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Secondary prevention with antiplatelet medications in patients with antiphospholipid antibody-related stroke

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Clinical guidelines recommend warfarin for patients with antiphospholipid syndrome (APS) and ischemic stroke; however, robust evidence is lacking. We investigated the clinical benefits of different categories of antithrombotic medications in ischemic stroke patients positive for antiphospholipid antibodies (aPLs) in real-world practice. We reviewed data from patients with ischemic stroke or transient ischemic attack who tested positive for aPLs. Based on their secondary preventive antithrombotic medications, patients were classified into antiplatelet and anticoagulant categories, and further into warfarin, single antiplatelet therapy (SAPT), dual antiplatelet therapy (DAPT), and direct oral anticoagulant groups. The outcome of interest was a composite of recurrent thrombosis and major bleeding events. Time-varying Cox proportional hazards model was used. Among 167 eligible patients, 28 experienced composite outcome events over 601.1 person-years. SAPT and DAPT demonstrated clinical benefits over warfarin (SAPT vs. warfarin, adjusted hazard ratio [95% confidence intervals], 0.24 [0.07–0.83]; DAPT vs. warfarin, 0.25 [0.08–0.81]). Notably, DAPT was advantageous regarding major bleeding (DAPT vs. warfarin, 0.10 [0.02–0.47]), while the risk of recurrent thrombotic events was comparable between the antiplatelet and warfarin groups. Antiplatelet therapy may be a safe and effective alternative to warfarin for secondary prevention of aPL- and APS-related stroke. Further prospective validation is required.

Keywords Antiphospholipid syndrome, Hemorrhage, Ischemic stroke, Secondary prevention, Thrombosis

Despite being one of the most common clinical presentations of antiphospholipid syndrome (APS)[1–3], little information is available regarding the optimal treatment strategy for ischemic stroke associated with antiphospholipid antibodies (aPLs) and APS. The latest stroke guidelines suggest prioritizing warfarin over low-dose aspirin for patients with ischemic stroke/transient ischemic attack (TIA) and APS[4]. Moreover, the failure of recent trials to evaluate the benefit of direct oral anticoagulants (DOACs), with warfarin designated as the standard control[5,6], has unintentionally reinforced the preference for warfarin for APS-related thrombosis. Nevertheless, it is important to note that the guideline recommendations for warfarin are based solely on a single small-scale randomized study[7], resulting in a low level of evidence supporting its validity. Other clinical guidelines for APS also mention warfarin as the standard treatment for patients with arterial thrombosis and APS[8–11]; however, these predominantly rely on outdated retrospective studies from the 1990s and expert opinions[12–15]. Conversely, studies have indicated that antiplatelet medications may exhibit similar or even superior effectiveness and safety compared to warfarin in patients with aPL- or APS-related stroke[16,17]. Thus, it is inappropriate to claim the superiority of warfarin over antiplatelet medications in APS-related stroke owing to the absence of conclusive evidence.

Warfarin is burdened with drawbacks, including a higher bleeding risk, interactions with drugs and food, and the need for regular blood sampling. Furthermore, unlike controlled clinical trial settings, real-world patients are

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prone to having a lower time in the therapeutic range for warfarin[18], which heightens the risks of thrombosis and bleeding. Given these circumstances, stroke physicians may be apprehensive about the prescription of lifelong warfarin for patients with APS-related stroke considering their young age and low stroke burden[19]. If alternative medications that provided similar clinical benefits were available, physicians would prefer them over warfarin. Therefore, to enhance clinical guidelines and address physicians' concerns, it is imperative to conduct high-quality prospective studies comparing warfarin and antiplatelet medications. The present study was designed to offer rationale and basic data ahead of implementing a prospective study on this topic. We aimed to compare the net clinical benefits, indicated by a composite outcome encompassing both recurrent thrombotic and major bleeding events, of secondary preventive antithrombotic medications in patients with aPL-related stroke.

Methods

Study population

Between February 2013 and June 2022, consecutive Korean patients with a history of ischemic stroke or TIA who tested positive for aPLs on one or more occasions at the Department of Neurology, Seoul National University Hospital (SNUH), were reviewed for eligibility. Patients with atrial fibrillation, active cancer, or those lost to follow-up for clinical events were excluded. Additionally, we excluded those who were not adequately followed up for aPL. Active cancer encompassed patients with cancer who were either currently undergoing treatment, had received treatment within the past six months, or were in a palliative care state. Patients who were prescribed low-molecular-weight heparin or no antithrombotic medication were also excluded because of the small number of patients. This study adhered to the principles outlined in the Declaration of Helsinki. The Institutional Review Board of the Seoul National University Hospital (IRB No. H-2304-059-1421) approved this study. The need for informed consent was waived owing to the retrospective nature of the study.

