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Prognosis and antiplatelet therapy of small single subcortical infarcts in penetrating artery territory: a post hoc analysis of the Third China National Stroke Registry

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ABSTRACT

Background Small single subcortical infarction (SSSI) may be classified as parent artery disease-related or only branch involved according to the stenosis of parent artery. The study aimed to evaluate short-term and long-term prognoses and the effectiveness of antiplatelet therapy in SSSI.

Methods We prospectively enrolled 2890 patients with SSSI from the Third China National Stroke Registry (CNSR-III) database from August 2015 to March 2018. We assessed clinical outcomes and antiplatelet treatment effects in patients with SSSI with and without parent artery stenosis (PAS) identified by magnetic resonance angiography.

Results Among 2890 patients with SSSI in the perforator territory of the middle cerebral artery and the basilar artery, there were 680 (23.53%) patients with PAS and 2210 (76.47%) patients without PAS, respectively. After adjusting for potential confounders, the PAS group had a greater initial stroke severity (OR 1.262, 95% CI 1.058 to 1.505; p=0.0097) and a higher risk of ischaemic stroke recurrence at 3 months (OR 2.266, 95% CI 1.631 to 3.149; p<0.0001) and 1 year (OR 2.054, 95% CI 1.561 to 2.702; p<0.0001), as well as composite vascular events at 3 months (OR 2.306, 95% CI 1.674 to 3.178; p<0.0001) and 1 year (OR 1.983, 95% CI 1.530 to 2.570; p<0.0001), compared with the non-PAS group. In both groups, dual antiplatelet therapy was not superior to single antiplatelet therapy in preventing stroke recurrence, composite vascular events and disability.

Conclusion PAS related to significantly higher rates of short-term and long-term stroke recurrence and composite vascular events, suggesting heterogeneous mechanisms in SSSI subgroups. The effectiveness of antiplatelet therapy for SSSI needs further investigation.

Key messages

What is already known on this topic

- Small single subcortical infarction (SSSI) in perforator territory has heterogeneous pathogenesis regarding the presence of parent artery disease.

What this study adds

- In this study, parent artery stenosis (PAS) was related to significantly higher rates of short-term and long-term stroke recurrence and composite vascular events. For SSSI, dual antiplatelet therapy was not superior to single antiplatelet therapy in preventing stroke recurrence, composite vascular events and disability.

How this study might affect research, practice or policy

- PAS can help predict the prognosis of SSSI and can be used as a solid standard in risk stratification. The antiplatelet therapy in second prevention for SSSI needs further investigation.

INTRODUCTION

Small single subcortical infarction (SSSI), commonly known as lacunar stroke, constitutes about 25% of ischaemic strokes.[1] It is defined as a small (<20 mm transversal diameter) lesion in the territory of a penetrating arteriole,[2] such as the basal ganglia, internal capsule and brainstem. Two major vascular pathologies of the brain damage have been suggested in patients with small-sized penetrating brain arteries and arterioles: (1) thickening of the arterial media and (2) obstruction of the origins of penetrating arteries by parent artery intimal plaques.[3] Thus, not only small-vessel disease but also large-artery atherosclerosis could result in SSSI.

Generally, SSSI is thought to have a more favourable outcome compared with other subtypes of stroke, such as atherothrombotic stroke and cardiogenic stroke.[4] Some studies on SSSI prognosis have produced

inconsistent or incomplete results due to overestimating the role of infarct size rather than different arterial pathology.[5] However, another study suggested no clinical and lesion-size differences between SSSI with or without parent artery stenosis (PAS); that is, there seemed to be no rationale for a specific size criterion for small-vessel infarction.[6] In addition, aspirin plus clopidogrel is accepted as effective antiplatelet therapy for reducing stroke recurrence in minor stroke and high-risk transient ischaemic attack (TIA).[7 8] However, in a Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) subgroup analysis, it is not significantly different from aspirin alone in preventing recurrent stroke for patients with and without intracranial artery stenosis (ICAS) .[9] Thus, less is known about the difference in prognosis and second prevention between the two aetiopathogeneses.

In this prespecified imaging substudy of the Third China National Stroke Registry (CNSR-III), we divided SSSI into parent artery-related and penetrating artery-related based on current imaging technology. The present study aimed to evaluate short-term and long-term prognoses and the effectiveness of dual antiplatelet therapy (DAPT) on preventing recurrent stroke in patients with SSSI of different aetiologies.

