ORIGINAL RESEARCH

Long-Term Prognostic Implications of Cerebral Microbleeds in Chinese Patients With Ischemic Stroke

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***Background*—**This study was performed to determine the clinical correlates and long-term prognostic implications of microbleed burden and location in Chinese patients with ischemic stroke.

***Methods and Results*—**We recruited 1003 predominantly Chinese patients with ischemic stroke who received magnetic resonance imaging at the University of Hong Kong. We determined the clinical correlates of microbleeds and the long-term risks (3126 patient-years of follow-up) of recurrent ischemic stroke and intracerebral hemorrhage (ICH) by microbleed burden (0 versus 1, 2–4, and ≥5) and location, adjusting for age, sex, and vascular risk factors and stratified by antithrombotic use. Microbleeds were present in 450 of 1003 of the study population (119/450 had ≥5, 187/450 had mixed location). Having ≥5 microbleeds was independently associated with prior antiplatelet and anticoagulant use, whereas microbleeds of mixed location were independently associated with hypertension and prior anticoagulant use (all $P<0.05$). Microbleed burden was associated with an increased risk of ICH (microbleed burden versus no microbleeds: 1 microbleed: multivariate hazard ratio: 0.59 [95% confidence interval, 0.07–5.05]; 2–4 microbleeds: multivariate hazard ratio: 2.14 [95% confidence interval, 0.50–9.12]; ≥5 microbleeds: multivariate hazard ratio: 9.51 [95% confidence interval, 3.25–27.81]; $P_{trend}<0.0001$), but the relationship of microbleed burden and risk of recurrent ischemic stroke was not significant ($P_{trend}=0.054$). Similar findings were noted in the 862 of 1003 patients treated with antiplatelet agents only (ICH: $P_{trend}<0.0001$; ischemic stroke $P_{trend}=0.096$). Multivariate analysis revealed that, independent of vascular risk factors, antithrombotic use, and other neuroimaging markers of small vessel disease, having ≥5 microbleeds (multivariate hazard ratio: 6.08 [95% confidence interval, 1.11–33.21]; $P=0.037$) was identified as an independent predictor of subsequent ICH, but neither microbleed burden nor location was predictive of recurrent ischemic stroke risk.

***Conclusions*—**In Chinese patients with ischemic stroke, a high burden of cerebral microbleeds was significantly associated with an increased risk of ICH; however, neither microbleed location nor burden was associated with recurrent ischemic stroke risk. **(*J Am Heart Assoc*. 2017;6:e007360. DOI: 10.1161/JAHA.117.007360.)**

Key Words: cerebral microbleed • intracerebral hemorrhage • ischemic stroke

Cerebral microbleeds are markers of underlying small vessel disease (SVD) burden.[1] They may be due to extravasation of red blood cells as a result of small vessel rupture or blood–brain barrier dysfunction (most commonly caused by hypertensive or cerebral amyloid angiopathy) but also may be secondary to an ischemic insult.[2,3]

Recent systematic reviews have demonstrated that the risk of recurrent ischemic stroke and intracerebral hemorrhage (ICH) increases with microbleed burden and that the risk of ICH increases more steeply than that of recurrent ischemic stroke.[4] Studies included in this systematic review, however, were small in sample size or had a short duration of follow-up

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Clinical Perspective

What Is New?

- In a large cohort of Chinese patients with ischemic stroke, we demonstrated that a high burden (≥5) of cerebral microbleeds is independently associated with an increased risk of intracerebral hemorrhage on long-term follow-up.
- Neither microbleed burden nor location was associated with risk of recurrent ischemic stroke after adjusting for confounding factors.
- In ischemic stroke patients on antiplatelet agents, the 5-year absolute risk of recurrent ischemic stroke outweighs that of intracerebral hemorrhage in patients with <5 cerebral microbleeds.
- In patients with ≥5 cerebral microbleeds, the 5-year absolute risk of intracerebral hemorrhage approached that of recurrent ischemic stroke.

What Are the Clinical Implications?