Data collection

Information on age, sex, hypertension, diabetes, hyperlipidemia, smoking, and history of arterial and venous thrombosis was collected from all patients at baseline. Testing for lupus anticoagulant (LA) was performed using an ACL TOP 750 analyzer (Instrumental Laboratory, Bedford, MA, USA), through a three-step procedure (screening, mixing, and confirmatory tests), employing diluted Russel viper venom and silica clotting time tests. Local cut-off values, based on healthy volunteer data, were used[20]. The HemosIL AcuStar testing system (Instrumentation Laboratory, Bedford, MA, USA) was used to conduct tests for anti-cardiolipin antibodies (aCL) and anti-β2-glycoprotein I antibodies (aβ2GPI). Positive results for lupus anticoagulant were determined by normalized screen-to-confirmatory ratios exceeding 1.21 for diluted Russel Viper venom time or 1.26 for silica clotting time. As per the manufacturer's instructions, the cutoff values for aCL and aβ2GPI IgG/IgM were set at 20 U/mL[21,22], which was above the upper 99th percentile value of the test results obtained from local healthy volunteers at the SNUH[23]. Additional details of the aPL assay have been described previously[24]. Data regarding aPLs were obtained, including test results for each aPL component, aCL/aβ2GPI titers, aPL positivity (single, double, or triple positivity), thrombotic risk profile of aPL (high-risk: positive for LA and/or ≥ 40 U/mL of aCL or aβ2GPI; moderate-risk: negative for LA and ≥ 40 U/mL of aCL or aβ2GPI; and low-risk: negative for LA and 20–40 U/mL of aCL or aβ2GPI)[25], and diagnosis of APS based on the Sydney criteria[26]. Prescription information for secondary preventive antithrombotic medications for stroke was collected for each patient throughout the follow-up period. Based on their secondary preventive antithrombotic medications, patients were classified into four-category and two-category classifications. The four-category classification included warfarin, single antiplatelet therapy (SAPT), dual antiplatelet therapy (DAPT), and DOAC groups. The two-category classification comprised the antiplatelet and anticoagulant groups. The classification of patients using both antiplatelet and anticoagulant agents was based on anticoagulant usage.

Clinical outcomes

The clinical outcomes of interest included recurrent thrombotic and major bleeding events from the time of initial antithrombotic medication prescription to the last follow-up. A recurrent thrombotic event was defined as a thrombosis occurring in any arterial or venous bed. Major bleeding events were defined as bleeding that met the criteria for Bleeding Academic Research Consortium type 3–5[27]. The composite outcome consisted of recurrent thrombosis and major bleeding, which served to evaluate the net clinical benefits of antithrombotic medications in stroke patients with aPLs.

Statistical analysis

Continuous variables were compared using the *t*-test or Mann–Whitney *U* test, as appropriate. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. During the follow-up period, a subset of patients experienced changes in their secondary preventive medications. To mitigate potential biases related to treatment changes during follow-up, a time-varying Cox proportional hazards model was used to assess the hazard ratio for composite outcomes based on the different categories of antithrombotic medications. Age and sex were initially adjusted for, followed by additional adjustment for variables with $p < 0.10$ in the baseline comparison. To visualize the incidence of clinical events, cumulative incidence curves were plotted using the Kaplan–Meier method. The log-rank test was used to compare the cumulative incidence of composite outcomes based on the use of antithrombotic medications. Analyses were conducted for both the four- and two-category classifications of antithrombotic medications. In addition to composite outcome analyses, separate analyses were performed for each component of the composite outcome, specifically for recurrent thrombosis and major bleeding events. Interaction tests were used to explore potential variations in the hazard ratios of clinical events according to key clinical factors, incorporating multiplicative interaction terms between two-category antithrombotic medication and the following factors: age group (< 50 or ≥ 50

years), sex, presence of any vascular risk factors (hypertension, diabetes, hyperlipidemia, or smoking), history of arterial or venous thrombosis, aPL positivity, aPL risk profile, and diagnosis of APS. Statistical significance was defined as a two-sided probability value < 0.05. All statistical analyses were performed using R version 4.2.2 (R Foundation, Vienna, Austria).