METHODS

Cohort

We derived data from the CNSR-III database. The protocol for case identification and data collection has been previously reported elsewhere.[10] Briefly, the CNSR-III is a nationwide clinical registry of ischaemic stroke or TIA based on aetiology, imaging and biological markers in China from August 2015 to March 2018. Consecutive patients were recruited consecutively if they were (1) aged >18 years, (2) patients with physician-diagnosed ischaemic stroke or TIA, (3) within 7 days from the onset of symptoms to enrolment and (4) patients who have provided consent to participant in the study. Patients were excluded if they had silent cerebral infarction with no symptoms or signs, or those who refused to participate in the registry.

Study population

Patients were included in this study if they had a single small infarction in the perforator territory of middle cerebral artery (MCA) and basilar artery (BA) (diameter <20 mm) based on diffusion-weighted imaging (DWI) sequence in the MRI subgroup. Patients were excluded if the infarction caused by other aetiologies according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[11] We also excluded patients missing data of magnetic resonance angiography (MRA), modified Rankin Scale (mRS), ischaemic stroke recurrence and composite vascular events. After these exclusions, our primary study population consisted of 2890 patients with acute isolated infarction (shown in figure 1).

Data collection and management

Patient information, including demographics, risk factors, comorbidities, medications, selected laboratory tests and

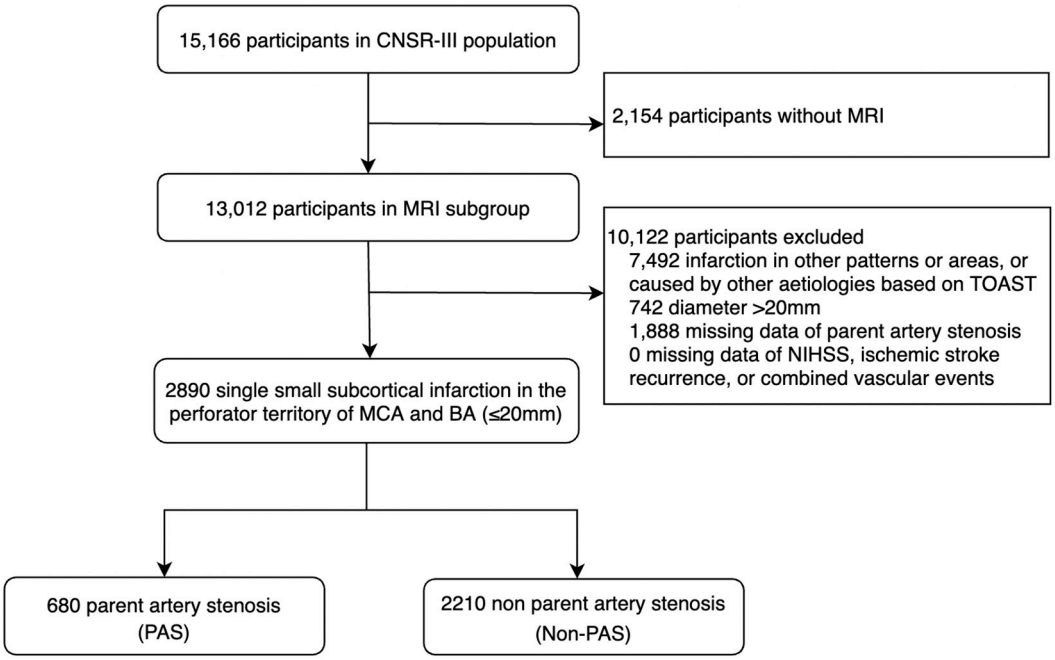

Figure 1 Study population. BA, basilar artery; CNSR-III, Third China National Stroke Registry; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PAS, parent artery stenosis; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

hospital-level characteristics, was collected systematically during hospitalisation and at discharge by trained research coordinators at each participating hospital. National Institutes of Health Stroke Scale (NIHSS) score at admission, ischaemic stroke recurrence, composite vascular event and mRS score at 3 months and 1 year after stroke onset were also collected.

Antiplatelet regimen types included single antiplatelet therapy (SAPT), DAPT, and none or missing. The SAPT was defined as aspirin at a dose of 100 mg/day or clopidogrel at a dose of 75 mg/day for the first 21 days. The DAPT was defined as clopidogrel at an initial dose of 300 mg followed by 75 mg/day for the first 21 days, plus aspirin at a dose of 100 mg/day. Based on the PAS and antiplatelet use, patients were further divided into four subgroups: PAS+DAPT, PAS+SAPT, non-PAS+DAPT and non-PAS+SAPT.