- Our findings suggest that in ischemic stroke patients, presence of cerebral microbleeds should not be considered a contraindication to antiplatelet agents if there are <5, as the risk of recurrent ischemic stroke outweighs the risk of intracerebral hemorrhage in this group of patients.
- In patients with ≥5 cerebral microbleeds, the long-term risk of intracerebral hemorrhage is similar to that of recurrent ischemic stroke; therefore, the potential risks and benefits of antiplatelet agents in this group of patients would need to be carefully balanced.

(15 studies with ≈9500 patient-years of follow-up).[4] The majority of these studies did not stratify results by antithrombotic use,[4] potentially resulting in heterogeneity. Furthermore, significant ethnic differences in microbleed location exist.[4] Asians with transient ischemic attack or ischemic stroke have a high prevalence of microbleeds of mixed location (8–40% versus 5–15% in white cohorts), whereas white patients with transient ischemic attack or ischemic stroke have a high prevalence of strictly lobar microbleeds (29–58% versus 6–27% in Asian cohorts), suggesting potential ethnic differences in underlying SVD etiology.[4] It appears that patients with microbleeds of mixed location have the highest risk of recurrent ischemic stroke or ICH,[4] but the underlying risk factors leading to this particularly severe subgroup of SVD remains uncertain. Finally, although recent small studies have shown that susceptibility-weighted imaging has superior reliability and sensitivity for microbleed detection compared with T2* gradient echo,[5,6] studies using susceptibility-weighted imaging in determining the prevalence and prognostic implications of microbleeds are scarce.[4]

We recently validated the prognostic value of the total SVD score and studied the prognostic implications of the individual components of the score, including microbleeds, in a large cohort of predominantly Chinese patients with ischemic stroke.[7] Because cerebral microbleeds are important predictors of subsequent ICH, we provide further details about the clinical and imaging correlates of microbleed burden and location and their long-term prognostic outcomes, stratified by antithrombotic use, in a large cohort of 1003 predominantly Chinese patients with ischemic stroke (≈3100 patient-years of follow-up), using susceptibility-weighted imaging.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

We prospectively studied 1076 predominantly Chinese patients with a diagnosis of acute ischemic stroke who received a magnetic resonance imaging (MRI) scan incorporating a hemosiderin-sensitive sequence at the University of Hong Kong MRI unit from March 1, 2008, to September 30, 2014.[7,8]

All patients gave written informed consent, or assent was obtained from relatives of patients who were unable to provide consent. The study was approved by the local research ethics committee.

We collected demographic data, atherosclerotic risk factors, premorbid antithrombotic use, details of hospitalization for the index event, and medications on discharge during face-to-face interviews and cross-referenced these with primary care and hospital records. Cause of ischemic stroke was classified according to the modified TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.[9] Ischemic stroke subtype was classified according to functional outcome, which was estimated by calculating the modified Rankin Scale on discharge.

All patients were scanned using a 3-T MRI scanner (Achieva; Philips Healthcare), and microbleeds were detected using susceptibility-weighted imaging. Details of scan parameters were provided in our previous publications.[7,8] A senior neuroradiologist (H.K.F.M.) supervised the interpretation of the MRI scans. Microbleeds were defined as rounded, hypodense foci up to 10 mm in size and were differentiated from microbleed mimics.[10] The locations and numbers of microbleeds were scored according to the Microbleed Anatomical Rating Scale,[11] and microbleed burden was graded as 0, 1, 2 to 4, and ≥5, as per recent systematic reviews.[4] The severity of white matter hyperintensity (WMH) was determined according to the Fazekas scale.[12] Subcortical WMH was graded as 0 (absent), 1 (puntate foci), 2 (beginning confluence of foci), and 3 (large confluent areas). Periventricular WMH was graded as 0 (no WMH except for small triangular foci surrounding the frontal horns), 1 (periventricular WMH surrounding the anterior and posterior horns with or without

