Prevalence and Effect of Cerebral Small Vessel Disease in Stroke Patients With Aspirin Treatment Failure–A Hospital-Based Stroke Secondary Prevention Registry

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Background: Breakthrough strokes during treatment with aspirin, termed clinical aspirin treatment failure (ATF), is common in clinical practice. The burden of cerebral small vessel disease (SVD) is associated with an increased recurrent ischemic stroke risk. However, the association between SVD and ATF remains unclear. This study investigated the prevalence and clinical characteristics of SVD in stroke patients with ATF.

Methods: Data from a prospective, and multicenter stroke with ATF registry established in 2018 in Taiwan were used, and 300 patients who developed ischemic stroke concurrent with regular use of aspirin were enrolled. White matter lesions (WMLs) and cerebral microbleeds (CMBs) were identified using the Fazekas scale and Microbleed Anatomical Rating Scale, respectively. Demographic data, cardiovascular comorbidities, and index stroke characteristics of patients with different WML and CMB severities were compared. Logistic regression analyses were performed to explore the factors independently associated with outcomes after ATF.

Results: The mean patient age was 69.5 ± 11.8 years, and 70.0% of patients were men. Among all patients, periventricular WML (PVWML), deep WML (DWML), and CMB prevalence was 93.3, 90.0, and 52.5%, respectively. Furthermore, 46.0% of the index strokes were small vessel occlusions. Severe PVWMLs and DWMLs were significantly associated with high CMB burdens. Patients with moderate-to-severe PVWMLs and

DWMLs were significantly older and had higher cardiovascular comorbidity prevalence than did patients with no or mild WMLs. Moreover, patients with favorable outcomes exhibited significantly low prevalence of severe PVWMLs ($p = 0.001$) and DWMLs ($p = 0.001$). After logistic regression was applied, severe WMLs predicted less favorable outcomes independently, compared with those with no to moderate PVWMLs and DWMLs [odds ratio (OR), 0.47; 95% confidence interval (CI), 0.25–0.87 for severe PVWMLs; OR, 0.40; 95% CI, 0.21–0.79 for severe DWMLs].

Conclusions: SVD is common in stroke patients with ATF. PVWMLs and DWMLs are independently associated with functional outcomes in stroke patients with ATF. The burden of SVD should be considered in future antiplatelet strategies for stroke patients after ATF.

INTRODUCTION

Stroke is the second leading cause of death worldwide and results in disability in a large proportion of survivors (1). Ischemic strokes account for ∼80% of strokes (2). Cerebral small vessel disease (SVD) refers to a group of pathological processes involving the small arteries, arterioles, venules, and capillaries of the brain, such as lacunar infarcts, white matter lesions (WMLs), and cerebral microbleeds (CMBs) (3). SVD plays a critical role in stroke. The total burden of SVD was reported to be positively associated with the risk of recurrent ischemic strokes and intracerebral hemorrhage (ICH) in patients with a prior transient ischemic attack (TIA) or ischemic stroke (4).

Antiplatelet therapy is recommended for non-cardioembolic ischemic stroke treatment and prevention (5). Aspirin is the most commonly used antiplatelet agent for the secondary prevention of ischemic stroke because of its low cost and availability (6). Aspirin was determined to reduce the risk of ischemic stroke by 22% in secondary prevention (7). However, patients who develop an ischemic stroke during aspirin treatment, termed clinical aspirin treatment failure (ATF), represent 30–40% and 40–50% of patients with stroke in clinical trials (8–10), and in clinical practice (11–13), respectively.

ATF has been reported to be associated with old age, high prevalence of comorbidities, history of cardiovascular disease, and prior symptomatic cerebrovascular disease (10, 13). However, the characteristics and effect of SVD in ATF remain unclear. SVD is associated with an increased risk of recurrent ischemic stroke (4). In addition, SVD is associated with cerebral endothelium dysfunction (14) and impairment of brain network connectivity (15). Therefore, we hypothesized that SVD is associated with, and could affect the functional outcome of stroke with ATF. In this research, the prevalence and clinical characteristics of WMLs and CMBs were investigated in stroke patients with ATF.

