Efficacy of dual antiplatelet therapy for preventing recurrence of arterial thrombosis in patients with antiphospholipid syndrome

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Conflict of interest

Tatsuya Atsumi reports personal fees from Chugai, during the conduct of the study; grants and personal fees from Astellas, grants and personal fees from Takeda, grants and personal fees from Mitsubishi Tanabe, grants and personal fees from Chugai, grants and personal fees from Pfizer, grants from Daiichi Sankyo, grants from Otsuka, personal fees from Eisai, personal fees from AbbVie, outside the submitted work. Shinsuke Yasuda reports grants and speaker's fee from Bristol-Myers Squibb Co., Speaker's fee from Chugai, Mitsubishi Tanabe, outside the submitted work. Masaru Kato reports grants from GSK, grants from Actelion, outside the submitted work. The other authors state that they have no conflict of interest.

Abstract

OBJECTIVE: Warfarin is regarded as the standard treatment for preventing thrombotic events in antiphospholipid syndrome (APS), but the recurrence rate is still high. Dual antiplatelet therapy (DAPT) has been shown to be effective for the prevention of acute coronary syndrome or stroke. The objective of this study was to evaluate the efficacy of DAPT for the prevention of thrombosis recurrence in APS patients with history of arterial thrombosis.

METHODS: This retrospective cohort study of APS patients was conducted at Hokkaido University Hospital between 1990 and 2016. The secondary prophylactic effects and safety of warfarin monotherapy (Wf), antiplatelet monotherapy (AP), warfarin and antiplatelet combination therapy (Wf + AP) and DAPT were evaluated. The primary endpoints were set as thrombosis-free and adverse events-free survival period. Adverse events were defined as severe bleeding and death.

RESULTS: A total of 90 APS patients were enrolled. Thrombotic recurrence was found in 40 patients (35 arterial and 5 venous thromboses) and serious adverse events in 20 patients (9 severe bleeding events and 14 deaths). Kaplan-Meier analysis demonstrated a 10-year recurrence-free survival rate of 62%. The recurrence rate per 100 patient-years were as follows: Wf: 11.6, AP: 5.5, Wf: + AP: 3.7, DAPT: 1.8. We demonstrated that DAPT significantly reduced the rate of recurrence compared with Wf (Log-rank p = 0.001). There

were no significant differences in the rate of serious adverse events among the groups.

CONCLUSION: DAPT might be considered as an effective and safe option for the prophylaxis of recurrent arterial thrombosis in APS.

Keywords

Antiphospholipid syndrome (APS), dual antiplatelet therapy (DAPT), arterial thrombosis, venous thrombosis, prophylaxis, safety

Rheumatology key messages

- This is the first study exploring dual antiplatelet therapy (DAPT) for APS patients.
- DAPT might be considered as an effective and safe option for APS patients.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by thrombotic events and pregnancy complications with persistently positive antiphospholipid antibodies (aPL) [1]. APS patients suffer from thrombosis in both arteries and veins, whilst protein C deficiency, Factor V Leiden, and other thrombophilia mostly affect the venous circulation.

According to the guidelines for the management of patients with APS, anticoagulation using warfarin is recommended for secondary prophylaxis of arterial/venous thrombosis by targeting the Prothrombin time-International normalized ratio (PT-INR) between 2.0 to 3.0 [2]. On the other hand, the APS Workshop guidelines recommend that APS patients with an arterial thrombotic event should be treated with warfarin at PT−INR >3.0 or with antiplatelet plus warfarin combination therapy at PT-INR between 2.0 to 3.0 [3]. The difference between these recommendations may be due to the discrepancy in their main objectives of avoiding treatment-related bleeding events [4] or preventing severe recurrent thrombosis [5]. However, a major limitation in both recommendations is that no definitive evidence has been shown to prevent recurrent arterial events.

Dual antiplatelet therapy (DAPT) is commonly used in clinical practice for the secondary prevention of arterial thrombotic events in patients at high recurrence risk. Defined as the combination of aspirin and a $P2Y_{12}$-receptor inhibitor, DAPT has demonstrated superior efficacy over anticoagulant therapy in coronary artery disease.