Table 1. Clinical and Imaging Characteristics of the Study Population

Baseline Clinical Characteristics (N=1003)	Results
Age, y, mean (SD)	69 (12)
Male (%)	601 (60)
Hypertension (%)	657 (66)
Diabetes mellitus (%)	284 (28)
Hyperlipidemia (%)	256 (26)
Ever smokers (%)	297 (30)
Atrial fibrillation (%)	130 (13)
Prior antiplatelet use (%)	218 (22)
Prior warfarin use (%)	20 (2)
Prior NOAC use (%)	3 (0.3)
Imaging characteristics	
Delay of scan from assessment, d, median (IQR)	4 (3–6)
Patients with microbleeds, n (%)	450 (45)
Patients with 1 microbleed, n (%)	184 (18)
Patients with 2–4 microbleeds (%)	147 (15)
Patients with ≥5 microbleeds (%)	119 (12)
Patients with strictly deep microbleeds (%)	61 (6)
Patients with strictly lobar microbleeds (%)	161 (16)
Patients with strictly infratentorial microbleeds (%)	41 (4)
Patients with microbleeds of mixed location (%)	187 (19)
Patients with Fazekas grade 3 subcortical WMH (%)	155 (15)
Patients with Fazekas grade 3 periventricular WMH (%)	30 (3)
Patients with >20 basal ganglia PVSs* (%)	69 (7)
Patients with >20 centrum semiovale PVSs* (%)	101 (10)
Patients with lacunes*	430 (44)
Postevent antithrombotic use	
Antiplatelets only	
Single antiplatelet, n (%)	725 (72)
Dual antiplatelet, n (%)	137 (14)
Anticoagulants only	
Warfarin, n (%)	50 (5)
NOAC, n (%)	35 (3)
Combined anticoagulant and antiplatelet, n (%)	19 (2)
Not on antithrombotic agents, n (%)	37 (4)
Outcome	
Follow-up time, mo, mean	37±20
Patient-years of follow-up	3126
Recurrent stroke, n (%)	113 (11)
Ischemic, n (%)	93 (9)
Fatal, n (%)	13 (14)
Intracerebral hemorrhage, n (%)	20 (2)
Fatal, n (%)	6 (30)
Death, n (%)	130 (13)
Vascular death, n (%)	60 (46)

IQR indicates interquartile range; NOAC, non–vitamin K antagonist oral anticoagulant; PVS, perivascular space; WMH, white matter hyperintensity.
*Data missing for 29 patients.

discrete WMHs), 2 (extensive patchy WMHs and their early confluent stages), and 3 (confluent, completely surrounding lateral ventricles). Basal ganglia (BG) and centrum semiovale perivascular spaces were defined as small (<3 mm) punctate (if perpendicular to the plane of scan) or linear (if longitudinal to the plane of scan) hyperintensities on T2 images in the BG or centrum semiovale based on a previously validated scale.[13] Lacunes were defined as rounded or ovoid lesions; >3 and <20 mm in diameter; in the BG, internal capsule, centrum semiovale, or brainstem; of cerebrospinal fluid signal density on T2 and FLAIR; and with no increased signal on diffusion-weighted imaging.[14] The intrarater κ for interpretation of microbleed burden (0, 1, 2–4, and ≥5) in 50 randomly selected scans was 0.81, and the interrater κ was 0.84.

As part of routine clinical care, recruited patients were followed up by a clinician every 3 to 6 months or more frequently if indicated. All patients were assessed for the following clinical outcomes: (1) recurrent stroke (ischemic and hemorrhagic) and (2) mortality. The definition of recurrent stroke required a sudden new neurological deficit fitting the definition of ischemic stroke or ICH, occurring after a period of unequivocal neurological stability and not attributable to cerebral edema, mass effect, or hemorrhagic transformation of the incident cerebral infarction. Patients with suspected recurrent stroke received repeated neuroimaging in the form of cranial computed tomography or MRI to support the diagnosis. Vascular death was defined as death due to lethal cardiac arrhythmias, acute coronary syndrome, congestive heart failure, fatal stroke, pulmonary embolism, aortic dissection, or unexplained sudden death. If needed, details of clinical outcomes were supplemented by electronic or paper medical records from individual primary care practices, hospitals, and the Deaths General Register Office.