MRI analysis and Interpretation

All patients underwent MRI on a 3T MR scanner. Imaging sequences obtained included three-dimensional time-of-flight MRA (repetition time, 20–25 ms; echo time, 3.3–3.9 ms; flip angle, 15°–20°; slice thickness, 0.65–1.0 mm); axial T2-weighted imaging (repetition time, 4500 ms; echo time, 8 ms); T1-weighted imaging (repetition time, 1200 ms; echo time, 11 ms); fluid-attenuated inversion recovery sequences (repetition time, 7000 ms; echo time, 94 ms); and diffusion-weighted imaging (repetition time, 3000 ms; echo time, 75 ms). All aforementioned sequences except MRA had 5 mm slice thickness and a 1.5 mm interslice gap.

MRIs were collected from individual centres in digital format and were reviewed centrally by two readers (JJ and Y-YX) blinded to the patients' clinical details. They reached a consensus if they disagreed on interpretations (shown in figure 2A–H).

On DWI, SSSIs were required to meet MRI criteria that included a lesion measuring less than 20 mm in diameter. Intracranial arteries were analysed with three-dimensional time-of-flight MRA. PAS was defined as any degree of MCA stenosis for basal ganglia infarcts or BA stenosis for pons infarcts. Infarctions and PAS were in the same sagittal plane (for infarction in the perforator territory of MCA) or axial plane (for infarction in the perforator territory of BA) according to multiweighted sequences.

Follow-up and clinical outcome evaluations

Patients were followed up for clinical outcomes at 3 months and 1 year annually. Information including functional status, cardiovascular/cerebrovascular events, recommended secondary prevention medication compliance and risk factor control was collected at each follow-up.

NIHSS score on administration was used as the index of stroke severity, and mRS score at discharge was used as the index of functional outcome. Disability was defined as an mRS score of ≥3. Composite vascular events were defined as ischaemic stroke, haemorrhagic stroke, myocardial infarction or vascular death. Our study examined patient-relevant outcomes of mRS score, haemorrhagic stroke, ischaemic stroke recurrence, and composite vascular events at 3 months and 1 year.

Ischaemic stroke was defined as an acute focal infarction of the brain or retina with one of the following: sudden onset of a new focal neurological deficit lasting fewer than 24 hours with clinical or imaging evidence of infarction, or rapid worsening of an existing focal neurological deficit lasting 24 hours or more, with imaging evidence of new ischaemic changes clearly distinct from the index ischaemic event. Haemorrhagic stroke was defined as acute extravasation of blood into the brain parenchyma or subarachnoid space with associated neurological symptoms.

Statistical analysis

Categorical variables were reported as absolute numbers with percentages, and continuous variables were reported as mean along with SD. Multivariable logistic regression analyses were used to investigate the associations between parental artery stenosis and outcomes (NIHSS score, mRS

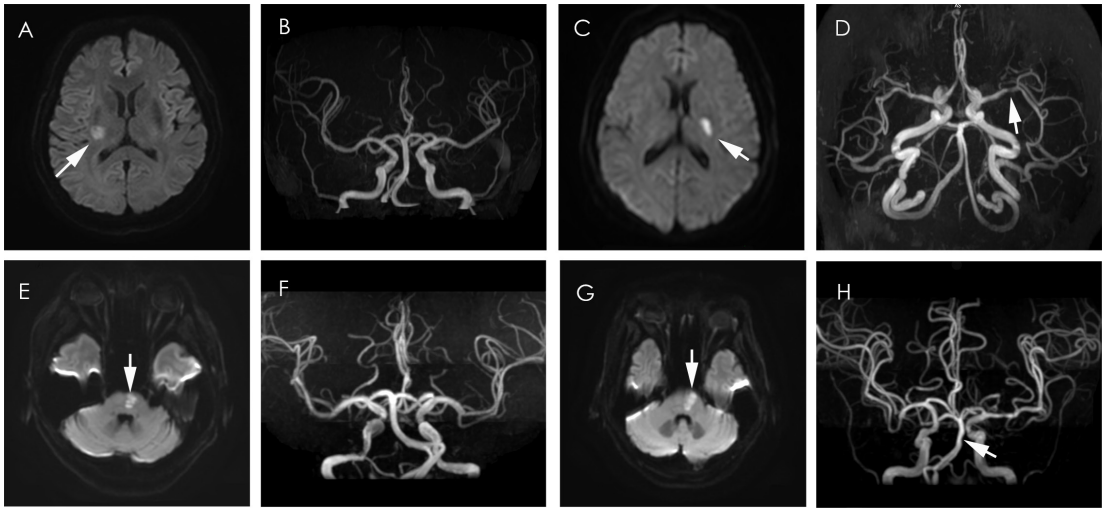

Figure 2 SSSI with and without parent artery stenosis in the MCA and BA perforator Territory. (A,B) SSSI (arrow) without disease of MCA. (C,D) SSSI (arrow) with MCA stenosis (arrow). (E,F) SSSI (arrow) without disease of BA (arrow). (G,H) SSSI (arrow) with BA stenosis (arrow). BA, basilar artery; MCA, middle cerebral artery; SSSI, small single subcortical infarction.