Results

Among the 403 aPL-positive patients with a history of ischemic stroke/TIA, 167 were eligible for the present study. The median [interquartile range] age was 56 [44; 65] years, and 93 (55.7%) patients were male. aPL testing was performed at a median [interquartile range] of 10 [2; 94.75] days after the index stroke event. Forty-four patients (19 on warfarin and 25 on DOAC) received anticoagulant medications, whereas 123 patients (32 on SAPT and 91 on DAPT) received antiplatelet medications as their initial secondary preventive treatment (Fig. 1).

The patients in the SAPT, DAPT, and DOAC groups were older, more likely to be male, and had higher rates of hypertension than those in the warfarin group. The warfarin and DOAC groups exhibited a greater likelihood of having prior venous thrombosis, positivity for LA, and high-risk aPL profiles than the SAPT and DAPT groups (Table 1). When patients were categorized into anticoagulant and antiplatelet groups, more patients in anticoagulant group were triple-positive for aPLs (Table S1). Secondary preventive medications were switched to other categories in 59 (35.3%) patients after a median [interquartile range] of 9.5 [4.2; 27.8] months from the first prescription. The primary reason for switching medications was due to the stabilized status of patients. Additional details regarding the other reasons are provided in Table S2.

The total follow-up period was 601.1 person-years, with observation durations for each group as follows: 58.7 person-years for warfarin, 229.0 person-years for SAPT, 285.9 person-years for DAPT, and 27.6 person-years for DOAC. Twenty-eight composite outcome events occurred, with 19 patients experiencing recurrent thrombosis (14 with ischemic stroke or TIA, 2 with acute coronary syndrome, 1 with deep vein thrombosis or pulmonary