Statistical Analyses

We determined the clinical predictors of a high (≥5) microbleed burden and of microbleeds of mixed location by determining relationships with age, male sex, vascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, smoking, atrial fibrillation), renal impairment (defined as a glomerular filtration rate <60 mL/min per 1.73 m^2, according

Table 2. Clinical Correlates of a High Burden (≥5) of Cerebral Microbleeds*

	Univariate OR (95% CI)	*P* Value	Age- and Sex-Adjusted OR (95% CI)	*P* Value	Multivariate† Adjusted OR (95% CI)	*P* Value
Age	1.01 (1.00–1.03)	0.096	1.02 (1.00–1.03)	0.066	0.98 (0.96–1.00)	0.090
Male sex	1.26 (0.85–1.88)	0.26	1.33 (0.89–1.99)	0.17	1.28 (0.78–2.11)	0.33
Hypertension	1.65 (1.07–2.55)	0.024	1.57 (1.01–2.44)	0.047	1.66 (0.98–2.79)	0.057
Diabetes mellitus	0.88 (0.57–1.36)	0.56	0.85 (0.55–1.32)	0.47	0.77 (0.46–1.28)	0.31
Hyperlipidemia	0.93 (0.60–1.46)	0.76	0.96 (0.61–1.49)	0.84	0.79 (0.47–1.34)	0.38
Ever smoker	1.04 (0.68–1.57)	0.87	0.94 (0.60–1.49)	0.79	1.07 (0.64–1.79)	0.79
Atrial fibrillation	0.96 (0.54–1.72)	0.90	0.86 (0.47–1.55)	0.61	0.56 (0.26–1.24)	0.15
GFR <60 mL/min/1.73 m^2	1.95 (1.28–2.98)	0.002	1.84 (1.18–2.87)	0.007	1.54 (0.92–2.59)	0.10
Premorbid antiplatelet use	1.38 (0.89–2.14)	0.15	1.29 (0.83–2.02)	0.26	2.01 (1.17–3.47)	0.012
Premorbid anticoagulant use	2.11 (0.77–5.79)	0.15	2.01 (0.73–5.54)	0.18	4.47 (1.17–17.10)	0.029
Fazekas grade 3 subcortical WMH	4.69 (3.09–7.13)	<0.0001	3.41 (2.33–4.99)	<0.0001	3.62 (2.24–5.85)	<0.0001
Fazekas grade 3 periventricular WMH	9.65 (4.58–20.35)	<0.0001	6.62 (3.09–14.17)	<0.0001	8.63 (3.58–20.84)	<0.0001
>20 Basal ganglia PVSs	7.79 (4.61–13.15)	<0.0001	4.33 (2.57–7.28)	<0.0001	6.07 (3.25–11.34)	<0.0001
>20 Centrum semiovale PVSs	0.89 (0.46–1.71)	0.72	1.43 (0.88–2.33)	0.15	0.72 (0.35–1.50)	0.38
Lacunes	1.28 (0.87–1.89)	0.21	1.36 (0.99–1.89)	0.062	1.25 (0.80–1.94)	0.33

CI indicates confidence interval; GFR, glomerular filtration rate; OR, odds ratio; PVS, perivascular space; WMH, white matter hyperintensity.
*Compared with <5 microbleeds as reference.
†Age, sex, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, smoking history, GFR <60 mL/min/1.73 m^2, and all neuroimaging markers of small vessel disease.

to the Chronic Kidney Disease Epidemiology Collaboration equation for Asian populations[15]), and premorbid use of antiplatelet agents or anticoagulants, as well as other neuroimaging markers of SVD (subcortical and periventricular WMH, BG and centrum semiovale perivascular spaces, lacunes). Logistic regression was used in a univariate model

Table 3. Clinical Characteristics of Patients With No, Strictly Deep, and Strictly Lobar Microbleeds and Microbleeds of Mixed Location