score, recurrent ischaemic stroke and composite vascular events). Age, sex, hypertension, diabetes mellitus and smoking were included in the model. Cumulative event curves were constructed with the Kaplan-Meier method for 3 month and 1 year recurrent ischaemic stroke and composite vascular events. In addition, we assessed whether outcomes differed in certain prespecified subgroups by different treatment with the use of multivariable logistic regression. The 'PAS+DAPT' subgroup was selected as the reference. Patients without antiplatelet therapy or missing data (n=72) were excluded in this model. Adjust factors included age, sex, hypertension, diabetes mellitus and smoking. All p values were two-sided, with p<0.05 considered statistically significant. All statistical analyses were performed using SAS V.9.4 software.

RESULTS

Characteristics of study participants

Among 2890 patients with SSSI (shown in figure 1), 680 (23.53%) patients had PAS and 2210 (76.47%) did not have PAS. Table 1 displayed the demographic, clinical and hospital characteristics according to the stenosis of the parent artery.

Patients with PAS were more likely to be female (39.12% vs 27.51%, p<0.0001) and older (64.23±10.35 vs 60.90±10.80, p<0.0001), and had a greater prevalence of cardiovascular risk factors (hypertension, diabetes mellitus and smoking) (p<0.0001) and a higher level of haemoglobin A1c (HbA1c) and low-density lipoprotein (LDL) (p<0.0001). The types of antiplatelet and lipid-lowering therapy for second prevention showed no difference between the two groups. In addition, there were significant differences in stroke recurrence, composite vascular events and function dependence at both 3 months and 1 year. However, haemorrhagic stroke was very rare and of no significant difference in both groups.

Association between PAS and outcomes

The number and rates of NIHSS at admission, stroke recurrence and other outcomes are listed in table 2 according to groups with and without PAS. After adjusting for potential confounders, we found that patients with PAS had a greater initial stroke severity (OR 1.262, 95% CI 1.058 to 1.505; p=0.0097) and a higher risk of ischaemic stroke recurrence at 3 months (OR 2.266, 95% CI 1.631 to 3.149; p<0.0001) and 1 year (OR 2.054, 95% CI 1.561 to 2.702; p<0.0001), as well as composite vascular events at 3 months (OR 2.306, 95% CI 1.674 to 3.178; p<0.0001) and 1 year (OR 1.983, 95% CI 1.530 to 2.570; p<0.0001), compared with the non-PAS group. However, no significant association between stenosis and mRS was observed at 3 months and 1 year after adjustment.

Risk of stroke recurrence and composite vascular events at 3 months and 1 year

Figure 3 showed Kaplan-Meier curves describing the time to event for the stroke recurrence, composite vascular events at 3 months and 1 year in the PAS and non-PAS groups. Kaplan-Meier survival curves showed that the 3-month rate of freedom from stroke recurrence was 89.56% of the PAS group and 94.89% of the non-PAS group (p<0.0001); the 1-year rate was 83.38% of the PAS group and 90.49% of the non-PAS group (p<0.0001) (shown in figure 3A,C).

The same result could be observed in composite vascular events. The curves indicated that composite vascular events increased for patients with stenosis at 3 months (p<0.0001) and 1 year (p<0.0001) (shown in figure 3B,D).

Antiplatelet therapy

Table 3 showed the regression model results respectively, by PAS and the therapy. The rates of ischaemic stroke recurrence and composite vascular events were significantly different between PAS and non-PAS groups. In PAS group, after considering for multiple testing, DAPT was not superior to SAPT in preventing composite vascular events (OR 0.563, 95% CI 0.330 to 0.963; p=0.0358) and improving functional outcome (OR 0.561, 95% CI 0.337 to 0.937; p=0.0270). There was no statistically significant evidence on the effects of DAPT versus SAPT on stroke recurrence and disability in the non-PAS group.

DISCUSSION

This national hospital-based study indicated that over three quarters of infarction occurred in SSSI patients without PAS. Furthermore, we found that the diagnosis of PAS could efficiently stratify the risk of recurrent stroke and composite vascular events within 3 months and 1 year of SSSI, while the parent disease was not associated with disability in both short and long terms. Our study may have important clinical implications with the large sample size of patients with SSSI included and comprehensive prognostic characteristics recorded.