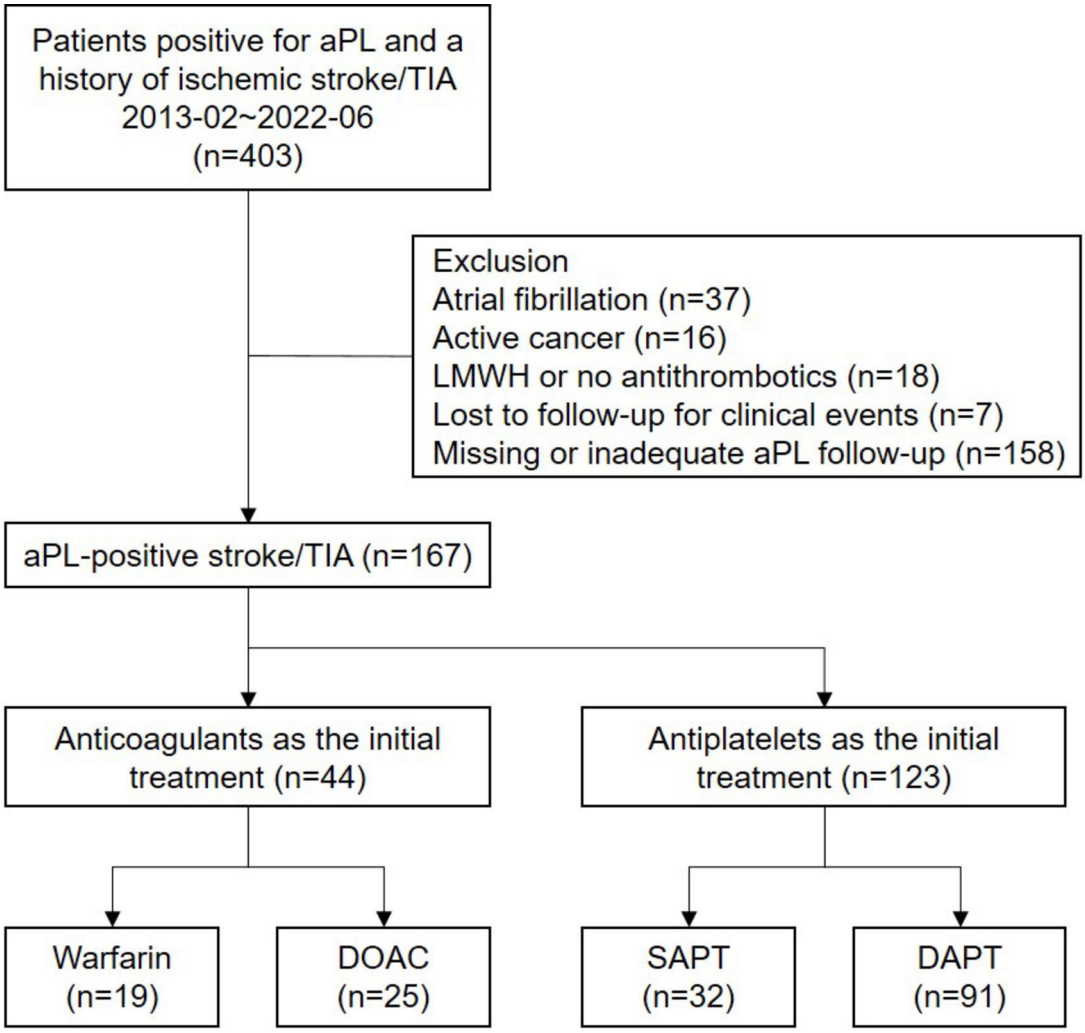

Fig. 1. Flowchart of patient inclusion and exclusion. *aPL* antiphospholipid antibody, *DAPT* dual antiplatelet therapy, *DOAC* direct oral anticoagulant, *LMWH* low-molecular-weighted heparin, *SAPT* single antiplatelet therapy, *TIA* transient ischemic attack.

	Warfarin ($n=19$)	SAPT ($n=32$)	DAPT ($n=91$)	DOAC ($n=25$)	p value
Age, years	49.4 ± 17.0	52.1 ± 13.3	54.6 ± 13.6	61.6 ± 13.1	0.021
Male sex	7 (36.8%)	14 (43.8%)	57 (62.6%)	15 (60.0%)	0.088
Hypertension	4 (21.1%)	16 (50.0%)	49 (53.8%)	10 (40.0%)	0.059
Diabetes	2 (10.5%)	4 (12.5%)	17 (18.7%)	9 (36.0%)	0.13
Hyperlipidemia	9 (47.4%)	16 (50.0%)	61 (67.0%)	15 (60.0%)	0.22
Smoking status					0.38
Nonsmoker	15 (78.9%)	20 (62.5%)	51 (56.0%)	13 (52.0%)	
Ex-smoker	1 (5.3%)	5 (15.6%)	11 (12.1%)	6 (24.0%)	
Current smoker	3 (15.8%)	7 (21.9%)	29 (31.9%)	6 (24.0%)	
Prior arterial thrombosis	4 (21.1%)	3 (9.4%)	15 (16.5%)	6 (24.0%)	0.46
Prior venous thrombosis	4 (21.1%)	0 (0.0%)	0 (0.0%)	5 (20.0%)	< 0.001
aPL positivity					0.13
Single positivity	9 (47.4%)	23 (71.9%)	65 (71.4%)	14 (56.0%)	
Double positivity	6 (31.6%)	8 (25.0%)	21 (23.1%)	7 (28.0%)	
Triple positivity	4 (21.1%)	1 (3.1%)	5 (5.5%)	4 (16.0%)	
LA positivity	10 (52.6%)	14 (43.8%)	39 (42.9%)	20 (80.0%)	0.010
aCL IgG positivity	14 (73.7%)	19 (59.4%)	57 (62.6%)	11 (44.0%)	0.22
aCL IgG titer	40.9 [28.1; 78.3]	39.5 [28.0; 44.0]	35.8 [24.1; 51.9]	46.2 [40.5; 90.2]	0.24
aCL IgM positivity	5 (26.3%)	4 (12.5%)	12 (13.2%)	3 (12.0%)	0.51
aCL IgM titer	31.0 [30.4; 33.9]	30.4 [25.6; 68.1]	23.1 [22.2; 36.5]	28.1 [26.6; 71.0]	0.41
aβ2GPI IgG positivity	6 (31.6%)	6 (18.8%)	12 (13.2%)	7 (28.0%)	0.13
aβ2GPI IgG titer	145.2 [34.5; 536.6]	36.7 [23.5; 103.0]	32.2 [26.8; 101.5]	206.9 [27.3; 341.9]	0.47
aβ2GPI IgM positivity	2 (10.5%)	2 (6.2%)	6 (6.6%)	2 (8.0%)	0.85
aβ2GPI IgM titer	113.8 ± 114.5	47.7 ± 36.9	67.8 ± 40.8	76.5 ± 62.7	0.71
aPL risk profile[a]					0.010
Low/moderate risk	9 (47.4%)	18 (56.2%)	52 (57.1%)	5 (20.0%)	
High risk	10 (52.6%)	14 (43.8%)	39 (42.9%)	20 (80.0%)	
Definite APS	12 (63.2%)	18 (56.2%)	42 (46.2%)	16 (64.0%)	0.28