	No Microbleeds (n=553)	Strictly Deep Microbleeds (n=61)	Strictly Lobar Microbleeds (n=161)	Microbleeds of Mixed Location (n=187)	*P* Value
Age, y (SD)	68 (12)	68 (13)	70 (12)	72 (12)	0.001
Male sex	321 (58)	37 (61)	92 (57)	123 (66)	0.27
Hypertension	340 (62)	38 (62)	112 (70)	140 (75)	0.005
Diabetes mellitus	152 (28)	14 (23)	50 (31)	52 (28)	0.66
Hyperlipidemia	138 (25)	11 (18)	47 (29)	48 (26)	0.39
Ever smoker	155 (28)	16 (26)	53 (33)	60 (32)	0.50
Atrial fibrillation	79 (14)	7 (12)	17 (11)	24 (13)	0.63
GFR <60 mL/min/1.73 m^2	102 (19)	8 (13)	39 (25)	56 (30)	0.002
Premorbid antiplatelet use	118 (21)	14 (23)	34 (21)	45 (24)	0.87
Premorbid anticoagulant use	12 (2)	0 (0)	2 (1)	8 (4)	0.14
Fazekas grade 3 subcortical WMH	58 (11)	11 (18)	20 (12)	60 (32)	<0.0001
Fazekas grade 3 periventricular WMH	8 (1)	2 (3)	1 (1)	18 (10)	<0.0001
>20 basal ganglia PVSs	20 (4)	4 (7)	8 (5)	35 (19)	<0.0001
>20 centrum semiovale PVSs	43 (8)	9 (15)	18 (11)	25 (13)	0.087
Lacunes	221 (42)	33 (55)	65 (41)	94 (51)	0.046

Data are shown as count (percentage) unless otherwise noted. GFR indicates glomerular filtration rate; PVS, periventricular space; WMH, white matter hyperintensity.

Table 4. Clinical Correlates of Cerebral Microbleeds of Mixed Location

	Unadjusted OR (95% CI)	*P* Value	Age- and Sex-Adjusted OR (95% CI)	*P* Value	Multivariate* Adjusted OR (95% CI)	*P* Value
Age	1.03 (1.01–1.04)	0.0002	1.03 (1.02–1.04)	<0.0001	1.01 (1.00–1.03)	0.13
Male sex	1.36 (0.97–1.90)	0.071	1.51 (1.07–2.12)	0.018	1.50 (1.00–2.25)	0.052
Hypertension	1.72 (1.20–2.47)	0.003	1.55 (1.08–2.24)	0.019	1.58 (1.05–2.39)	0.029
Diabetes mellitus	0.97 (0.68–1.38)	0.86	0.92 (0.64–1.31)	0.64	0.81 (0.54–1.21)	0.29
Hyperlipidemia	1.01 (0.70–1.45)	0.96	1.05 (0.73–1.52)	0.80	0.96 (0.64–1.45)	0.85
Ever smoker	1.15 (0.82–1.63)	0.41	1.05 (0.71–1.53)	0.82	1.16 (0.77–1.74)	0.48
Atrial fibrillation	0.99 (0.61–1.59)	0.95	0.79 (0.48–1.29)	0.35	0.56 (0.30–1.05)	0.070
GFR <60 mL/min/1.73 m^2	1.83 (1.28–2.62)	0.001	1.52 (1.04–2.21)	0.030	1.34 (0.88–2.05)	0.17
Premorbid antiplatelet use	1.18 (0.82–1.71)	0.39	1.02 (0.70–1.50)	0.91	1.31 (0.84–2.03)	0.24
Premorbid anticoagulant use	2.39 (1.00–5.72)	0.051	2.19 (0.91–5.30)	0.081	4.33 (1.42–13.25)	0.010
Fazekas grade 3 subcortical WMH	3.59 (2.47–5.21)	<0.0001	3.41 (2.33–4.99)	<0.0001	2.56 (1.70–3.87)	<0.0001
Fazekas grade 3 periventricular WMH	7.14 (3.37–15.09)	<0.0001	6.62 (3.09–14.17)	<0.0001	5.68 (2.49–12.97)	<0.0001
>20 basal ganglia PVSs	5.15 (3.12–8.53)	<0.0001	4.33 (2.57–7.28)	<0.0001	3.35 (1.90–5.90)	<0.0001
>20 centrum semiovale PVSs	1.46 (0.90–2.37)	0.13	1.43 (0.88–2.33)	0.15	1.33 (0.79–2.25)	0.28
Lacunes	1.37 (1.00–1.89)	0.052	1.36 (0.99–1.89)	0.062	1.29 (0.91–1.84)	0.16