Although there have been no reports of retrospective/prospective studies that compare the effectiveness and safety of DAPT in APS patients [6], the benefit of antiplatelet therapy is highly suggestive as most arterial thromboses recur as arterial thrombosis [7, 8]. Although arterial thrombosis in APS is reported most frequently in Japan compared to other countries, still the low prevalence of disease makes prospective trials very difficult [5, 8]. Therefore, our longitudinal APS cohort was used to evaluate the benefit of DAPT in patients with a history of arterial thrombosis.

Methods

This retrospective cohort study of patients with APS, was conducted in a single institution. Patients with the diagnosis of APS was extracted from the autoimmune disease database of our outpatient clinic between April 1990 and March 2016, and the diagnosis verified by the attending physicians and authors according to the Sydney-revised Sapporo criteria for definite APS [1]. The coexistence of systemic lupus erythematosus was diagnosed according to the American College of Rheumatology (ACR) revised criteria [9].

We enrolled APS patients with a history of an arterial thrombotic event who received prophylactic treatment for recurrent thrombosis for at least 2 years. The observation period of each patient was defined to begin at the time of the first arterial thrombotic event, regardless of previous venous thrombotic events or pregnancy complications and end either at the time of an event (recurrence of arterial and/or venous thrombosis, severe bleeding event, or death)

or at the end of medical records. APS patients without manifestations of arterial thrombosis or with followed-up periods less than 2 years were excluded. The selection of the prophylactic regimen was based on the individual physician's judgement in accordance with the standard medical care in Japan at the time. All treating physicians were board-certified rheumatologists by the Japan College of Rheumatology, and therapeutic regimen administered following the corresponding guidelines of APS [2] and stroke [10].

Patients were divided into four groups based on their treatment regimen: warfarin monotherapy (Wf); single antiplatelet therapy (AP); warfarin and antiplatelet combination therapy (Wf + AP); or dual antiplatelet therapy (DAPT) (Figure S1). Specific antiplatelet drugs included aspirin, ticlopidine, clopidogrel, cilostazol, dipyridamole, beraprost sodium, sarpogrelate hydrochloride, and dilazep dihydrochloride (Table S1). Anticoagulant refers specifically to warfarin in this study as patients on treatment with direct oral anticoagulants were excluded due to off label use of these agents for arterial thrombosis without atrial fibrillation in Japan. None of the patients were on hydroxichloroquine. In Japan, hydroxichloroquine has been used off-label for SLE until its approval on July 2015.

The primary endpoints were set as event free survival period and events were defined as the recurrence of thrombosis in either arterial or venous circulation, severe bleeding events, and death. The presence of thrombosis was confirmed by imaging and severe bleeding was defined as those events that required hospitalization and/or blood

transfusion.

Risk factors for arterial thrombosis including hypertension, diabetes mellitus, dyslipidaemia, glucocorticoid use and smoking were recorded at the end of the observation period. Antiphospholipid antibodies were assayed in all the patients at the first visit to the autoimmune outpatient clinic and at least the second time, separated by at least twelve weeks (definition of risk factor and aPL assay are shown in supplementary data). The antiphospholipid score (aPL-S), a quantitative marker that represents aPL profile, was calculated in each patient [11].

This study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by Hokkaido University Hospital ethics committee (approval number: 017-0034).

Statistical analysis

Categorical variables were described as counts and percentages. Continuous variables were expressed as the median and quartiles. To identify differences between groups, the Mann–Whitney U test and the Kruskal-Wallis test were performed. Kaplan-Meier curves were applied to estimate the value of secondary prevention therapy and safety, using thrombotic events and mortality/severe bleeding events. Cox regression analysis was performed to identify the risk factors for recurrence according to therapy and variables related to arterial

thrombosis. In all statistical analyses, $p < 0.05$ was taken to indicate statistical significance. All statistical analyses were performed using JMP® Pro 12.2.0 (SAS Institute Inc., Cary, North Carolina, USA).

Results

One hundred and twelve patients out of the 206 patients in the APS cohort had a history of arterial thrombosis as the first thrombotic event and received a prophylactic regimen. Ninety patients met the inclusion criteria and were enrolled in this analysis. Patients were divided into four groups according to the regimen as follows: Wf (n=13), AP (n=41), Wf + AP (n=21) or DAPT (n=15) (Figure S1).