Table 1. Baseline characteristics according to initial secondary preventive antithrombotic medications administered for aPL-related stroke. The data are expressed as No. (%), mean ± standard deviation, or median [interquartile range]. *aβ2GPI* anti-β2-glycoprotein I antibody, *aCL* anti-cardiolipin antibody, *aPL* antiphospholipid antibody, *APS* antiphospholipid syndrome, *DAPT* dual antiplatelet therapy, *DOAC* direct oral anticoagulant, *LA* lupus anticoagulant, *SAPT* single antiplatelet therapy. [a]Low-risk profile: negative for lupus anticoagulant and low titer (20–40 U/mL) of aCL/aβ2GPI; moderate-risk profile: negative for lupus anticoagulant and moderate-to-high titer (≥ 40 U/mL) of aCL/aβ2GPI; high-risk profile: positive for lupus anticoagulant and/or moderate-to-high titer of aCL/aβ2GPI.

thromboembolism, 1 with common iliac artery occlusion, and 1 with cerebral venous thrombosis), 10 with major bleeding events (6 with intracranial bleeding, 2 with gastrointestinal bleeding, 1 with vaginal bleeding, and 1 with massive menorrhagia), and 1 experiencing both events.

Patients treated with SAPT or DAPT had a lower incidence of composite outcomes compared to those on warfarin, as illustrated in Fig. 2a–c. After adjusting for clinical factors, the SAPT/DAPT group exhibited a lower risk of composite outcome events compared to the warfarin group. In a separate analysis of each component of the composite outcome, DAPT group had a significantly lower risk of major bleeding than the warfarin group, while the risk of recurrent thrombotic events was similar across the SAPT/DAPT and warfarin groups (Table 2). Comparisons between the anticoagulant and antiplatelet groups also demonstrated similar results (Fig. 2d–f and Table S3).

No significant impact of clinical factors on the composite outcome was observed in the comparison between antiplatelets and anticoagulants based on subgroup analysis. However, trends were observed, suggesting that antiplatelets might be more beneficial than anticoagulants in younger patients and those with definite APS. The hazard ratio for composite outcome from using antiplatelets was higher in patients with triple positivity than in those with single/double aPL positivity, despite not reaching statistical significance (Fig. 3).

Discussion

Patients with aPL- and APS-related stroke are prescribed antiplatelet medications more frequently than warfarin for secondary prevention in clinical practice. Antiplatelet medications provided better net clinical benefits to warfarin in these patients. The primary reason for this was the significant reduction in the risk of major bleeding events, which offered a substantial advantage over warfarin.