MATERIALS AND METHODS
Participants

This study was conducted using data from a prospective, and multicenter registry of specific stroke patients with ATF, established in 2018 in Taiwan. Eligible patients were older than 20 years, developed an ischemic stroke (the index stroke) within 60 days before recruitment, and had a regular use of aspirin 7 days before the index stroke. The indication of aspirin was primary or secondary prevention of cardiovascular or cerebrovascular events, and the dose of aspirin was 50 to 100 mg per day according to the prescription of the physician. Patients who received intravenous thrombolysis and endovascular thrombectomy for the index stroke could be included. Exclusion criteria were a history of antiplatelet agents use other than aspirin, a known or high risk of cardioembolism, a history of anticoagulant use, an impaired medical adherence and contraindication to magnetic resonance imaging (MRI) examination.

A comprehensive evaluation, including demographic and medical history data collection, physical and neurological examination, blood biochemistry examination, carotid artery ultrasonography, transcranial color Doppler, and cerebral MRI with magnetic resonance angiography, was performed for each patient. The hypertension referred to either a diastolic and systolic blood pressure of ≥90 and ≥140 mmHg, respectively, or the use of antihypertensive medications. The hyperlipidemia referred to a total cholesterol ≥160 mg/dl or a low-density lipoprotein ≥100 mg/dl. The Essen Stroke Risk Score (ESRS), a 10-point scale derived from Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial (16), was applied to predict the risk of recurrent ischemic stroke after the index stroke, based on the cardiovascular comorbidities (17, 18). The diagnosis of ischemic stroke was confirmed by a neurologist based on the clinical symptoms of stroke and a cerebral MRI. Stroke severity was evaluated using the National Institutes of Health Stroke Scale (NIHSS) score, and functional outcomes were determined using the modified Rankin scale (mRS). Neurological deterioration was defined based on the increase in NIHSS scores during hospitalization or at discharge, compared with the initial NHISS. A favorable functional outcome was defined as an mRS score of 0–2 at discharge. The stroke subtype was classified according to the TOAST criteria (19).

WML and CMB Grading

All MRIs were performed following a standardized MRI protocol, including axial diffusion-weighted imaging, axial T2-weighted fluid-attenuated inversion recovery imaging (FLAIR), and gradient recalled echo (GRE) T2*-weighted imaging or susceptibility-weighted imaging (SWI) with whole-brain coverage. Four experienced stroke neurologists, blinded to the clinical course and outcome of the patients, assessed the WMLs and CMBs of the cerebral MRI by using FLAIR and GRE or SWI, respectively.

WMLs were visually determined to be periventricular WMLs (PVWMLs) and deep WMLs (DWMLs) using the modified Fazekas scale (20, 21), which is the most frequently used assessment tool for WMLs. The Fazekas scale is a 4-point scale: 0 (no WML), 1 (mild WML), 2 (moderate WML), and 3 (severe WML). The definition, location, and number of CMBs were determined using a validated visual rating scale, the Microbleed Anatomical Rating Scale (MARS) (22). Patients were divided into two subgroups: with and without CMBs.

Ethical Statements

All centers were required to receive approval from their Institutional Review Board before initiation of this study. All patients, or their legal representatives, provided written informed consent before inclusion.

Statistical Analysis

Statistical analysis was performed using SPSS (version 22.0). All statistical tests were two-tailed, and an $\alpha \geq 0.05$ was considered significant. Analysis of variance or independent student t-tests were used for continuous variables and chi-squared test was used for categorical variables to evaluate the differences and trends in demographic data, cardiovascular comorbidities, and severities and subtypes of the index stroke based on WML severity and CMB presence and burden.

Independent student t and the chi-square tests were performed to assess the differences in WMLs and CMBs between patients with and without a neurological deterioration and favorable outcome. Furthermore, a multivariable logistic regression analysis was conducted, in which a neurological deterioration and favorable outcome were used as dependent variables to compare the effect of WMLs and CMBs on the stroke outcome after ATF, after adjustment for the effects of age, sex, ESRS scores, and TOAST classification of the index stroke.