Baseline Characteristics

Patients' baseline characteristics are summarized in Table 1. Seventy three out of 90 (81%) were female, and cerebral infarction (81/90 patients (90%)) was the most frequent incident thrombotic event. The median observation period was 8 years [interquartile range (IQR) 5–13]. No statistically significant differences were found in risk factors for arterial thrombosis among the 4 groups (Table 1, S2). The frequency of coronary heart disease (CHD), deep vein thrombosis (DVT), pulmonary embolism (PE) and superficial thrombophlebitis were statistically significantly different among the 4 groups at baseline (p=0.025, p=0.022, p=0.004, p=0.017, respectively).

Recurrence rate

Recurrent events were observed in 40 patients (recurrence rate 4.96 per 100 patient-years) with 35 arterial and 5 venous thromboses (Table S3). The most common arterial and venous thrombotic recurrence was cerebral infarction and DVT in 29 (32.2%) and 3 patients (3.3%), respectively. There were statistically significant differences in the recurrence rates of cerebral infarction among the 4 groups (p=0.004), with AP (p=0.024), Wf + AP (p=0.034), and DAPT (p=0.001) having significantly lower incidences relative to Wf.

Thrombosis-free intervals during treatment calculated by the Kaplan–Meier method are presented in Figure 1. Warfarin monotherapy was less effective for prevention of thrombosis than other treatment options (Log-rank p = 0.0027). INR levels in Wf group were for moderate-intensity: PT-INR between 1.5 to 2.5 (on recurrence; median PT-INR, [range] 2.17 [1.75 - 2.39]). The frequency of thrombotic recurrence between Wf and DAPT, and also between Wf and Wf + AP were statistically significantly different (Log-rank p = 0.001, p = 0.009, respectively). Warfarin monotherapy had the highest rate of recurrence (11.58 per 100 patient-years). In the other group, the recurrence rate expressed as per 100 patient-years, were as follows: AP: 5.47, Wf + AP: 3.72, DAPT: 1.81. Warfarin monotherapy was identified as an independent risk factor in adjusted Cox proportional hazards models (Hazard Ratio 4.23, 95% confidence interval 1.69 - 10.38, p = 0.003) (Table S4). Since the patients with high

risk of ischemic heart disease might have an impact on the results, the sub-analysis excluding patients with recurrence of cardiac events were performed; Wf monotherapy was still identified as an independent risk factor (Figure S2).

Safety assessment

Severe bleeding events and/or mortality occurred in 20 patients (22.2%, 3.58 per 100 patient-years) (Table S3). During the follow-up period, there were 9 patients (10%) with severe bleeding events and 14 deaths (15.6%). Three patients died of a severe bleeding (aortic dissection in AP, alveolar haemorrhage in Wf + AP, aortic aneurysm rupture in DAPT), and 2 patients died of cerebral infarction. Other causes of death were interstitial pneumonia (n=2), and infection/sepsis, lung cancer, amyotrophic lateral sclerosis and drowning (n=1 each). In three patients, the causes of death could not be identified. No statistically significant differences in frequency of severe bleeding or death were observed among the 4 groups (Figure S3). Per 100 patient-years, serious bleeding events and/or mortality rate in the four groups were as follows: Wf : 0.59, AP: 2.14, Wf + AP: 2.21, DAPT: 2.89.

Discussion

In this study, we found that the effectiveness of DAPT as a secondary prophylaxis against arterial thrombosis in APS patients was similar to that of Wf + AP and superior to warfarin

alone. The differences in efficacy may be attributed to the constitutional difference in arterial thrombi initiated as platelet aggregates, and venous thrombi consisting mainly of fibrin [12], with the former being more effectively prevented by anti-platelet agents. The high recurrence rate of cerebral infarction in the Wf monotherapy group is suggestive of this mechanism (Table S3).

Considering that most recurrences took place in the same vascular bed as the original thrombosis, most physicians were choosing secondary prevention therapy including warfarin for the patients with the past history of venous thrombosis (Table 1). In fact, warfarin monotherapy was effective in preventing new venous thrombosis occurrence (recurrence rate: 1.05 per 100 patient-years), but without similar effectiveness for arterial thrombosis (recurrence rate: 10.53 per 100 patient-years). Although the average PT-INR (2.17) herein for the Wf group was lower than those recommended in the guidelines (target PT-INR (2.5-3.5)), this reflects the real world management of warfarin treatment at the time of administration. Previous studies in APS also reported the difficulty to keep the optimal PT-INR range without bleeding events [13].