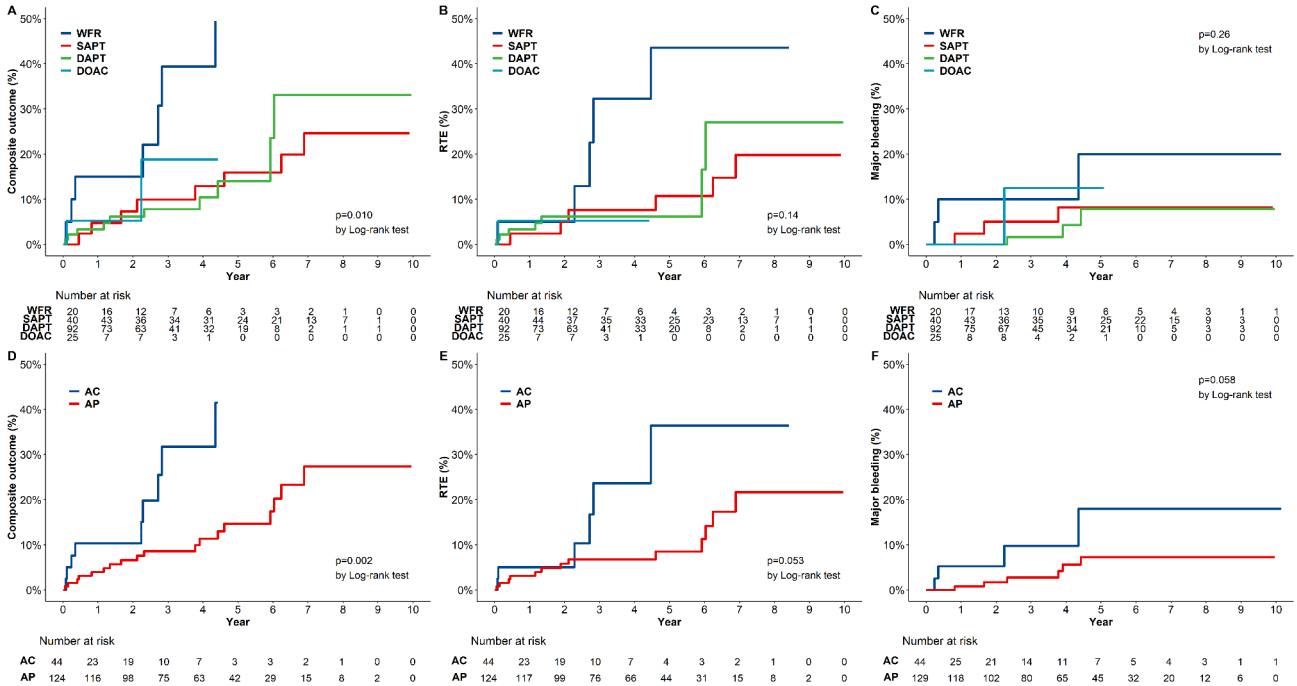

Fig. 2. Cumulative incidence curves for clinical outcomes according to secondary preventive antithrombotic medications for aPL-related stroke. Cumulative incidences of (**a**,**d**) the composite outcome, (**b**,**e**) recurrent thrombotic events, and (**c**,**f**) major bleeding. Log-rank tests were performed to determine whether the cumulative incidence differed significantly according to the secondary preventive treatment employed. *AC* anticoagulant, *AP* antiplatelet, *aPL-stroke* antiphospholipid antibody-related stroke, *DAPT* dual antiplatelet therapy, *DOAC* direct oral anticoagulant, *RTE* recurrent thrombotic event, *SAPT* single antiplatelet therapy, *WFR* warfarin.

	Warfarin	SAPT	DAPT	DOAC
Composite outcome	8/20 (40.0%)	8/68 (11.8%)	10/105 (9.5%)	2/25 (8.0%)
Follow-up duration, years	2.5 [1.4; 4.4]	2.5 [1.1; 5.2]	2.5 [0.9; 4.3]	0.5 [0.1; 2.2]
Unadjusted HR	1	0.25 (0.09–0.70)	0.27 (0.11–0.70)	0.49 (0.10–2.38)
Model 1[a]	1	0.29 (0.10–0.88)	0.30 (0.10–0.84)	0.47 (0.09–2.50)
Model 2[b]	1	0.24 (0.07–0.83)	0.25 (0.08–0.81)	0.45 (0.08–2.41)
Recurrent thrombotic event	5/20 (25.0%)	6/71 (8.5%)	7/106 (6.6%)	1/25 (4.0%)
Follow-up duration, years	2.5 [1.4; 4.5]	2.5 [1.2; 5.0]	2.4 [0.8; 4.3]	0.5 [0.1; 2.2]
Unadjusted HR	1	0.30 (0.09–1.01)	0.32 (0.10–1.04)	0.38 (0.04–3.28)
Model 1[a]	1	0.37 (0.10–1.37)	0.39 (0.10–1.49)	0.40 (0.04–3.94)
Model 2[b]	1	0.38 (0.09–1.62)	0.41 (0.10–1.80)	0.38 (0.04–3.57)
Major bleeding	3/20 (15.0%)	3/68 (4.4%)	3/106 (2.8%)	1/25 (4.0%)
Follow-up duration, years	3.0 [1.6; 5.9]	2.6 [1.1; 5.5]	2.5 [1.0; 4.3]	0.5 [0.3; 2.5]
Unadjusted HR	1	0.35 (0.07–1.76)	0.23 (0.05–1.16)	0.68 (0.06–7.18)
Model 1[a]	1	0.35 (0.06–2.13)	0.21 (0.04–1.04)	0.59 (0.06–5.90)
Model 2[b]	1	0.19 (0.03–1.29)	0.10 (0.02–0.47)	0.59 (0.04–9.32)

