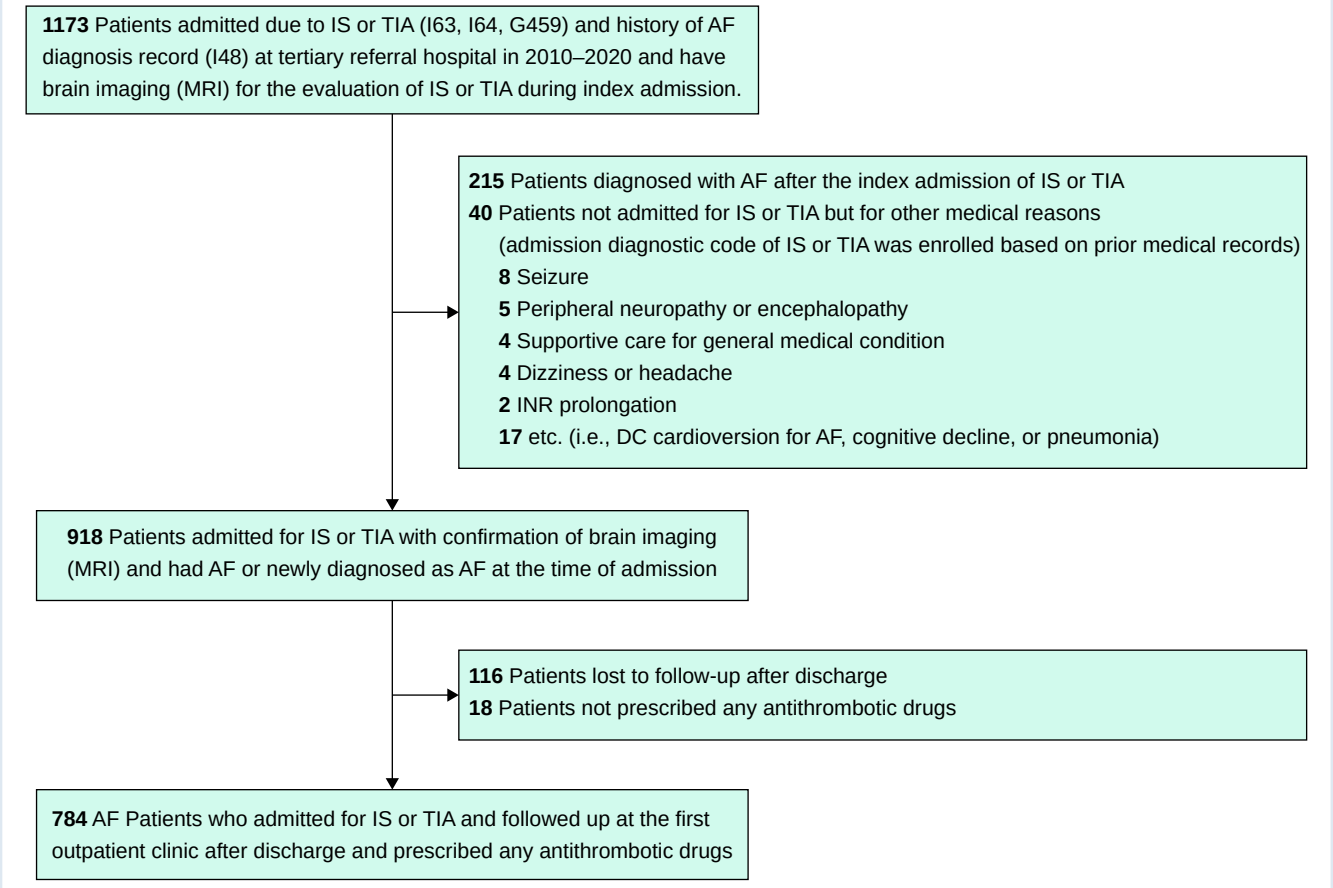


Figure 1 Inclusion of study population. AF, atrial fibrillation; DC, direct current; IS, ischaemic stroke; MRI, magnetic resonance imaging; TIA, transient ischaemic attack.

stroke event, 41.1% of the patients were not utilizing OAC or APT. Nearly half of the patients were on either OAC alone or APT(s) alone [OAC alone, 24.2%; APT(s) alone, 30.2%]. Those who are on both OAC and APT(s) were 4.6%.

During the admission period of index stroke, 97.9% of the patients received a prescription for either OAC or APT(s). Among these, 53.4% of patients for both OAC and APT(s), while 33.4% were prescribed OAC exclusively. With regard to the change of prescription pattern during admission, 59.5% ($n = 546$) patients newly initiated OAC, whereas 19.6% ($n = 180$) continued previous OAC regimen and 7.7% ($n = 71$) switched to the other type of OAC from that used before the index stroke (see Supplementary material online, *Table S1*). For APT, 38.7% ($n = 355$) of patients newly initiated APT during admission and 12.9% of patients maintained prior APT regimen.