In this study, we described the epidemiological characteristics of the short-term and long-term prognoses of SSSI. Our data showed that the characteristics of SSSI are heterogeneous between PAS and non-PAS groups. Compared with the non-PAS, PAS was more likely to be related to atherosclerosis indicators. Our observation was consistent with the previous studies that diabetes and coronary heart disease were more prevalent in patients with large-artery atherosclerosis than in those with small-vessel disease,[12 13] while in a study on subcortical infarction in MCA territory, there were no clinical differences between infarctions caused by MCA and small vessels.[6] Atherosclerosis indicators, including hypertension, diabetes and smoking, could cause not only intracranial atherosclerosis but also microatheroma and lipohyalinosis.[14 15] However, it remains unknown which pathological change is dominant and symptomatic in certain high-risk populations.

The proportion of minor strokes at admission (NIHSS score <4) was 52.28% in our study. Three-month and 1-year ischaemic stroke recurrences were 5.26% and 7.79%, respectively. Nearly 90% of patients had favourable

Table 1 Baseline characteristics

Characteristics	Total N=2890	Non-PAS n=2210 (76.47%)	PAS n=680 (23.53%)	P value
Age	61.68±10.79	60.90±10.80	64.23±10.35	<0.0001
BMI	24.84±3.30	24.85±3.29	24.82±3.35	0.4375
Sex (female), n (%)	874 (30.24)	608 (27.51)	266 (39.12)	<0.0001
Medical history, n (%)				
Ischaemic stroke	544 (18.82)	400 (18.10)	144 (21.18)	0.0727
TIA	42 (1.45)	31 (1.40)	11 (1.62)	0.6821
Myocardial infarction	39 (1.35)	26 (1.18)	13 (1.91)	0.1462
Atrial fibrillation	71 (2.46)	48 (2.17)	23 (3.38)	0.0746
Hypertension	1924 (66.57)	1411 (63.85)	513 (75.44)	<0.0001
Hyperlipidaemia	210 (7.27)	157 (7.10)	53 (7.79)	0.5444
Diabetes mellitus	693 (23.98)	487 (22.04)	206 (30.29)	<0.0001
Peripheral artery disease	23 (0.80)	17 (0.77)	6 (0.88)	0.7716
Smoking, n (%)	955 (33.04)	787 (35.61)	168 (24.71)	<0.0001
HbA1c (%)	6.55±1.72	6.45±1.67	6.89±1.82	<0.0001
Missing	1175	896	279	
LDL (mmol/L)	2.56±1.07	2.51±1.05	2.71±1.13	<0.0001
Missing	116	82	34	
Antiplatelet therapy, n (%)				
Single antiplatelet	1196	929 (42.04)	267 (39.26)	0.3449
Dual antiplatelet	1622	1229 (55.61)	393 (57.79)	
None or missing	72	52 (2.35)	20 (2.94)	
Statin therapy, n (%)				
Statin standard treatment	727 (25.16)	551 (24.93)	176 (25.88)	0.6843
Statin intensive treatment	2163 (74.84)	1659 (75.07)	504 (74.12)	0.6175
Thrombolytic therapy, n (%)	176 (6.09)	139 (6.29)	37 (5.44)	0.4185
MRI features				
Diameter of infarction	11.51±4.41	11.47±4.36	11.69±4.60	0.2017
Outcomes, n (%)				
NIHSS score				
<4	1511 (52.28)	1195 (54.07)	316 (46.47)	0.0005
≥4	1379 (47.72)	1015 (45.93)	364 (53.53)	
3 months				
Ischaemic stroke	152 (5.26)	87 (3.94)	65 (9.56)	<0.0001
Composite vascular event	160 (5.54)	91 (4.12)	69 (10.15)	<0.0001
Haemorrhagic stroke	4 (0.14)	2 (0.09)	2 (0.29)	0.2117
mRS score				
0–2	2547 (89.34)	1973 (90.50)	574 (85.54)	0.0003
3–6	304 (10.66)	207 (9.50)	97 (14.46)	
Missing	39	30	9	
12 months				
Ischaemic stroke	225 (7.79)	137 (6.20)	88 (12.94)	<0.0001
Composite vascular events	254 (8.79)	157 (7.10)	97 (14.26)	<0.0001
Haemorrhagic stroke	19 (0.66)	14 (0.63)	5 (0.74)	0.7739
mRS score				
0–2	2561 (90.78)	1986 (92.03)	575 (86.73)	<0.0001
3–6	260 (9.22)	172 (7.97)	88 (13.27)	
Missing	69	52	17	

BMI, body mass index; HbA1c, haemoglobin A1c; LDL, low-density lipoprotein; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PAS, parent artery stenosis; TIA, transient ischaemic attack.