Table 2. Hazard ratios of clinical outcomes according to secondary preventive antithrombotic medications. The data are expressed as No. (%), median [interquartile range], or HR (95% CI). *CI* confidence interval, *DAPT* dual antiplatelet therapy, *DOAC* direct oral anticoagulant, *HR* hazard ratio, *SAPT* single antiplatelet therapy. [a]Adjusted for age and sex. [b]Adjusted for age, sex, hypertension, past venous thrombosis, and antiphospholipid antibody risk profile.

For decades, remarkable progress has been made in both the diagnostic and therapeutic domains of stroke practice. The widespread use of diffusion-weighted imaging techniques has facilitated the accurate diagnosis of minor stroke with a low lesion burden. Additionally, the development of novel antiplatelet and anticoagulant agents has significantly expanded available treatment options. However, the current clinical guidelines for APS-

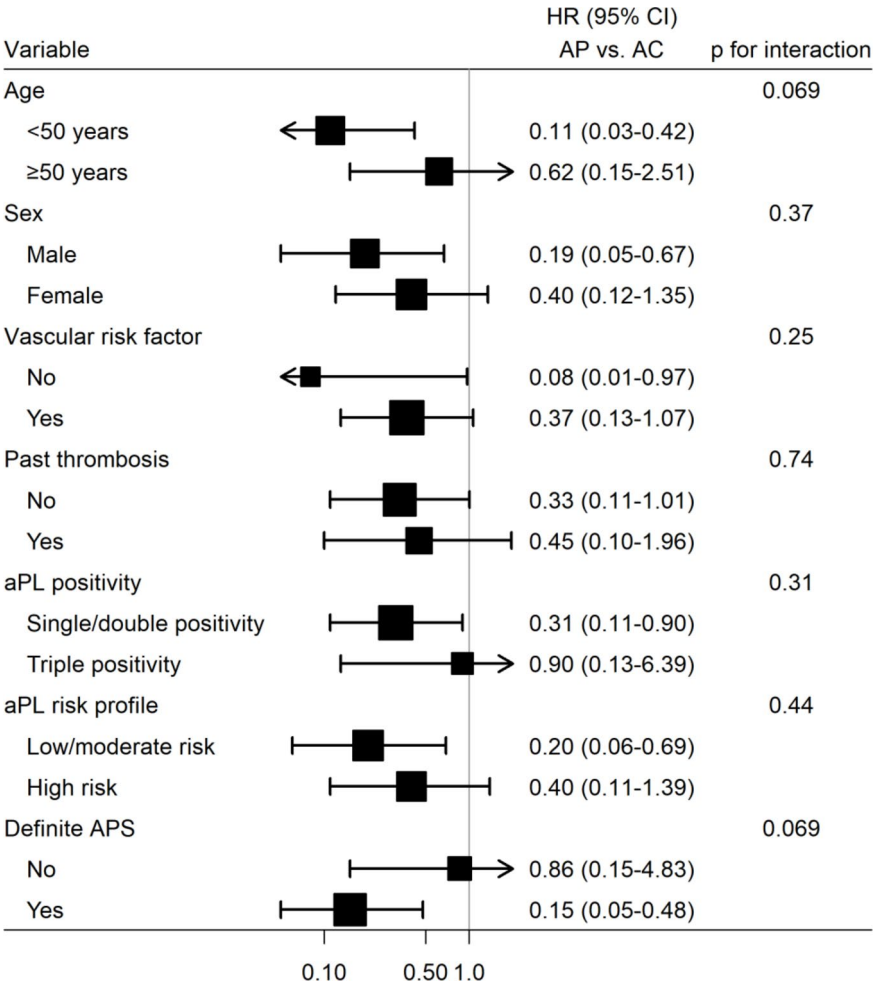

Fig. 3. Hazard ratios of the composite outcome stratified by key clinical factors. Hazard ratios for composite outcomes stratified by clinical factors. The hazard ratios for antiplatelets compared to anticoagulants were adjusted for the variables of the model 2 in Table 2 and plotted on a log scale. The horizontal lines represent 95% confidence intervals. Probability values were computed for the multiplicative interaction terms in the adjusted Cox models. *AC* anticoagulant, *AP* antiplatelet, *aPL* antiphospholipid antibody, *APS* antiphospholipid syndrome, *CI* confidence interval, *HR* hazard ratio.