At the first clinic visit after discharge, 87.4% ($n = 802$) of the patients' data were available. Among these, 88.7% ($n = 711$) patients were prescribed OAC, and 30.8% ($n = 247$) were taking APT(s); and 21.7% ($n = 174$) patients were on both OAC and APT(s). The majority of the patients (80.0%) continued OAC prescribed during admission, and approximately one-third (28.8%) discontinued APT, which was prescribed during admission (see Supplementary material online, *Table S1*).

One year after the index stroke, data for 69.9% ($n = 642$) of the total population were accessible. The distribution of the antithrombotics regimen was similar to that of the first clinic after discharge; 68.8% maintained OAC alone, 20.7% used both OAC and APT(s), and 7.6% are prescribed APT(s) alone.

OAC monotherapy at the first clinic and the related clinical factors

Overall, among the patients with available antithrombotics data at the first clinic, 537 (68.5%) patients were taking OAC alone regimen, 73 (9.3%) were on APT(s) alone, and 174 (22.2%) were on OAC/APT(s) (OAC with single APT, $n = 165$; OAC with dual APTs, $n = 9$). The comparison of baseline characteristics among patients with OAC alone vs. APT(s) alone vs. OAC/APT(s) at the first clinic following discharge is described in *Table 1*. The comparison between Groups A and B is described in Supplementary material online, *Table S2*. Patients with OAC alone had the largest mean left atrial diameter (49.9 ± 7.8 mm, $P = 0.002$) and the greatest proportion of simultaneous diagnosis of AF and stroke (38.2%, $P = 0.020$). CE was the major aetiology of stroke in patients with OAC alone (82.5%) with a significantly higher proportion than APT(s) alone (42.5%) and OAC/APT(s) (50.6%) group ($P < 0.001$). Meanwhile, patients with APT(s) alone were the oldest (75.2 ± 10.8 years, $P = 0.002$) with the highest CHA_2DS_2-VASc score (3.7 ± 1.7, $P < 0.001$) and HAS-BLED score (2.8 ± 1.0, $P = 0.004$). Those with OAC/APT(s) combination therapy had the highest proportion of vascular disease (36.8%, $P < 0.001$) among the groups.

On multivariable logistic regression model (*Table 2*), clinical factors associated with the prescription of OAC alone were larger left atrial size [OR (95% CI), 1.026 (1.002–1.051); $P < 0.001$], simultaneous diagnosis of AF and the index stroke [OR (95% CI), 1.631 (1.115–2.386); $P = 0.012$], and CE as an aetiology of stroke [OR (95% CI),