A systematic review and meta-analysis of DAPT for secondary prevention of myocardial infarction and stroke has shown that long-term use of DAPT was associated with lower mortality compared to other prophylactic regimen [14]. Although treatment-related bleeding events are of serious concern during DAPT, we did not find an increased bleeding

risk, most likely due to the younger age of our APS population (median age 45 years [range 31.3 - 53.0 years]) compared to the non-APS thrombotic population (average age ±standard deviation: 64.4 ± 9.5 years) [14]. Older age have been reported as a risk of treatment-related bleeding [15]. While aspirin is the most frequently used antiplatelet drug, aspirin has a major disadvantage of “aspirin resistance” [16]. In fact, aspirin resistance were reported in 27% of patients [17] and were associated with short and long-term mortality in patients with acute ischemic stroke [18]. The use of DAPT may be an effective strategy to resolve this issue.

There are some important limitations to be considered in this single centre Japanese study. Although longitudinal data of at least two years in 90 patients is worth reporting, appropriate reproducibility is warranted in a multi-centered study. On a similar note, APS patients with diverse ethnic and genetic backgrounds need to be considered. In terms of study design, selection bias inherent to the retrospective observational design warrants further confirmation of the superiority of DAPT in a prospective fashion. Furthermore, the small number of patients on DAPT precluded our comparison among the specific antiplatelet regimens, and the small number of patients on each treatment may contribute to the safety assessment. Although cerebral infarction was confirmed by brain MRI or magnetic resonance angiogram or angiography in all patients, differential diagnosis between cerebral infarction and cerebral vasculitis may be difficult in some patients with SLE and APS due to the diagnostic limitations. Nevertheless, we believe our study would shed a light to any

prospective clinical study focused on the prophylaxis of arterial thrombosis using DAPT in APS patients.

In conclusion, our results indicate that DAPT might be an effective option for preventing arterial thrombosis in patients with APS.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite

antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295-306.

2. Keeling D, Mackie I, Moore GW, Greer IA, Greaves M. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haematol. 2012;157(1):47-58.

3. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, Brey R, Crowther M, Derksen R, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on antiphospholipid antibodies. Lupus. 2011;20(2):206-18.

4. Ruiz-Irastorza G, Hunt BJ, Khamashta MA. A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies. Arthritis Rheum. 2007;57(8):1487-95.

5. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum. 2002;46(4):1019-27.

6. Bala MM, Celinska-Lowenhoff M, Szot W, Padjas A, Kaczmarczyk M, Swierz MJ, et al. Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome. Cochrane Database Syst Rev. 2017;10:Cd012169.

7. Ruiz-Irastorza G, Khamashta MA, Hunt BJ, Escudero A, Cuadrado MJ, Hughes GR.

Bleeding and recurrent thrombosis in definite antiphospholipid syndrome: analysis of a series of 66 patients treated with oral anticoagulation to a target international normalized ratio of 3.5. Arch Intern Med. 2002;162(10):1164-9.

8. Fujieda Y, Atsumi T, Amengual O, Odani T, Otomo K, Kato M, et al. Predominant prevalence of arterial thrombosis in Japanese patients with antiphospholipid syndrome. Lupus. 2012;21(14):1506-14.

9. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25(11):1271-7.

10. Ishihara H, Suzuki M. [Japanese Guidelines for the Management of Stroke 2015: overview of the chapter on Subarachnoid Hemorrhage]. Nihon Rinsho. 2016;74(4):677-80.

11. Otomo K, Atsumi T, Amengual O, Fujieda Y, Kato M, Oku K, et al. Efficacy of the antiphospholipid score for the diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events. Arthritis Rheum. 2012;64(2):504-12.

12. Mackman N. Triggers, targets and treatments for thrombosis. Nature. 2008;451(7181):914-8.

13. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramon E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis. 2015;74(6):1011-8.

14. Fanari Z, Malodiya A, Weiss SA, Hammami S, Kolm P, Weintraub WS. Long-term use of dual antiplatelet therapy for the secondary prevention of atherothrombotic events: Meta-analysis of randomized controlled trials. Cardiovasc Revasc Med. 2017;18(1):10-5.

15. Li L, Geraghty OC, Mehta Z, Rothwell PM. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet. 2017;390(10093):490-9.

16. Hankey GJ, Eikelboom JW. Aspirin resistance. Lancet. 2006;367(9510):606-17.

17. Ikeda T, Taniguchi R, Watanabe S, Kawato M, Kondo H, Shirakawa R, et al. Characterization of the antiplatelet effect of aspirin at enrollment and after 2-year follow-up in a real clinical setting in Japan. Circ J. 2010;74(6):1227-35.