RESULTS

Study Participants

The cohort comprised 300 patients who developed an acute ischemic stroke during aspirin treatment, confirmed based on clinical symptoms and cerebral MRI. The mean age of the patients was 69.5 ± 11.8 years, and 70.0% of the patients were men. The mean ESRS score of the patients was 5.1 ± 1.3. For the index stroke, the mean initial and discharge NIHSS scores of the patients was 5.5 ± 5.0 and 4.8 ± 4.9, respectively. In the TOAST classification, 32.0% of strokes were large artery atherosclerosis and 46.0% were small vessel occlusions. The

TABLE 1 | Demographic characteristics of the participants.

N = 300 (CMB = 236)	
Age, year, mean (±SD)	69.5 (±11.8)
Sex, male, *n* (%)	210 (70.0)
BMI, mean (±SD)	25.2 (±4.0)
Medical history	
Hypertension, yes, *n* (%)	262 (87.3)
Diabetes, yes, *n* (%)	156 (52.0)
Hyperlipidemia, yes, *n* (%)	198 (66.0)
Stroke/TIA, yes, *n* (%)	212 (70.7)
Coronary artery disease, yes, *n* (%)	49 (16.3)
Essen stroke risk score, mean (±SD)	5.1 (±1.3)
Index stroke	
Initial NIHSS, mean (±SD)	5.5 (±5.0)
Discharge NIHSS, mean (±SD)	4.8 (±4.9)
Neurological deterioration, yes, *n* (%)	27 (9.0)
Favorable outcome (mRS 0–2), yes, *n* (%)	158 (52.7)
TOAST classification	
Large artery atherosclerosis, *n* (%)	96 (32.0)
Small vessel occlusion, *n* (%)	138 (46.0)
Fazekas Scale (periventricular), *n* (%)	
0	20 (6.7)
1	74 (24.7)
2	144 (48.0)
3	62 (20.7)
Fazekas Scale (deep white matter), *n* (%)	
0	30 (10.0)
1	126 (42.0)
2	90 (30.0)
3	54 (18.0)
Presence of CMB, yes, *n* (%)	124 (52.5)
Number of CMB, mean (±SD)	3.8 (±9.2)

CMB, cerebral microbleeds; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack.

demographic characteristics, prevalence of vascular risk factors, severities of the index stroke, and presence of SVD are displayed in **Table 1**.

WMLs

Among all patients, 93.3% had PVWMLs, and 90.0% had DWMLs. Furthermore, 74 (24.7%), 144 (48.0%), and 62 (20.7%) patients displayed mild, moderate, and severe PVWMLs, respectively; 126 (42.0%), 90 (30.0%), and 54 (18.0%) patients had mild, moderate, and severe DWMLs, respectively. The relationships between severities of WMLs, vascular risk factors, and stroke index are presented in **Tables 2**, **3**. The age differed significantly between patients with different severities of PVWMLs ($p_{trend} < 0.001$) and DWMLs ($p_{trend} < 0.001$). PVWML and DWML severities increased along with age. Furthermore, PVWMLs and DWMLs were significantly associated with numbers of CMBs ($p_{trend} = 0.004$ for PVWMLs, and $p_{trend} < 0.001$ for DWMLs). Patients with severe PVWMLs

TABLE 2 | Relationship between periventricular white matter lesions and characteristics of stroke patients with aspirin treatment failure.