Table 1 Baseline characteristics of the study population

	Total	Antithrombotic drug regimen at the first clinic visit after discharge from the index admission[a]			*P*-value
	N = 918	OAC alone[b] *N* = 537 (67.0%)	APT(s) alone[c] *N* = 73 (9.3%)	OAC/APT(s)[d] *N* = 174 (22.2%)	
Age	72.6 ± 10.0	71.3 ± 9.9	75.2 ± 10.8	72.9 ± 8.6	0.002
Male	544 (59.3%)	321 (59.8%)	44 (60.3%)	110 (63.2%)	0.715
Body mass index (kg/m^2)	24.0 ± 3.3	24.0 ± 3.3	23.2 ± 3.2	24.6 ± 3.4	0.012
Comorbidities					
Hypertension	588 (64.1%)	333 (62.0%)	52 (71.2%)	117 (67.2%)	0.191
Diabetes mellitus	260 (28.3%)	137 (25.5%)	23 (31.5%)	57 (32.8%)	0.132
Congestive heart failure	78 (8.5%)	46 (8.6%)	7 (9.6%)	16 (9.2%)	0.940
Stroke/TIA/TE	198 (21.6%)	106 (19.7%)	14 (19.2%)	36 (20.7%)	0.952
Vascular disease	162 (17.6%)	62 (11.5%)	24 (32.9%)	64 (36.8%)	<0.001
Ischaemic heart disease	135 (14.7%)	54 (10.1%)	21 (28.8%)	52 (29.9%)	
Peripheral artery disease, aortic plaque	18 (2.0%)	7 (1.3%)	1 (1.4%)	7 (4.0%)	
Both	9 (1.0%)	1 (0.2%)	2 (2.7%)	5 (2.9%)	
Dyslipidaemia	188 (20.5%)	108 (20.1%)	16 (21.9%)	46 (26.4%)	0.207
Valvular heart disease	120 (13.1%)	68 (12.7%)	3 (4.1%)	26 (14.9%)	0.502
CHA_2DS_2-VASc score	3.3 ± 1.7	3.1 ± 1.6	3.7 ± 1.7	3.6 ± 1.7	<0.001
HAS-BLED score	2.5 ± 1.1	2.4 ± 1.1	2.8 ± 1.0	2.6 ± 1.1	0.004
Smoking					0.410
Never smoker	584 (63.6%)	327 (60.9%)	46 (63.0%)	111 (63.8%)	
Ex-smoker	242 (26.4%)	146 (27.2%)	21 (28.8%)	51 (29.3%)	
Current smoker	91 (9.9%)	64 (11.9%)	6 (8.2%)	12 (6.9%)	
Current drinking	282 (30.8%)	178 (33.1%)	19 (26.0%)	56 (32.2%)	0.472
Medications					
ACEi/ARB	241 (26.3%)	135 (25.1%)	25 (34.2%)	48 (27.6%)	0.244
Beta blockers	267 (29.1%)	148 (27.6%)	29 (39.7%)	55 (31.6%)	0.082
Calcium channel blockers	179 (19.5%)	98 (18.2%)	19 (26.0%)	35 (20.1%)	0.276
Diuretics	121 (13.2%)	66 (12.3%)	9 (12.3%)	19 (10.9%)	0.885
Statin	215 (23.5%)	111 (20.7%)	18 (24.7%)	56 (32.2%)	0.008
Laboratory values					
White blood cell (10^3/μL)	7.9 ± 2.9	7.8 ± 2.6	7.7 ± 2.7	7.8 ± 2.8	0.951
Haemoglobin (g/dL)	13.4 ± 2.1	13.6 ± 2.0	13.4 ± 2.0	13.6 ± 1.9	0.691
Haematocrit (%)	40.2 ± 5.6	40.6 ± 5.4	39.9 ± 5.4	40.6 ± 5.5	0.532
BUN (mg/dL)	18.6 ± 9.2	18.1 ± 8.6	20.8 ± 10.0	17.8 ± 7.4	0.029
Creatinine (mg/dL)	1.1 ± 0.9	1.1 ± 0.7	1.4 ± 1.8	1.1 ± 0.7	0.015
eGFR (mL/min/1.73 m2)	71.4 ± 24.0	73.0 ± 23.4	67.7 ± 26.5	70.8 ± 23.6	0.177
Total cholesterol (mg/dL)	159.9 ± 38.4	159.9 ± 36.5	165.0 ± 31.5	159.3 ± 40.1	0.531
Triglyceride (mg/dL)	95.6 ± 44.5	95.7 ± 44.3	97.4 ± 35.9	102.0 ± 48.9	0.311
HDL-cholesterol (mg/dL)	47.9 ± 13.8	48.0 ± 14.0	47.8 ± 13.0	48.0 ± 13.4	0.990
LDL-cholesterol (mg/dL)	97.1 ± 33.5	97.3 ± 31.2	99.6 ± 29.3	96.2 ± 37.0	0.763
Echocardiographic parameters					
LVEF (%)	57.5 ± 8.8	58.0 ± 8.2	58.2 ± 9.1	56.7 ± 9.9	0.212
LAD (mm)	50.1 ± 8.6	49.9 ± 7.8	46.4 ± 7.4	49.6 ± 6.6	0.002
E/E′	15.8 ± 13.5	15.9 ± 15.7	15.8 ± 14.3	14.4 ± 6.9	0.509

Continued

Table 1 *Continued*

	Total	Antithrombotic drug regimen at the first clinic visit after discharge from the index admission[a]			*P*-value
	N = 918	OAC alone[b] *N* = 537 (67.0%)	APT(s) alone[c] *N* = 73 (9.3%)	OAC/APT(s)[d] *N* = 174 (22.2%)	
AF information					
Type					0.255
Paroxysmal AF	465 (50.7%)	290 (54.0%)	46 (63.0%)	89 (51.1%)	
Non-paroxysmal AF	403 (43.9%)	231 (43.0%)	24 (32.8%)	82 (47.1%)	
Family history of AF	9 (1.0%)	6 (1.1%)	0 (0.0%)	2 (1.1%)	0.656
CIED	40 (4.5%)	25 (4.7%)	2 (2.7%)	6 (3.4%)	0.638
Stroke information					
Simultaneous diagnosis of AF and stroke	310 (33.8%)	205 (38.2%)	21 (28.8%)	48 (27.6%)	0.020
Time from AF diagnosis to incident stroke (days)	110.0 (0.0–1036.0)	27.5 (0.0–831.0)	360.0 (0.0–1043.0)	367.0 (0.0–1326.0)	0.083
Aetiology of stroke (TOAST classification)					<0.001
LAA	55 (6.0%)	6 (1.1%)	17 (23.3%)	27 (15.5%)	
CE	653 (71.1%)	443 (82.5%)	31 (42.5%)	88 (50.6%)	
SVO	23 (2.5%)	5 (0.9%)	3 (4.1%)	13 (7.5%)	
OD	5 (0.5%)	1 (0.2%)	0 (0.0%)	2 (1.1%)	
UD	182 (19.8%)	82 (15.3%)	22 (30.1%)	44 (25.3%)	
Microbleeds or haemorrhagic transformation on brain MRI	334 (38.4%)	192 (37.6%)	26 (35.6%)	69 (39.7%)	0.574
Duration of admission (days)	8.0 (5.0–16.0)	13.9 ± 20.1	10.9 ± 10.1	12.5 ± 14.5	0.341
Time from discharge to the first visit (days)	20.0 (14.0–27.0)	20.0 (13.0–27.0)	22.0 (17.0–27.0)	20.0 (14.0–27.0)	0.859