CI indicates confidence interval; GFR indicates glomerular filtration rate; OR, odds ratio; PVS, periventricular space; WMH, white matter hyperintensity.
*Age, sex, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, smoking, GFR <60 mL/min/1.73 m^2, and all neuroimaging markers of small vessel disease.

adjusted for age and sex and in a multivariate adjusted model, adjusted for all variables. A cutoff of ≥5 was used because having ≥5 microbleeds has been shown in recent systematic reviews to be associated with a steep rise in ICH risk compared with <5 microbleeds.[4]

We used Kaplan–Meier survival analysis to calculate the 5-year risk of recurrent ischemic stroke and ICH among all patients, censored at death or March 31, 2015. Risks of adverse events by microbleed burden and microbleed location were compared with the log-rank test. We also used competing-risks regression[16] to estimate the subdistribution hazard ratios (SHRs) for development of a recurrent ischemic stroke and ICH in patients with presence of microbleeds and with 1, 2 to 4, and ≥5 microbleeds, compared with those with no microbleeds as a reference. Death was treated as a competing risk event in the analysis of recurrent ischemic stroke and ICH, whereas noncardiovascular death was treated as a competing risk event for vascular death. Three models were used: (1) an unadjusted model, (2) a model adjusted for age and sex, and (3) a model adjusted for age, sex, and vascular risk factors known to be associated with stroke and death, including hypertension, hyperlipidemia, diabetes mellitus, smoking history, and atrial fibrillation. We stratified our analysis by antithrombotic use by performing subgroup analyses of 862 antiplatelet users (anticoagulant users excluded), 50 patients on warfarin, and 35 patients on non–vitamin K antagonist oral anticoagulants (antiplatelet users excluded) on discharge.

Finally, we determined the independent predictors of recurrent ischemic stroke and ICH in a competing-risks multivariate adjusted regression model by incorporating age, sex, all vascular risk factors, antiplatelet and warfarin use, microbleed burden and location (strictly deep, strictly lobar, and strictly infratentorial), and other neuroimaging markers of SVD into the model.

All analyses were done with SPSS version 22 (IBM Corp) and STATA version 14.0 (StataCorp).

Results

A total of 1076 patients with ischemic stroke received an MRI stroke protocol at the University of Hong Kong MRI unit during the period from March 1, 2008, to September 30, 2014. In total, 73 patients (6.8%) had incomplete clinical or imaging data or were lost to follow-up and were excluded from the final analysis. These patients did not differ in terms of mean age, sex, or prevalence and burden of microbleeds compared with the 1003 patients included in the main analysis (all $P>0.05$). Clinical and neuroimaging characteristics of the study population are shown in Table 1. The mean age of the study population was 69 years, and 60% were men. Overall, 66% had a past history of hypertension. In addition, 45% (450/1003) had presence of microbleeds, of which 26% (119/450) had ≥5 microbleeds and 42% (187/450) had microbleeds of mixed location. Furthermore, 36% (161/450) and 14% (61/450) of patients with microbleeds were strictly

Table 5. Event Rate and 5-Year Absolute Risks of Recurrent Ischemic Stroke and Intracerebral Hemorrhage, Stratified by Microbleed Burden, Location, and Antithrombotic Use