Table 2 Associations of stenosis and outcomes

				Unadjusted		Adjusted	
		Total	Events, n (%)	OR (95% CI)	P value	OR (95% CI)	P value
NIHSS score ≥4	Non-PAS	2210	1015 (45.93)	Reference	–	Reference	–
	PAS	680	364 (53.53)	1.356 (1.142 to 1.611)	0.0005	1.262 (1.058 to 1.505)	0.0097
3 months							
mRS score 3–6*	Non-PAS	2210	207 (9.50)	Reference	–	Reference	–
	PAS	680	97 (14.46)	1.611 (1.244 to 2.086)	0.0003	1.200 (0.902 to 1.598)	0.2112
Ischaemic stroke recurrence	Non-PAS	2210	87 (3.94)	Reference	–	Reference	–
	PAS	680	65 (9.56)	2.475 (1.795 to 3.414)	<0.0001	2.266 (1.631 to 3.149)	<0.0001
Composite vascular events	Non-PAS	2210	91 (4.12)	Reference	–	Reference	–
	PAS	680	69 (10.15)	2.516 (1.840 to 3.441)	<0.0001	2.306 (1.674 to 3.178)	<0.0001
1 year							
mRS score 3–6*	Non-PAS	2210	172 (7.97)	Reference	–	Reference	–
	PAS	680	88 (13.27)	1.767 (1.345 to 2.322)	<0.0001	1.266 (0.939 to 1.708)	0.1225
Ischaemic stroke recurrence	Non-PAS	2210	137 (6.20)	Reference	–	Reference	–
	PAS	680	88 (12.94)	2.163 (1.655 to 2.827)	<0.0001	2.054 (1.561 to 2.702)	<0.0001
Composite vascular events	Non-PAS	2210	157 (7.10%)	Reference	–	Reference	–
	PAS	680	97 (14.26%)	2.090 (1.623 to 2.693)	<0.0001	1.983 (1.530 to 2.570)	<0.0001

Adjustment for baseline characteristics includes age, sex, history of hypertension, history of diabetes and smoking.
*(mRS) Adjustment for baseline characteristics includes age, sex, history of hypertension, history of diabetes, smoking and NIHSS score.
CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratios; PAS, parent artery stenosis.

functional outcomes in both the short and long terms. Similarly, a systematic review in the UK indicated that the risk of recurrence among lacunar patients during the first month ranged from 0% to 4%, and that from 1 month to 12 months was 5%–8%.[16] In a CHANCE subgroup study, stroke recurrence rates of the single acute infarction group was 8.68%.[17] Our study confirmed these general findings but also indicated a differentiation by infarct aetiology.

Louis Caplan first used branch atheromatous disease to describe an occlusion or stenosis at the origin of a deep penetrating artery of the brain,[18] either isolated micro-atheromata in the branch's orifice or plaques seated in the wall of the parent artery, leading to a small internal

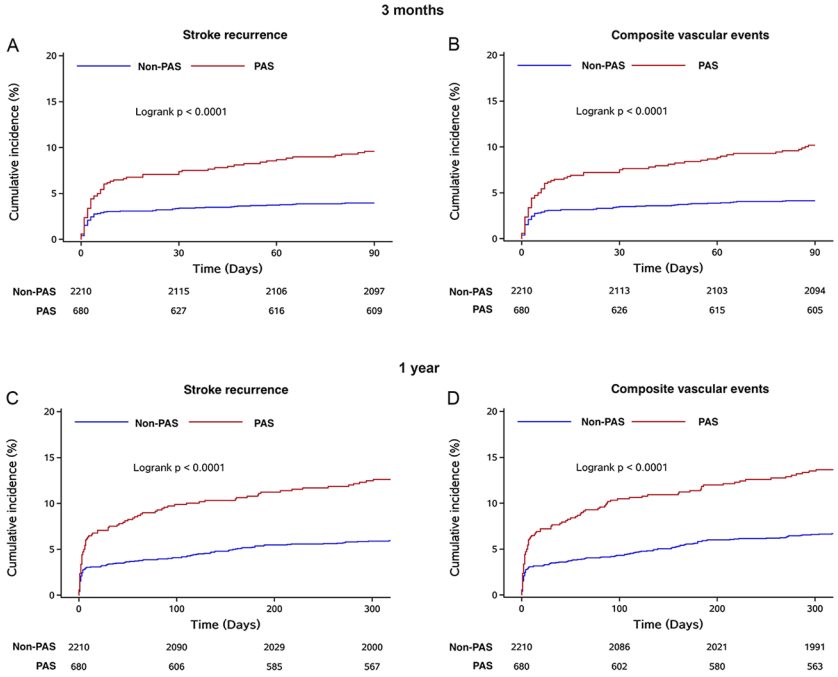

Figure 3 Probability of survival free of stroke recurrence, composite vascular events in 3 months and 1 year. PAS, parent artery stenosis.