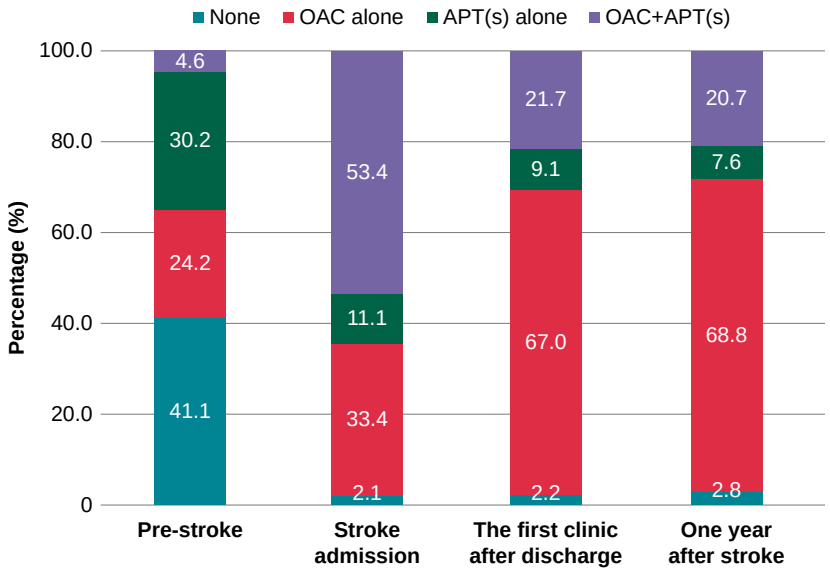
Percentages may not total 100.0 because of rounding.
ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; APT, antiplatelet; ARB, angiotensin II receptor blockers; BUN, blood urea nitrogen; CE, cardioembolism; CIED, cardiac implantable electronic device; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LAA, large artery atherosclerosis; LAD, left atrial diameter; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; OAC, oral anticoagulant; OD, other determined aetiology; SVO, small-vessel occlusion; TE, thromboembolism; TIA, transient ischaemic attack; UD, undetermined aetiology.
[a]Patients who have available data at the first clinic visit following discharge from the index admission. Those who were not prescribed any antithrombotics at the first clinic were excluded to reduce the potential confounding effect of underlying medical conditions that precluded the use of antithrombotic medications. The sum is not equal to the number of total population due to the exclusion of patients not prescribed antithrombotics and those lost to follow-up.
[b]Warfarin, *n* = 248 (46.2%); apixaban, *n* = 129 (24.0%); dabigatran, *n* = 63 (11.7%); rivaroxaban, *n* = 67 (12.5%); edoxaban, *n* = 30 (5.6%).
[c]Aspirin, *n* = 20 (27.4%); clopidogrel, *n* = 9 (12.3%); others, *n* = 6 (8.2%); dual APTs, *n* = 38 (52.1%).
[d][Warfarin, *n* = 89 (51.2%); apixaban, *n* = 40 (23.0%); dabigatran, *n* = 21 (12.1%); rivaroxaban, *n* = 15 (8.6%); edoxaban, *n* = 9 (5.2%)], [aspirin, *n* = 105 (60.3%); clopidogrel, *n* = 44 (25.3%); others, *n* = 16 (9.2%); dual APTs, *n* = 9 (5.2%)].

4.249 (2.954–6.111); $P < 0.001$]. Patients with pre-existing vascular disease were less likely to receive OAC alone; they were more commonly prescribed either exclusive APT(s) or a combination of APT alongside OAC [OR (95% CI), 0.238 (0.152–0.373); $P < 0.001$].

Primary and secondary outcomes

Among those with available prescription information at the first clinic following discharge from the index stroke ($n = 784$), there were 490 events of NCO, 98 events of recurrent stroke, 127 events of any bleeding, 314 events of hospitalization or ED visits for CV events, and 264 deaths during a median follow-up of 2.1 (0.7–4.9) years. The overall incidence rate per 100 patient-year (PY) was 20.1 for NCO; 3.4 for recurrent stroke; 4.6 for any bleeding; 14.0 for hospitalization or ED visits for CV events; and 6.9 for death.

The cumulative risk of the primary outcome, NCO, according to the antithrombotic therapy regimen at the first clinic after discharge from the index stroke [OAC alone vs. APT(s) alone vs. OAC/APT(s)] are presented in *Figure 3* and Supplementary material online, *Table S3*. At 7.0 years from the occurrence of index stroke, compared to OAC alone, APT(s) alone showed a significantly higher risk of NCO (adjusted HR 1.471, 95% CI 1.079–2.004, $P = 0.015$). The combination of OAC and APT(s) showed comparable risk of NCO with OAC alone (adjusted HR 1.155, 95% CI 0.927–1.440, $P = 0.198$). When comparing between Group A and Group B, the risk of NCO in Group B was significantly higher than in Group A: adjusted HR (95% CI), 1.234 (1.014–1.500), $P = 0.036$ [i.e. adjusted HR of Group A compared to Group B was 0.811 (0.666–0.986)] (see Supplementary material online, *Table S4* and Supplementary material online, *Figure S1*).



	n = 918	*n* = 918	*n* = 802	*n* = 642
OAC+APT(s)	42 (4.6%)	490 (53.4%)	174 (21.7%)	133 (20.7%)
APT(s) alone	277 (30.2%)	102 (11.1%)	73 (9.1%)	49 (7.6%)
OAC alone	222 (24.2%)	307 (33.4%)	537 (67.0%)	442 (68.8%)
None	377 (41.1%)	19 (2.1%)	18 (2.2%)	18 (2.8%)

Figure 2 Peri-stroke prescription pattern of antithrombotics. OAC, oral anticoagulant; APT, antiplatelet. Percentages may not total 100.0 because of rounding.