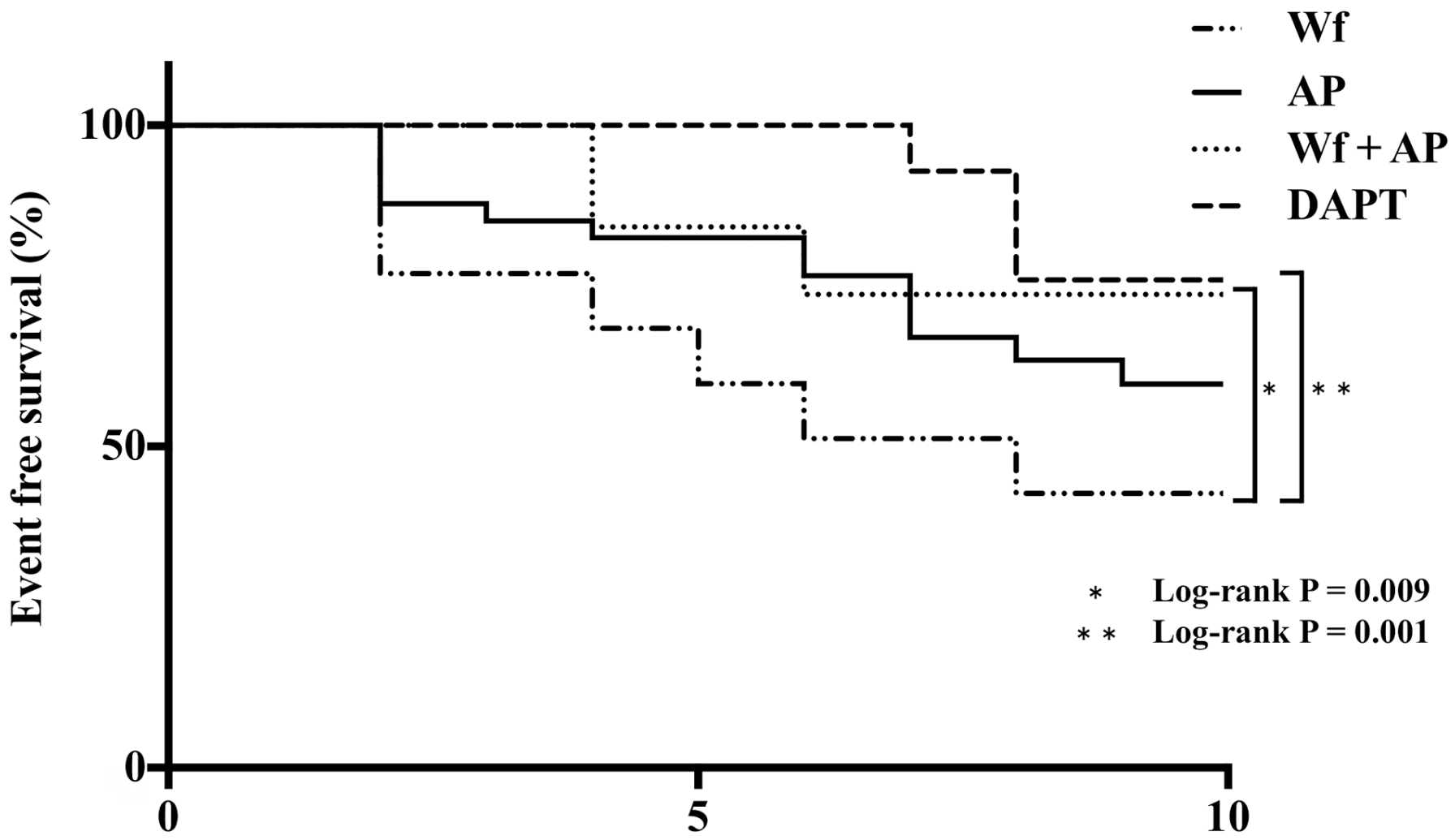
18. Ozben S, Ozben B, Tanrikulu AM, Ozer F, Ozben T. Aspirin resistance in patients with acute ischemic stroke. J Neurol. 2011;258(11):1979-86.

Figure Legend

Figure 1. Ten-years thrombosis-free survival.