Periventricular WML	Absent	Mild	Moderate	Severe	*p*-value	*p* for trend
N	20 (6.7%)	74 (24.7%)	144 (48.0%)	62 (20.7%)		
Age, year, mean (±SD)[a]	56.9 (±14.9)	63.9 (±10.6)	72.1 (±10.5)	74.4 (±9.8)	<0.001**	<0.001**
Sex, male, *n* (%)[b]	16 (80.0)	52 (70.3)	102 (70.8)	40 (64.5)	0.595	0.250
CMB, mean (±SD)[a]	1.9 (±7.5)	1.9 (±5.1)	2.9 (±6.9)	8.7 (±14.5)	<0.001**	0.004*
Medical history[b]						
Hypertension, yes, *n* (%)	11 (55.0)	66 (89.2)	129 (89.6)	56 (90.3)	<0.001**	0.005*
Diabetes, yes, *n* (%)	10 (50.0)	43 (58.1)	67 (46.5)	36 (58.1)	0.286	0.996
Hyperlipidemia, yes, *n* (%)	15 (75.0)	52 (70.3)	95 (66.0)	36 (58.1)	0.382	0.087
Stroke/TIA, yes, *n* (%)	13 (65.0)	48 (64.9)	102 (70.8)	49 (79.0)	0.307	0.073
Coronary artery disease, yes, *n* (%)	4 (20.0)	8 (10.8)	29 (20.1)	8 (12.9)	0.272	0.926
Essen stroke risk score, mean (±SD)[a]	4.1 (±1.4)	4.7 (±1.3)	5.3 (±1.2)	5.6 (±1.3)	<0.001**	<0.001**
Index stroke[a]						
Initial NIHSS, mean (±SD)	5.5 (±4.9)	5.6 (±5.7)	5.2 (±4.7)	6.2 (±4.8)	0.631	0.654
Discharge NIHSS, mean (±SD)	4.6 (±3.7)	4.8 (±5.5)	4.6 (±4.9)	5.5 (±4.4)	0.685	0.521
TOAST classification, *n* (%)[b]					0.012*	0.847
Large artery atherosclerosis	6 (30.0)	31 (41.9)	39 (27.1)	20 (32.3)		
Small vessel occlusion	6 (30.0)	26 (35.1)	76 (52.8)	30 (48.4)		

CMB, cerebral microbleeds; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack; WML, white matter lesions.
[a] Analysis of variance; [b] Chi-squared test.
*p < 0.05; **p < 0.001.

TABLE 3 | Relationship between deep white matter lesions and characteristics of stroke patients with aspirin treatment failure.

Deep WML	Absent	Mild	Moderate	Severe	*p*-value	*p* for trend
N	30 (10.0%)	126 (42.0%)	90 (30.0%)	54 (18.0%)		
Age, year, mean (±SD)[a]	58.7 (±13.8)	68.5 (±11.8)	72.1 (±9.6)	73.7 (±10.2)	<0.001**	<0.001**
Sex, male, *n* (%)[b]	22 (73.3)	92 (73.0)	64 (71.1)	32 (59.3)	0.293	0.104
CMB, mean (±SD)[a]	0.4 (±0.6)	2.3 (±6.1)	3.8 (±7.7)	9.0 (±15.6)	<0.001**	<0.001**
Medical history[b]						
Hypertension, yes, *n* (%)	23 (76.7)	110 (87.3)	80 (88.9)	49 (90.7)	0.278	0.110
Diabetes, yes, *n* (%)	16 (53.3)	70 (55.6)	41 (45.6)	29 (53.7)	0.528	0.575
Hyperlipidemia, yes, *n* (%)	19 (63.3)	88 (69.8)	58 (64.4)	33 (61.1)	0.660	0.426
Stroke/TIA, yes, *n* (%)	22 (73.3)	83 (65.9)	62 (68.9)	45 (83.3)	0.121	0.112
Coronary artery disease, yes, *n* (%)	2 (6.7)	20 (15.9)	21 (23.3)	6 (11.1)	0.095	0.536
Essen stroke risk score, mean (±SD)[a]	4.4 (±1.3)	5.0 (±1.4)	5.2 (±1.1)	5.6 (±1.4)	0.001*	<0.001**
Index stroke[a]						
Initial NIHSS, mean (±SD)	4.8 (±4.3)	5.5 (±5.1)	5.1 (±4.8)	6.7 (±5.5)	0.209	0.127
Discharge NIHSS, mean (±SD)	4.4 (±4.4)	4.6 (±4.8)	4.5 (±4.9)	6.1 (±5.1)	0.190	0.127
TOAST classification, *n* (%)[b]					0.089	0.848
Large artery atherosclerosis	10 (33.3)	43 (34.1)	25 (27.8)	18 (33.3)		
Small vessel occlusion	9 (30.0)	57 (45.2)	48 (53.3)	24 (44.4)		

CMB, cerebral microbleeds; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack; WML, white matter lesions.
[a] Analysis of variance; [b] Chi-squared test.
*p < 0.05; **p < 0.001.

and DWMLs had significantly high CMB burdens. The ESRS scores varied significantly between PVWMLs and DWMLs severity groups ($p_{trend} < 0.001$ for both). Patients with no or mild PVWMLs and DWMLs had significantly low ESRS scores. Patients with severe PVWMLs and DWMLs showed a trend toward a high prevalence of hypertension ($p_{trend} = 0.005$ for

PVWMLs and $p_{trend} = 0.110$ for DWMLs). Patients with severe PVWMLs and DWMLs had a trend toward an increase in initial and discharge NIHSS scores. Patients with moderate-to-severe PVWMLs had significantly high rates of stroke caused by small vessel occlusion, whereas the distribution of TOAST stroke subtype did not differ significantly based on DWML severity.