Table 3 Outcomes at 3 months by PAS and antiplatelet therapy

Outcomes at 3 months		Total N=2818	Events, n (%)	Unadjusted OR (95% CI)	Unadjusted P value	Adjusted OR (95% CI)	Adjusted P value
Recurrence of ischaemic stroke	PAS+DAPT	393	44 (11.2)	Reference	–	Reference	–
	PAS+SAPT	267	19 (7.12)	0.627 (0.366 to 1.073)	0.0887	0.605 (0.352 to 1.039)	0.0687
	Non-PAS+DAPT	1229	51 (4.15)	0.361 (0.241 to 0.541)	<0.0001	0.392 (0.260 to 0.590)	<0.0001
	Non-PAS+SAPT	929	36 (3.88)	0.338 (0.218 to 0.526)	<0.0001	0.363 (0.232 to 0.567)	<0.0001
Composite vascular events	PAS+DAPT	393	47 (11.96)	Reference	–	Reference	–
	PAS+SAPT	267	19 (7.12)	0.586 (0.344 to 0.998)	0.0493	0.563 (0.330 to 0.963)	0.0358
	Non-PAS+DAPT	1229	54 (4.39)	0.358 (0.242 to 0.529)	<0.0001	0.389 (0.262 to 0.579)	<0.0001
	Non-PAS+SAPT	929	37 (3.98)	0.325 (0.211 to 0.500)	<0.0001	0.347 (0.225 to 0.537)	<0.0001
Haemorrhagic stroke	PAS+DAPT	393	1 (0.25)	Reference	–	Reference	–
	PAS+SAPT	267	0	0	0.9980	0	0.9982
	Non-PAS+DAPT	1229	2 (0.16)	0.638 (0.058 to 7.036)	0.7136	0.753 (0.066 to 8.658)	0.8200
	Non-PAS+SAPT	929	0	0	0.9963	0	0.9962
mRS 3–6 (missing 25)*	PAS+DAPT	388	60 (15.46)	Reference	–	Reference	–
	PAS+SAPT	263	33 (12.55)	0.784 (0.497 to 1.239)	0.2975	0.561 (0.337 to 0.937)	0.0270
	Non-PAS+DAPT	1220	106 (8.69)	0.520 (0.370 to 0.731)	0.0002	0.672 (0.465 to 0.972)	0.0350
	Non-PAS+SAPT	912	99 (10.86)	0.666 (0.471 to 0.940)	0.0209	0.731 (0.501 to 1.066)	0.1034

Adjustment for baseline characteristics includes age, sex, history of hypertension, history of diabetes and smoking.
*(mRS) Adjustment for baseline characteristics includes age, sex, history of hypertension, history of diabetes, smoking and NIHSS.
CI, confidence interval; DAPT, dual antiplatelet therapy; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratios; PAS, parent artery stenosis; SAPT, single antiplatelet therapy.

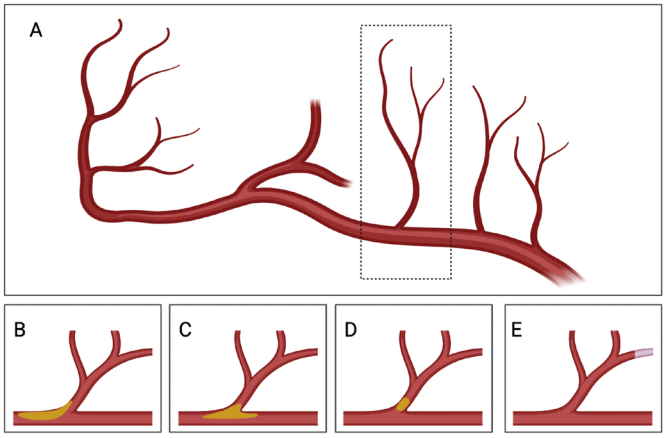

Figure 4 Presumed mechanism of infarcts in penetrating artery territory. (A) Plaque in parent artery obstructing a branch. (B) Junctional plaque extending into the branch. (C) Microatheroma formed at the orifice of a branch. (D) Emboli from unstable microatheromatous plaque. (E) Fibrinoid degeneration or lipohyalinosis of the distal perforating artery. Y-YZ drew and created this figure with full permission. The authors confirm that this figure was not a reuse of previously published work.