Data were estimated using the Kaplan-Meier curves. P-values <0.05. Ten-years thrombosis-free survival rate was 62%. Warfarin was less effective for prevention of thrombosis than other treatment options (Log-rank P=0.0027). There was statistically significant difference in the frequency of thrombotic recurrence events between Wf and dual

antiplatelet therapy (DAPT) (＊＊Log-rank P = 0.001) or Wf + AP combination therapy (＊ Log-rank P = 0.009). The intensity of warfarin therapy on recurrence was at a moderate-intensity level (median PT-INR, [range] 2.17 [1.75 - 2.39]).



Wf (N)	13	13	13	9	9	8	7	7	6	5	4
AP (N)	41	41	41	33	32	29	28	24	19	17	15
Wf + AP (N)	21	21	21	20	19	19	16	13	13	11	11
DAPT (N)	15	15	15	15	15	15	15	14	11	11	11

Table 1. Baseline clinical and demographic characteristics of the patients

	Total (N=90)	Wf (N=13)	AP (N=41)	Wf + AP (N=21)	DAPT (N=15)	P-value
Female (%)	73 (81.1%)	10 (76.9%)	37 (90.2%)	14 (66.7%)	12 (80.0%)	0.156
Median age at disease onset (IQRrange): years	45 [31-53]	34 [26-51]	46 [34-56]	46 [29-53]	44 [36-51.5]	0.594
Median follow up period (range): years	8 [5-13]	6 [2-10]	7 [4-12]	9 [6-17]	11 [7.5-14]	0.072
Primary APS	37 (41.1%)	4 (30.8%)	20 (48.8%)	9 (42.9%)	4 (26.7%)	0.397
Secondary APS (SLE) on steroids	53 (58.9%)	9 (69.2%)	21 (51.2%)	12 (57.1%)	11 (73.3%)	0.397
Smoking	31 (37.8%)	5 (38.5%)	15 (36.6%)	6 (28.6%)	5 (33.3%)	0.916
Hypertension	51 (56.7%)	9 (69.2%)	25 (61.0%)	9 (42.9%)	7 (46.7%)	0.341
Dyslipidemia	40 (44.4%)	9 (69.2%)	18 (43.9%)	9 (42.9%)	4 (26.7%)	0.151
Diabetes Mellitus	16 (17.8%)	2 (15.4%)	5 (12.2%)	5 (23.8%)	4 (26.7%)	0.527
aPL-S	31 [14-50.5]	33 [13.0-71.0]	26 [13.0-42.0]	35 [15.0-54.5]	33 [20.0-41.0]	0.434
Arterial thrombosis						
Cerebral infarction	81 (90.0%)	11 (84.6%)	39 (95.1%)	20 (95.2%)	11 (73.3%)	0.115
Coronary heart disease	8 (8.9%)	2 (15.3%)	2 (4.9%)	0	4 (26.7%)	0.025*
Arterial ischemia in legs	3 (3.3%)	0	1 (2.4%)	2 (9.5%)	0	0.296
Mesenteric artery occlusion	3 (3.3%)	1 (7.7%)	1 (2.4%)	1 (4.8%)	0	0.612
Central retinal artery occlusion	2 (2.2%)	0	1 (2.4%)	1 (4.8%)	0	0.737
Renal infarction	1 (1.1%)	0	0	1 (4.8%)	0	0.400
Past history of venous thrombosis	18 (20.0%)	8 (61.5%)	2 (4.9%)	6 (28.6%)	2 (13.3%)	0.002*
Deep vein thrombosis	14 (15.6%)	5 (38.5%)	2 (4.9%)	5 (23.8%)	2 (13.3%)	0.022*
Pulmonary embolism	7 (7.8%)	4 (30.8%)	0	2 (9.5%)	1 (6.7%)	0.004*
Superficial thrombophlebitis	2 (2.2%)	0	0	0	2 (13.3%)	0.017*

*P-values <0.05. P-values are multiple comparison between 4 groups and were estimated using Kruskal-Wallis test. Age, follow-up period and antiphospholipid score (aPL-S) are presented as the median (IQR: Interquartile range 25th -75th). N: number of patients, Wf: warfarin monotherapy, AP: antiplatelet monotherapy, Wf + AP: warfarin and antiplatelet combination therapy, DAPT: dual antiplatelet therapy, APS: antiphospholipid syndrome. SLE: systemic lupus erythematosus