CMBs

In total, 236 patients were evaluated for CMBs. CMBs were identified in 124 (52.5%) patients; the mean number of CMBs was 3.8 ± 9.2. Among patients with CMBs, 41 (33.1%) patients had a single lesion, 39 (31.5%) had 2–4 CMBs, and 44 (35.5%) patients had ≥ 5 CMBs. The comparisons of demographic characteristics and detailed information for the index stroke between the dichotomous and burdens of CMBs are presented in **Table 4**.

For associations between CMBs and other parameters, no significant differences in age, sex, vascular risk factors, and ESRS scores were observed between patients with and without CMBs. The presence of CMBs was associated with moderate-to-severe PVWMLs ($p < 0.001$) and DWMLs ($p < 0.001$). There were increasing prevalence of moderate-to-severe PVWMLs and DWMLs along with increasing CMBs burden ($p_{trend} < 0.001$ for both). No association was observed between the presence and burden of CMBs and the severity of the index stroke, indicated by initial and discharge NIHSS scores. The distribution of the TOAST stroke subtype differed significantly between patients with and without CMBs ($p = 0.011$). A high prevalence of stroke due to small vessel occlusion was observed in patients with CMBs.

Index Stroke Outcomes

For the outcome of the index stroke, 27 (9.0%) patients experienced a neurological deterioration, and 158 (52.7%) patients had a favorable functional outcome. The relationships between neurological deterioration, favorable functional outcomes, and SVD severity are presented in **Table 5**. Neurological deterioration was not associated with age, sex, presence of WMLs and CMBs, and TOAST stroke subtype. Patients with favorable outcomes were significantly younger ($p < 0.001$), and a larger proportion of patients was male ($p = 0.009$) and with low cardiovascular comorbidities ($p < 0.001$), compared to patients with unfavorable outcomes. Furthermore, PVWML and DWML severities were associated with functional outcomes. Patients with severe PVWMLs and DWMLs had less favorable outcomes compared with those with no to moderate PVWMLs and DWMLs ($p = 0.001$ for both). The presence and number of CMBs were not associated with functional outcomes.

After logistic regression was applied, the severe PVWMLs and DWMLs were associated with non-significant risks of increased neurological deterioration. Severe WMLs predicted significantly less favorable outcomes independently, compared with those with no to moderate PVWMLs and DWMLs [odds ratio (OR), 0.47; 95% confidence interval (CI), 0.25–0.87 for severe PVWMLs; OR, 0.40; 95% CI, 0.21–0.79 for severe DWMLs]. The burden of CMBs was not associated with a neurological deterioration and functional outcome (**Table 6**).

DISCUSSION

The present study reported the prevalence and clinical characteristics of SVD in ATF. The prevalence of PVWMLs, DWMLs and CMBs were 93.3, 90.0, and 52.5%, respectively. Age and cardiovascular comorbidities, particularly hypertension, were major risks for both PVWMLs and DWMLs in ATF.

The severity of PVWMLs and DWMLs increased with age. Small vessel occlusion contributed to the most of ischemic stroke with ATF, compared with other TOAST classifications. Both PVWMLs and DWMLs were associated with functional outcomes after stroke. Furthermore, the extent of WMLs was associated with the CMB burden. However, CMBs were not significantly associated with stroke severity, neurological deterioration, or functional outcomes.