capsule or pontine infarct (shown in figure 4). Thus, PAS could help to predict the prognosis of SSSI and be used as a solid standard in risk stratification. In this study, we found that the PAS predicts higher NIHSS score at admission, ischaemic stroke recurrence and composite vascular events after adjusting for age and other known predictors of poor outcome in stroke. In a subgroup study of CHANCE, severe ICAS or occlusion doubles the risk of recurrent stroke in minor stroke and TIA.[9] Our study was consistent with previous studies and indicated that PAS increased short-term and long-term risk in stroke recurrence and composite vascular events in SSSI. We also examined the relationship between PAS and functional disability at 3 months and 1 year. However, it did not provide differences regarding disability in the short and long terms after considering the NIHSS score at admission and related risk factors. Therefore, PAS was a crucial aetiology of SSSI and plays a significant role in stroke recurrence, despite not being related to the severity of disability.

In our study, dual antiplatelet use had no absolute advantage over single antiplatelet use on stroke recurrence, composite vascular events and disability. Previous research has indicated that DAPT was more efficient in treating ischaemic stroke caused by large-artery atherosclerosis.[19] Despite the finding that the PAS group could be more related to intracranial atherosclerosis, DAPT was not superior to SAPT on preventing composite vascular events and improving functional outcome. The fact that patients with PAS in our study did not have significantly more indicators of atherosclerosis than non-PAS ones might be one underlying cause. In addition, antiplatelet regimes were not related to good outcomes in patients without PAS. The results confirmed the findings of previous studies that DAPT was not associated with the reduction in recurrent strokes in single small strokes. In a subgroup analysis of the CHANCE study, patients who had minor stroke with single acute infarction seem to benefit less from dual antiplatelet treatment.[17] The Secondary Prevention of Small Subcortical Strokes trial indicated that dual antiplatelet treatment did not reduce the risk of ischaemic stroke.[20] This finding indicates that in different types of ischaemic cerebrovascular disease, the role of platelets and the components of thrombosis are different. The reason might be that thrombosis may have a minimal role in precipitating occlusions of small penetrating cerebral arteries.[2] A study indicating that procoagulant platelets are lower in lacunar stroke than non-lacunar stroke confirmed the suggestion.[21]

Meanwhile, in this study, DAPT did not increase haemorrhagic stroke. Our result was consistent with previous studies. In the CHANCE study and the Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation Management, and Avoidance (CHARISMA) trial, the risk of intracranial bleeding did not increase when clopidogrel was added to aspirin.[8 22] While in the Platelet-Oriented Inhibition in New TIA and Minor Ischaemic Stroke trial, the increase of haemorrhagic stroke in the dual antiplatelet group might be due to the prolonged usage of clopidogrel.[7]

Therefore, the effective therapy for secondary prevention in SSSI needs further investigation.

Limitations

First, parent artery disease might be underdiagnosed in our study.[23 24] High-resolution and ultrafield MRI has been proven capable of revealing cerebral perforating arteries[25 26] and describing in much more detail intracranial vessel wall changes.[27] That might enhance our understanding of the mechanism of stroke in the territory of perforating arteries.[28]

Second, it seems very difficult to identify the aetiologies more detailed by current clinical routine imaging examinations. Isolated atherosclerosis in the branch's orifice or mild plaque occluding the orifice cannot be detected even by high-resolution MRI. White matter intensity and other MRI markers could be evidence for cerebral small-vessel disease. However, atherosclerotic lesions, microatheroma and fibrohyalinosis often coexist, and the aetiologies are challenging to distinguish. Thus, the distinction criteria of aetiologies we used were practical and critical in clinical practice.

Third, in this study, we were unable to evaluate early neurological deterioration, which is a characteristic clinical manifestation in acute pontine or basilar ganglia infarction and might relate to unfavourable outcomes.[14 29]

Fourth, we did not have detailed data about TOAST classification of recurrent ischaemic strokes in follow-up. One study suggested that cardiogenic embolism might contribute to stroke recurrence in patients who had lacunar stroke.[30] This could explain the non-ideal efficacy of DAPT in our study. However, there was evidence that

recurrent strokes were more likely to be lacunar if the index event was lacunar.[16] Thus, the mechanism of SSSI and the recurrence needs further investigation.

CONCLUSION

In conclusion, PAS is related significantly to higher short-term and long-term stroke recurrence and composite vascular events, suggesting heterogeneous mechanisms in SSSI subgroups. The antiplatelet therapy in the second prevention of SSSI needs further investigation.

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