For secondary outcomes, OAC/APT(s) combination therapy was associated with a higher risk of recurrent stroke (adjusted HR 1.620, 95% CI 1.021–2.569, $P = 0.040$) and marginally higher risk of any bleeding (adjusted HR 1.491, 95% CI 0.989–2.250, $P = 0.057$) than OAC alone (*Figure 4* and Supplementary material online, *Table S3*). Comparisons of Groups A and B are presented in Supplementary material online, *Table S4* and Supplementary material online, *Figure S1*. Group B has a 1.667-hold higher risk of recurrent stroke and 1.499-fold higher risk of any bleeding than Group A (both $P < 0.05$). Group B also presented a marginally higher risk of hospitalization or ED visits for CV events and all-cause death.

Sensitivity analyses

The lowest risk of NCO in patients with OAC alone was maintained after adjusting all covariates selected based on the inter-group differences ($P < 0.05$) (see Supplementary material online, *Table S5*) and excluding patients who were admitted in the COVID-19 era (see Supplementary material online, *Table S6*).

Subgroup analyses

Subgroup analyses were performed for the outcomes presenting significant differences (NCO, recurrent stroke, and any bleeding) according to the antithrombotic therapy regimen prescribed at the first clinic (Group A vs. Group B). For NCO, male patients of Group B presented a more accentuated higher risk than females (*P*-for-interaction = 0.039) (see Supplementary material online, *Figure S2A*). The higher risk of recurrent stroke and any bleeding in Group B than in Group A was also consistent across the subgroups (see Supplementary material online, *Figure S2B* and *C*). Although there were no significant interactions, patients of male, age under 75 years, with a prior history of stroke, with CE as a stroke aetiology, and simultaneous diagnosis of AF and stroke presented numerically higher risk increment of recurrent stroke in Group B than Group A.

Discussion

In this retrospective cohort of patients with AF who were admitted for an acute IS, our major findings can be summarized as follows: (1) among total, 33.8% of patients were concurrently diagnosed with AF and IS; (2) 71.1% of IS was CE, while remained 28.9% of IS was non-CE; (3) nearly two-thirds of patients with AF continued OAC monotherapy and one-third utilized antithrombotic therapy including APT, either APT(s) alone or combination of OAC and APT(s) for secondary prevention after index stroke; and (4) compared to OAC monotherapy, patients with APT(s) monotherapy from the early post-stroke period presented a 47% higher risk of NCO, and patients with OAC/APT(s) combination therapy was related to 62% significantly higher risk of recurrent stroke and marginally higher risk of any bleeding than OAC monotherapy by 49%.

Our study provides detailed clinical features of patients with prevalent or newly diagnosed AF who experienced acute IS and suggests an opportunity to assess community practice on antithrombotic strategies for secondary stroke prevention in AF. The 18.9% lower risk of NCO in the OAC monotherapy group than the others reverberates the importance of guideline-adherent antithrombotic therapy irrespective of comorbidities or the aetiology of index stroke.[15,17]

Our cohort of patients with AF and IS includes in-depth descriptions of clinical situations. An intriguing observation is that approximately

Table 2 Clinical factors associated with the exclusive oral anticoagulation use at the first clinic

Clinical factors	Univariable		Multivariable	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age[a]	0.778 (0.662–0.916)	0.003	0.830 (0.657–1.048)	0.118
Hypertension	0.753 (0.547–1.037)	0.083	0.856 (0.562–1.304)	0.469
Diabetes mellitus	0.715 (0.514–0.994)	0.046	0.771 (0.499–1.190)	0.240
Vascular disease	0.236 (0.163–0.342)	<0.001	0.238 (0.152–0.373)	<0.001
CHA_2DS_2-VASc score	0.827 (0.754–0.906)	<0.001	1.083 (0.916–1.280)	0.353
LAD	1.021 (1.000–1.042)	0.045	1.026 (1.002–1.051)	0.035
Simultaneous diagnosis of AF and stroke	1.593 (1.147–2.211)	0.005	1.631 (1.115–2.386)	0.012
CE as an aetiology of stroke	5.069 (3.628–7.082)	<0.001	4.249 (2.954–6.111)	<0.001

AF, atrial fibrillation; CE, cardioembolism; CI, confidence interval; LAD, left atrial diameter; OR, odds ratio.
[a]For 10-year increase.