ATF is associated with increased cardiovascular event and mortality risks (23). Therefore, patients with ATF require a comprehensive investigation to identify the contributing factors. Different categories of ATF can be distinguished in stroke patients. ATF may exceed functional resistance to aspirin, and could be associated with multiple factors, including advanced age, non-compliance, pharmacodynamic interaction, comorbidities, and undetected cardioembolic sources or atherosclerotic disease (13, 23, 24). In addition, ischemic stroke with ATF could be associated with prior ischemic stroke, particularly lacunar stroke (10, 12, 25). However, to the best of our knowledge, the burden of SVD in stroke patients with ATF has not been well-established.

The prevalence of moderate-to-severe PVWMLs and DWMLs in Asian stroke patients are estimated at 40–53%, and 29–41%, respectively (26, 27). CMBs are present in 20–40% of stroke patients (28). The cohort of stroke with ATF in this study has numerically higher prevalence of WMLs and CMBs than general stroke patients. In addition, a positive relationship between WMLs severity and CMBs burden was demonstrated. The presence and burden of WMLs and CMBs indicate endothelial dysfunction (14), which contribute to platelet activation (29), and then decrease platelet response to aspirin. In addition, the severity of WMLs was positively correlated with cardiovascular comorbidities, which could contribute to aspirin resistance via cyclooxygenase (COX)-1-independent mechanisms (30). The small vessel occlusions of the TOAST classification contributed to 46.0% of stroke after ATF in this study, a higher incidence compared to that of other Asian countries (31–33). Therefore, the high SVD burden could be associated with ATF in stroke patients.

The presence of severe PVWMLs and DWMLs was independently associated with an unfavorable short-term functional outcome in stroke patients with ATF, which was in line with reports regarding outcomes of general stroke patients with WMLs (34, 35). Recovery from stroke involves widespread neural network to compensate for the damaged neural connections (36). SVD are associated with impairment of neural connectivity, which supports the finding that WMLs could contribute to poor functional outcome in stroke patients with ATF.

The optimal antiplatelet regimen for patients with stroke and ATF remains undetermined. Moreover, the safety should be considered when determining antiplatelet regimens in patients with ATF. A meta-analysis suggested that adding to or replacing aspirin with another antiplatelet agent is associated with fewer recurrent stroke and cardiovascular events than maintaining aspirin monotherapy (37). Clopidogrel is the most used alternative antiplatelet agent in ATF. However, the therapeutic efficacy was heterogeneous. Two cohort studies in Asia indicated that dual antiplatelet therapy (DAPT; clopidogrel

TABLE 4 | Relationship between cerebral microbleeds and characteristics of stroke patients with aspirin treatment failure.

	Cerebral microbleeds (N = 236)							
	Dichotomous			**Burden**				
	No CMB	**CMB**	**p-value**	**0**	**1–4**	**≥5**	**p-value**	**p for trend**
N	112 (47.5%)	124 (52.5%)		112	80	44		
Age, year, mean (±SD)[a]	68.6 (±13.3)	69.9 (±11.0)	0.419	68.6 (±13.3)	69.4 (±12.0)	70.8 (±8.9)	0.585	0.302
Sex, male, n (%)[b]	81 (72.3)	79 (63.7)	0.157	81 (72.3)	51 (63.7)	28 (63.6)	0.368	0.207
Moderate-to-severe PVWML, n (%)[b]	64 (57.1)	99 (79.8)	<0.001**	64 (57.1)	62 (77.5)	37 (84.1)	0.001*	<0.001**
Moderate-to-severe DWML, n (%)[b]	41 (36.6)	78 (62.9)	<0.001**	41 (36.6)	45 (56.3)	33 (75.0)	<0.001**	<0.001**
Medical history[b]								
Hypertension, yes, n (%)	95 (84.8)	107 (86.3)	0.748	95 (84.8)	69 (86.3)	38 (86.4)	0.950	0.770
Diabetes, yes, n (%)	59 (52.7)	62 (50.0)	0.681	59 (52.7)	44 (55.0)	18 (40.9)	0.297	0.294
Hyperlipidemia, yes, n (%)	75 (67.0)	80 (64.5)	0.692	75 (67.0)	53 (66.3)	27 (61.4)	0.796	0.548
Stroke/TIA, yes, n (%)	78 (69.6)	88 (71.0)	0.824	78 (69.6)	52 (65.0)	36 (81.8)	0.142	0.275
Coronary artery disease, yes, n (%)	21 (18.8)	18 (14.5)	0.382	21 (18.8)	14 (17.5)	4 (9.1)	0.330	0.185
Essen stroke risk score, mean (±SD)[a]	5.2 (±1.4)	5.1 (±1.2)	0.517	5.2 (±1.4)	5.1 (±1.1)	5.0 (±1.4)	0.760	0.474
Index stroke[a]								
Initial NIHSS, mean (±SD)	5.9 (±5.0)	5.5 (±5.3)	0.540	5.9 (±5.0)	5.0 (±4.7)	6.2 (±6.4)	0.386	0.695
Discharge NIHSS, mean (±SD)	5.1 (±4.8)	4.7 (±5.0)	0.536	5.1 (±4.8)	4.5 (±4.6)	5.2 (±5.8)	0.601	0.928
TOAST classification, n (%)[b]			0.011*				0.101	0.118
Large artery atherosclerosis	46 (41.1)	28 (22.6)		46 (41.1)	18 (22.5)	10 (22.7)		
Small vessel occlusion	38 (33.9)	64 (51.6)		38 (33.9)	41 (51.2)	23 (52.3)		