	All Patients (n=1003)				Antiplatelet Users* (n=862)				Warfarin Users† (n=50)			
	Recurrent Ischemic Stroke		Intracerebral Hemorrhage		Recurrent Ischemic Stroke		Intracerebral Hemorrhage		Recurrent Ischemic Stroke		Intracerebral Hemorrhage	
	Event Rate‡	5-Year Absolute Risk (%)	Event Rate‡	5-Year Absolute Risk (%)	Event Rate‡	5-Year Absolute Risk (%)	Event Rate‡	5-Year Absolute Risk (%)	Event Rate‡	5-Year Absolute Risk (%)	Event Rate‡	5-Year Absolute Risk (%)
No microbleeds	42/553 (7.6)	9.1	5/553 (0.9)	1.1	35/470 (7.4)	9.0	3/470 (0.6)	0.7	2/28 (7.1)	7.3	1/28 (3.6)	5.0
Microbleed presence	51/450 (11.3)	13.9	15/450 (3.3)	4.9	42/392 (10.7)	14.1	13/392 (3.3)	4.6	4/22 (18.2)	24.7	2/22 (9.1)	14.7
1 microbleed	20/184 (10.9)	13.3	1/184 (0.5)	1.1	17/163 (10.4)	11.8	1/163 (0.6)	1.3	2/12 (16.7)	20.5	0/12 (0)	0
2–4 microbleeds	16/147 (10.9)	13.3	3/147 (2.0)	4.1	12/124 (9.7)	11.1	2/124 (1.6)	2.1	0/6 (0)	0	1/6 (16.7)	100
≥5 microbleeds	15/119 (12.6)	15.8	11/119 (9.2)	12.3	13/105 (12.4)	16.0	10/105 (9.5)	13.1	2/4 (50.0)	62.5	1/4 (25.0)	33.3
Strictly deep	8/61 (13.1)	16.4	0/61 (0)	0	6/57 (10.5)	14.5	0/57 (0)	0	0/2 (0)	0	0/2 (0)	0
Strictly lobar	19/161 (11.8)	14.6	1/161 (0.6)	1.2	16/137 (11.7)	13.2	1/137 (0.7)	1.4	2/8 (25.0)	46.7	0/8 (0)	0
Strictly infratentorial	6/41 (14.6)	22.5	0/41 (0)	0	5/35 (14.3)	15.2	0/35 (0)	0	0/4 (0)	0	0/4 (0)	0
Mixed	18/187 (9.6)	11.3	14/187 (7.5)	10.8	15/163 (9.2)	10.9	12/163 (7.4)	9.6	2/8 (25.0)	30.0	2/8 (25.0)	58.3

*Anticoagulant users excluded.
†Antiplatelet users excluded.
‡Event rate is shown as number of events in each subgroup/total number of patients in each subgroup (percentage).

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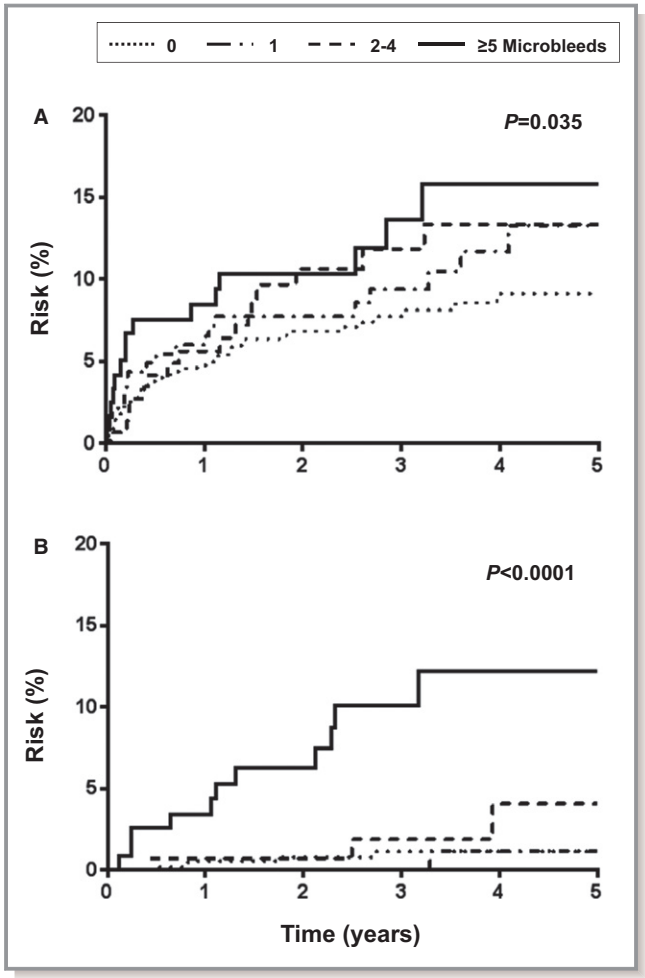