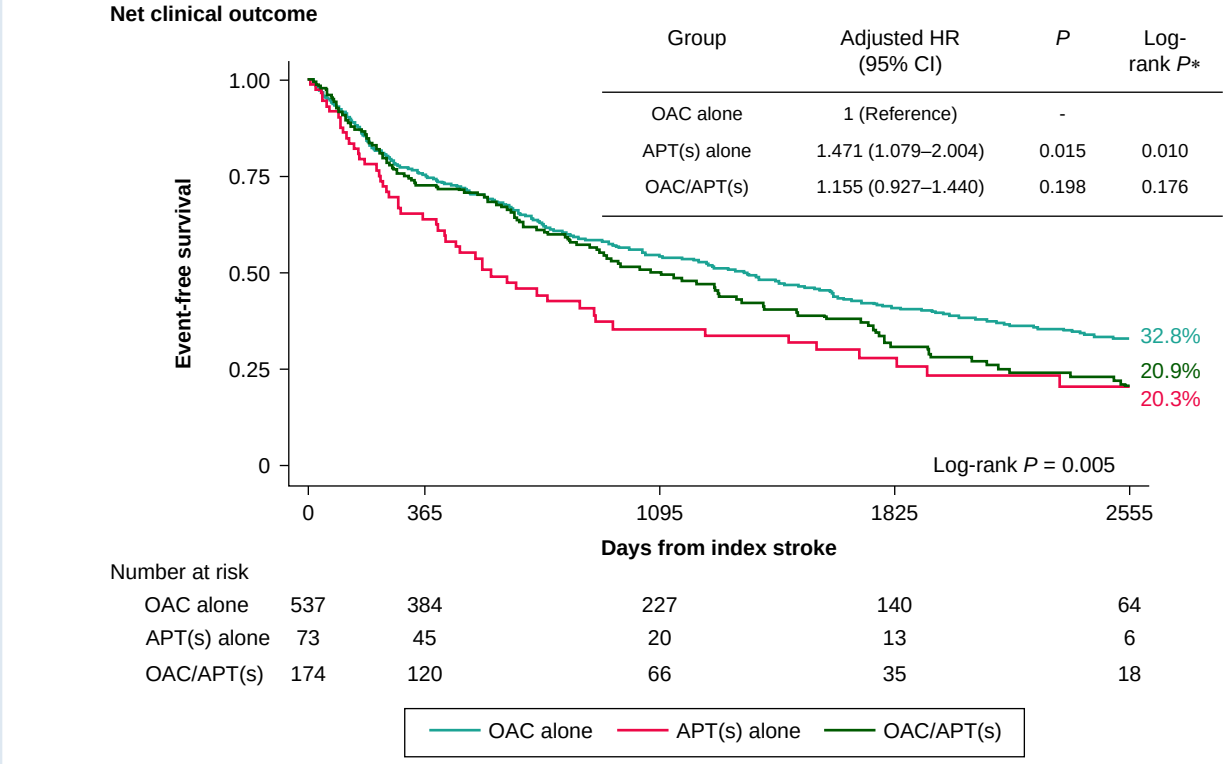


Figure 3 Cumulative risks of net clinical outcome in atrial fibrillation after discharge from the index stroke stratified by antithrombotics therapy at the first clinic visit. HR, hazard ratio; OAC, oral anticoagulant; APT, antiplatelet. Hazard ratios were adjusted by age, sex, hypertension, diabetes mellitus, stroke aetiology, and type of AF (paroxysmal AF vs. non-paroxysmal AF). *Bonferroni's corrected *P*-values.

one-third of patients with AF who were admitted for IS were newly diagnosed with AF during the hospitalization for stroke. In accordance with previous reports of hospital-based and nationwide cohort data that 18.0–29.0% of patients with AF-related stroke occurred without a pre-stroke AF diagnosis,[10,18,19] such a sizable portion would suggest the potential advantage of AF screening, which could be coupled with OAC prescription thereby stroke prevention. Moreover, we noted that a considerable proportion of strokes have non-CE aetiology even in patients with AF, and this is consistent with the prior report that non-atrial aetiology has been estimated at 40.0% of strokes in AF.[20–23] Although it remains speculative and lacks a reliably established method to determine stroke mechanism,[21] the significant prevalence of non-CE stroke in AF indicates that the risk of stroke in AF cannot be fully explained by atrial myopathy and rhythm disturbance associated