related stroke do not fully reflect these advancements. The studies that currently serve as references supporting the use of warfarin were conducted 20–30 years ago[12–15], and they may be susceptible to selection bias due to the challenges in diagnosing minor strokes during that period. Considering our recent study suggesting that the majority of patients with aPL- and APS-related stroke present with minor stroke symptoms and a low lesion burden[19], it is possible that the recommendations for warfarin may be relevant only to a small subset of these patients (i.e., high-risk patients with major stroke). Furthermore, most recommendations are based on studies primarily examining low-dose aspirin as an exclusive antiplatelet medication[7,12–16], leading to a knowledge gap regarding the clinical roles of other antiplatelet agents and DAPT[4,11]. Incorporating diagnostic and therapeutic advancements, this study demonstrated a comparable overall clinical benefit and lower risk of major bleeding in patients treated with antiplatelet medications as opposed to warfarin. To confirm these findings, we have launched a multicenter randomized prospective study (ClinicalTrials.gov: NCT05995600) to compare the efficacy and safety of clopidogrel-based antiplatelet medications with warfarin in patients with APS and ischemic stroke/TIA.

Although the exact mechanisms of APS-related thrombosis are not fully understood, it has been reported that aPLs activate various vascular and immune cells (e.g., platelets, endothelial cells, monocytes, and neutrophils) and interact with the coagulation pathway, contributing to the initiation of thrombosis[28]. The involvement of cellular components in APS-related thrombosis provides a mechanistic rationale for the role of antiplatelet medications in patients with APS-related stroke. However, based on previous studies, the mechanisms underlying APS-related thrombosis may differ according to several factors, such as aPL positivity. Notably, triple-positive APS has been associated with higher tissue factor and complement activity[29,30], implying a potential decrease in the benefits of antiplatelet medications for this subgroup. Although not statistically significant, our subgroup analysis may indicate antiplatelet therapy may provide lesser clinical benefits for patients with triple-positive

for aPLs compared to those with single/double positivity, suggesting a need for tailored secondary prevention strategies accordingly. Further studies are warranted to establish the optimal prevention of APS-related stroke based on aPL positivity.

This study had several limitations. First, owing to the retrospective design of the study, there may be potential sources of bias that have not been fully addressed. For example, data on mortality, a key clinical outcome, are unavailable for many patients, limiting the evaluation of their association with antithrombotic agents. Information on the etiology of stroke was not systematically collected, and therefore, was not available for analysis. Potential causes of stroke other than aPL such as large-vessel atherosclerosis may have confounded the results, making it challenging to isolate the specific effects of aPL. Factors, such as obesity and hormonal therapy, which may affect thromboembolism, were not assessed. Second, nearly half of the patients were excluded from this study due to inadequate follow-up for aPL testing at the required intervals to meet the diagnostic criteria. As evidenced in our previous study, low awareness of APS-related stroke among physicians remains a concern in stroke management[24]. Therefore, it is crucial to enhance awareness by revising the clinical guidelines for APS-related stroke following well-designed prospective studies. Third, approximately half of the included patients were transiently positive for aPL and were not confirmed to have definite APS. Because aPL results can be affected by infections or anticoagulant use during sampling, our findings should be interpreted with caution. Finally, it was not possible to provide meaningful suggestions regarding the use of DOAC in patients with aPL-related stroke because of the short follow-up period. Despite the increased risk of thrombotic events with DOAC use in recent trials[5,6], there may still be a potential role for DOAC in a specific subgroup of APS-related stroke patients, such as in patients with low-to-moderate risk profiles or single/double positivity. Other observational studies may provide valuable clues into this issue.

Suboptimal clinical guidelines for secondary prevention of APS-related stroke pose a challenging dilemma for stroke physicians. In the present study, antiplatelet use in patients with aPL- and APS-related stroke was associated with favorable secondary prevention effects and greater safety than warfarin. Future prospective studies are required to provide definitive information on this topic.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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