CMB, cerebral microbleeds; DWML, deep white matter lesions; NIHSS, National Institutes of Health Stroke Scale; PVWML, periventricular white matter lesions; SD, standard deviation; TIA, transient ischemic attack.

[a]Independent student t test and analysis of variance.

[b]Chi-squared test.

*p < 0.05; **p < 0.001.

TABLE 5 | Risk factors and predictors for neurological deterioration and favorable outcome in stroke patients with aspirin treatment failure.

	Neurological deterioration		p-value	Favorable outcome (mRS 0–2)		p-value
	Absent	Present		Absent	Present	
N	273 (91.0%)	27 (9.0%)		142 (47.3%)	158 (52.7%)	
Age, year, mean (±SD)[a]	69.3 (±11.8)	71.9 (±12.1)	0.273	73.0 (±11.1)	66.4 (±11.7)	<0.001**
Sex, male, n (%)[b]	195 (71.4)	15 (55.6)	0.086	89 (62.7)	121 (76.6)	0.009*
Essen stroke risk score, mean (±SD)[a]	5.1 (±1.3)	5.4 (±1.2)	0.288	5.4 (±1.3)	4.8 (±1.3)	<0.001**
Severe PVWML, n (%)[b]	55 (20.1)	7 (25.9)	0.479	41 (28.9)	21 (13.3)	0.001*
Severe DWML, n (%)[b]	48 (17.6)	6 (22.2)	0.549	37 (26.1)	17 (10.8)	0.001*
Presence of CMB, yes, n (%)[b]	113 (52.1)	11 (57.9)	0.626	56 (49.1)	68 (55.7)	0.309
Number of CMB, mean (±SD)[a]	4.0 (±9.5)	2.3 (±4.2)	0.455	3.4 (±7.0)	4.2 (±10.9)	0.516
CMB ≥ 5, yes, n (%)[b]	41 (18.9)	3 (15.8)	0.739	22 (19.3)	22 (18.0)	0.803
TOAST classification, n (%)[b]			0.598			0.584
Large artery atherosclerosis	86 (31.5)	10 (37.0)		47 (33.1)	49 (31.0)	
Small vessel occlusion	127 (46.5)	11 (40.7)		62 (43.7)	76 (48.1)	

CMB, cerebral microbleeds; DWML, deep white matter lesions; mRS, modified Rankin scale; PVWML, periventricular white matter lesions; SD, standard deviation.
[a]Independent student t-test.
[b]Chi-squared test.
*p < 0.05; **p < 0.001.

TABLE 6 | A multivariable logistic regression analysis to estimate the odds ratio (OR) of burdens of white matter lesions and cerebral microbleeds for neurological deterioration and favorable outcome in stroke patients with aspirin treatment failure.