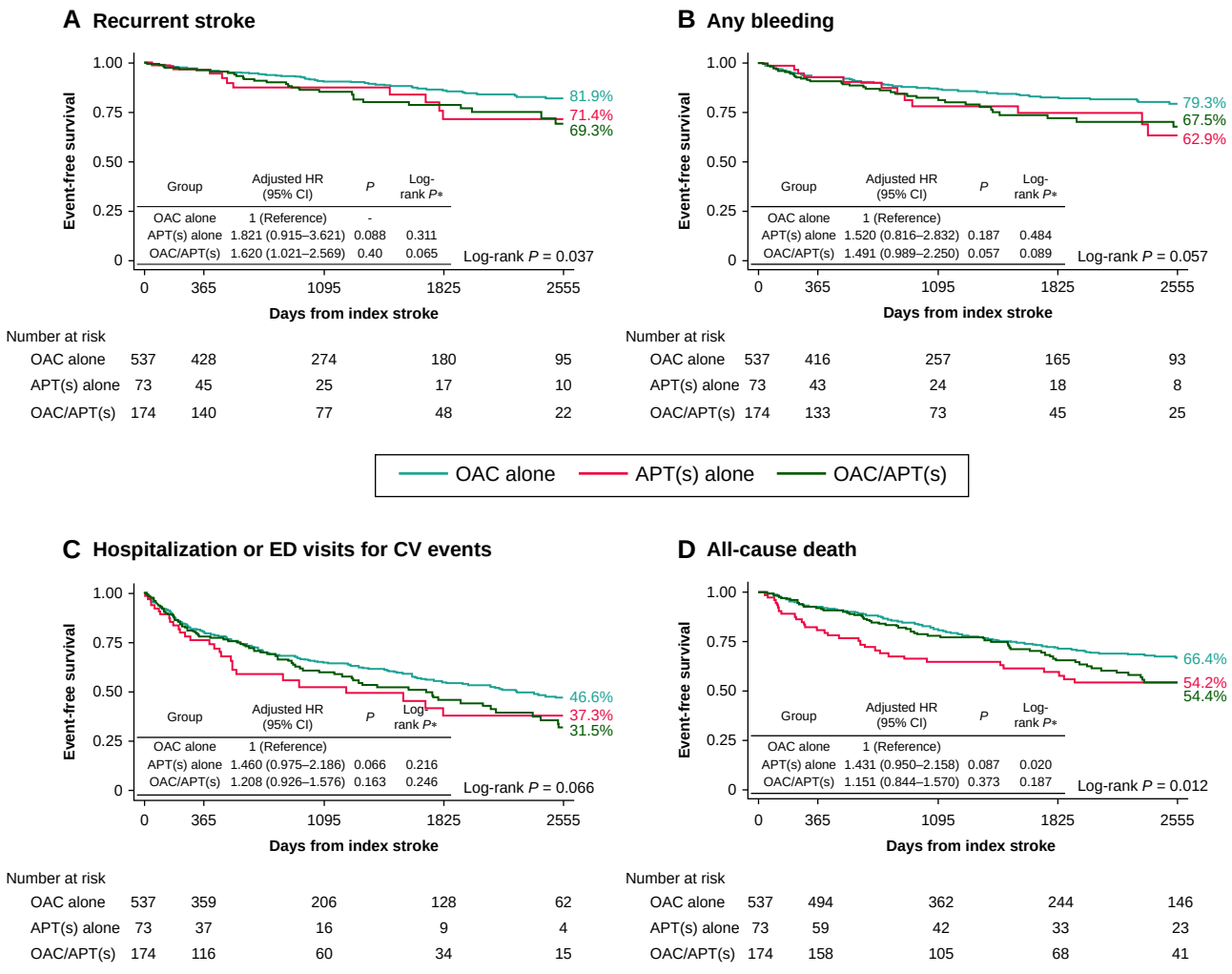


Figure 4 Cumulative risks of (*A*) recurrent stroke, (*B*) any bleeding, (*C*) hospitalization or emergency department visits for cardiovascular events, and (*D*) death in atrial fibrillation after discharge from the index stroke stratified by antithrombotics at the first clinic visit. HR, hazard ratio; OAC, oral anticoagulant; APT, antiplatelet. Hazard ratios were adjusted by age, sex, hypertension, diabetes mellitus, stroke aetiology, and type of AF (paroxysmal AF vs. non-paroxysmal AF). *Bonferroni's corrected *P*-values.

with AF.[24] This suggests that stroke risks in AF could be mitigated with alternative antithrombotic therapies based on stroke subtypes, creating opportunities for varying antithrombotic options to be considered by both neurologists and cardiologists.

Using the contemporary hospital-based data, we demonstrated the temporal prescription pattern of antithrombotic drugs in patients with AF and stroke. The antithrombotic drugs at the first clinic visit following discharge from stroke admission were likely to be continued up to one year after the index stroke. The associated clinical factors related to OAC monotherapy were a larger left atrium, simultaneous diagnosis of AF and stroke, and an identified stroke aetiology concluded as CE, which indicates a stronger causal link between AF and stroke.[18] The presence of vascular disease was related to less use of OAC monotherapy, namely, additive APT use or APT monotherapy, which aligns with the current preference for APT use in patients with multiple vascular risk factors such as coronary artery disease.[10,25,26]

In addition, we noted that an appreciable portion of patients (11.3%) were not prescribed OAC, despite OAC being a standard of care to prevent stroke in patients with AF.[6,15,27] The underuse of OAC in patients with AF has also been documented in both Europe and the USA.[28–30] Also, a retrospective Danish cohort reported that 37.5% of patients with AF and stroke did not receive OAC following stroke.[31] Non-prescription of OAC on discharge from stroke in patients with AF, which is contrary to the guideline, has also been reported in a Canadian prospective cohort study.[32] Our data echo the under-utilization of OACs in community practice, indicating the necessity to improve physician adherence to clinical guidelines. At the same time, it also indicates that guidelines may not fully address all clinical ambiguities and uncertainties involved in determining the optimal antithrombotic treatment in patients with AF and stroke, consequently leading to an area to decide OAC usage on physicians' own discretion.

Several studies examined the association between post-stroke antithrombotic drugs and long-term clinical outcomes.[31–33] Not only the recurrent stroke risk, we investigated any recorded bleeding event, hospitalization or ED visits for CV events, and all-cause death. The composite of defined events, NCO, was 18.1% lower in the OAC monotherapy group, which was primarily driven by a significantly lower risk of recurrent stroke and marginally lower risks of any bleeding and

hospitalization or ED visits for CV events. Similar findings have been supported by prior studies of Danish nationwide registries; post-stroke OAC therapy (with or without APT) was related to 19% lower risk of recurrent thromboembolic events without significant difference in bleeding complications than no antithrombotic therapy.[31] Korean-linked data of patients with IS due to AF and LAA concluded that OAC monotherapy is associated with lower risks of composite outcome (recurrent IS, intracranial haemorrhage, myocardial infarction, and all-cause death) than APT(s) monotherapy or OAC/APT(s) combination regimes.[33] Although the included patients and comparative groupings of antithrombotic therapy is slightly different among studies, it is consistently demonstrated that a combination of OAC and APT(s) is associated with a higher risk of bleeding complications and has limited evidence to support risk reductions in composite clinical outcomes.[7,34–37]

In our analysis of distinct antithrombotic drug groups, we noted that the lower risks of primary and secondary outcomes in OAC monotherapy group [i.e. higher risks in APT(s) mono- or combination group] were mainly attributed to higher occurrence of outcomes in APT(s) monotherapy group. It can be interpreted that OAC, whether prescribed as standalone treatment or in combination with APT(s), has an essential role in secondary prevention in patients with AF and IS. Interestingly, we should appreciate that OAC/APT(s) combination therapy presents a higher risk of recurrent stroke than OAC monotherapy, which might originate from the comorbidities necessitating concurrent APT(s) therapy, also accompanies a higher tendency of any bleeding requiring appropriate patient selection to decide combination therapy.

On the other hand, the comparison of overall clinical benefits between OAC monotherapy and OAC/APT(s) combination therapy seems inconclusive as evidenced by the accompanying event survival curves. The ADD-ON (ClinicalTrials.gov ID: NCT04010955) is an ongoing multicentre registry-based study investigating the effectiveness and safety of additional APT to edoxaban in patients with AF-acute IS and significant atherosclerosis. The additive role of APT to standalone OAC therapy in patients with AF and IS has been specified in cases of comorbid atherosclerosis,[32,33] which emphasizes the necessity of tailored antithrombotic therapy strategy in patients with AF and acute IS.

Our subgroup analysis results—the lower risk of NCO, recurrent stroke, and any bleeding in the OAC monotherapy group irrespective of stroke aetiology—is in line with the current guideline that the combination of APT(s) and anticoagulation is typically not indicated for secondary stroke prevention with very few exceptions.[1,3] Nonetheless, as the benefit of lower risk in NCO, recurrent stroke, and any bleeding was numerically greater in AF with stroke of CE aetiology, it is still important to define stroke subtype whenever possible and identify individualized treatment target as emphasized in guidelines.[3,38–40]

Limitations

Our study has several limitations. First, we might underdetect the AF-IS patients during the identification of the study population using ICD-10 codes as it is established for administrative databases rather than research purposes, thus may not accurately represent the final diagnosis. Also, there might be a selection bias in the study population as the analysis was performed from a retrospective observational cohort of a single tertiary referral centre. The peri-stroke and long-term maintenance antithrombotic drug regimen in patients with AF would require representativeness through further multicentre cohort investigation. Secondly, the subsequent decrement of evaluable patients, potential change in the antithrombotic drug regimen during follow-up, and lack of information on the compliance of antithrombotic drugs might all introduce bias in the association between the antithrombotics regimen and the clinical outcomes. Thirdly, unmeasured confounding may remain, and a causal relationship between antithrombotic drugs at the first clinic and clinical outcomes cannot be answered. Nonetheless, our study demonstrates the practical implication of antithrombotic drugs for secondary stroke prevention in AF by providing detailed clinical scenarios, which are only accessible by a thorough examination of clinical practices.

Conclusion

Among patients with AF who were admitted for the care of acute IS, approximately one-third of the stroke aetiology was non-CE. Although the majority was taking OAC monotherapy, nearly 30.0% of patients were prescribed either APT(s) monotherapy or the combination of OAC and APT(s). As OAC monotherapy presents a lower risk of NCO than APT(s) monotherapy or the combination of OAC and APT(s), primarily driven by the significantly decreased risk of recurrent stroke and any bleeding, it is essential to promote good adherence to OAC and carefully assess the need for the additional APT(s) in patients with AF and IS.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

All data generated or analysed during this study are included in this published article and its supplemental information files. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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