	Neurological deterioration		Favorable outcome (mRS 0–2)	
	OR (95% CI)	p-value[a]	OR (95% CI)	p-value[a]
PVWML				
Fazekas 0–2 (N = 238)	1 (Reference)		1 (Reference)	
Fazekas 3 (N = 62)	1.20 (0.46–3.10)	0.709	0.47 (0.25–0.87)	0.016*
DWML				
Fazekas 0–2 (N = 246)	1 (Reference)		1 (Reference)	
Fazekas 3 (N = 54)	1.08 (0.40–2.91)	0.885	0.40 (0.21–0.79)	0.008*
CMB				
0 (N = 112)	1 (Reference)		1 (Reference)	
1–4 (N = 80)	1.37 (0.46–4.02)	0.572	1.63 (0.86–3.09)	0.135
≥5 (N = 44)	0.91 (0.22–3.81)	0.896	1.23 (0.57–2.64)	0.592

CI, confidence interval; CMB, cerebral microbleeds; DWML, deep white matter lesions; mRS, modified Rankin scale; PVWML, periventricular white matter lesions.
[a]Multivariable logistic regression analysis, adjusted for age, sex, Essen stroke risk score, and TOAST classification of the index stroke.
*p < 0.05.

plus aspirin) or clopidogrel monotherapy was associated with reduced recurrent vascular events in patients with ATF than was aspirin monotherapy (38, 39). However, the Secondary Prevention of Small Subcortical Strokes Trial (SPS3) cohort reported that the addition of clopidogrel to aspirin therapy did not reduce vascular events compared with aspirin monotherapy in patients with a lacunar stroke with ATF (10).

Ticagrelor, a direct-acting antiplatelet agent that reversibly binds and inhibits the P2Y12 receptor on platelets, has been investigated for secondary vascular events prevention after acute ischemic stroke. In ischemic stroke with ATF, treatment with ticagrelor could reduce the risk of recurrent ischemic stroke, but increase combination of major or minor bleedings (40). However, combination of ticagrelor and aspirin does not decrease the incidence of composite of stroke or death and disabling stroke compared with aspirin after ischemic stroke with ATF (41, 42).

Cilostazol was the second most commonly used antiplatelet agent after ATF to add to or replace aspirin in an Asian cohort (39). The cilostazol monotherapy reduced recurrent, ischemic and hemorrhagic stroke compared with aspirin, and cilostazol combination with aspirin or clopidogrel did not increase hemorrhagic stroke prevalence in patients with non-cardioembolic stroke (43).

The burden of SVD has a predictive value for ICH after TIA or ischemic stroke (4), particularly among those with multiple CMBs receiving treatment with antiplatelet agents (44). Therefore, the optimal antiplatelet strategy

after ATF warrants further consideration, given the SVD burden. Cilostazol reduced hemorrhagic stroke prevalence in patients with multiple CMBs and reduced total stroke in patients with mild-to-moderate WMLs compared with aspirin (45). However, evidence on the safety of antiplatelet regimens in patients combined with ATF and SVD is scarce.

The novelty of this study is that the clinical association between SVD and ATF was well-presented. The association between WMLs and poor functional outcome in stroke patients with ATF was shown to be significant. However, there are several limitations to our study. First, this study adapted a cross-sectional and observational design, and there is no control group in this registry. Therefore, it limited the interpretation of causal association of SVD on ATF. In addition, we could not determine the long-term effect of SVD on stroke recurrence and cognition after adjustment of antiplatelet regimens. Second, all patients in this study were Taiwanese, limiting the generalizability to other populations. Third, the registry enrolled stroke patients taking aspirin regularly 7 days before the index stroke. However, the precise duration of aspirin treatment before the index stroke was not recorded.

In conclusion, WMLs severity is highly correlated with age, cardiovascular comorbidities and CMBs burden. PVWMLs and DWMLs are significantly associated with functional outcomes in stroke patients with ATF. Further antiplatelet strategy after ATF considering the burden of SVD should be warranted.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of all centers in this study. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

H-HH and A-CC: study concept, design, and supervision. P-SC, P-SS, C-HLiu, Y-FS, R-CT, C-HLie, HP, S-CH, Y-TT, T-SC, and S-LW: acquisition and integrity of data. P-SC, P-SS, C-HLiu, and Y-FS: analysis and interpretation of data, statistical analysis and drafting the article. All authors contributed to the critical revision of the article for important intellectual content, agreed to the final version of the manuscript.

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