Figure 1. Risk of recurrent ischemic stroke (A) and intracerebral hemorrhage (B) in ischemic stroke patients with increasing cerebral microbleed burden. Statistical significance of differences in risk determined by log rank test.

lobar and strictly deep, respectively, in location. In total, 425 of 1003 (42%) patients were classified as having an ischemic stroke due to small vessel occlusion, 342 of 1003 (34%) had ischemic stroke due to large artery atherosclerosis, and 124 of 1003 (12%) had a cardioembolic stroke. On discharge, the mean modified Rankin Scale was 2.0±2.0. Moreover, 862 of 1003 of the population were prescribed antiplatelets only, 85 of 1003 used an anticoagulant only (50/85 warfarin, 35/85 non–vitamin K antagonist oral anticoagulant), and 19 of 1003 were on an antiplatelet and an anticoagulant. Thirty-seven patients were not on an antithrombotic agent at discharge.

A high microbleed burden (≥5) was independently associated with premorbid antiplatelet use (multivariate adjusted odds ratio: 2.01; 95% confidence interval [CI], 1.17–3.47; *P*=0.012) and anticoagulant use (adjusted odds ratio: 4.47; 95% CI, 1.17–17.10; *P*=0.029) as well as a severe burden of subcortical and periventricular WMH and BG perivascular spaces (all *P*<0.0001; Table 2). There was a trend that a high microbleed burden was also associated with a history of hypertension (*P*=0.057). A comparison of clinical and neuroimaging characteristics of patients with microbleeds of different locations is shown in Table 3. Compared with patients with no, strictly deep, or strictly lobar microbleeds, patients with mixed microbleeds were older (*P*=0.001), had a higher prevalence of hypertension (*P*=0.005), renal impairment (*P*=0.002), and overall more severe burden of SVD (Table 3). Multivariate analysis revealed that hypertension (adjusted odds ratio: 1.58; 95% CI, 1.05–2.39; *P*=0.029); premorbid anticoagulant use (adjusted odds ratio: 4.33; 95% CI, 1.42–13.25; *P*=0.010); and severe burden of subcortical, periventricular WMH, and BG perivascular spaces (all

Table 6. Cox Regression Analyses of Risk of Recurrent Ischemic Stroke and Intracerebral Hemorrhage With Presence vs Absence of Microbleeds, Stratified by Antithrombotic Use

	Unadjusted SHR (95% CI)	*P* Value	Age and Sex Adjusted SHR (95% CI)	*P* Value	Multivariate* Adjusted SHR (95% CI)	*P* Value
Recurrent ischemic stroke						
All patients (n=1003)	1.52 (1.01–2.29)	0.044	1.40 (0.93–2.11)	0.11	1.49 (0.97–2.27)	0.067
Antiplatelet users† (n=862)	1.47 (0.94–2.31)	0.092	1.33 (0.85–2.10)	0.21	1.41 (0.88–2.26)	0.15
Warfarin users‡ (n=50)	2.74 (0.51–14.51)	0.24	…	…	…	…
NOAC users‡ (n=35)	2.64 (0.46–15.14)	0.28	…	…	…	…
Intracerebral hemorrhage						
All patients (n=1003)	3.71 (1.35–10.21)	0.011	3.46 (1.23–9.78)	0.019	3.52 (1.26–9.85)	0.016
Antiplatelet users† (n=862)	5.28 (1.51–18.51)	0.009	4.84 (1.37–17.06)	0.014	4.64 (1.29–16.70)	0.019
Warfarin users‡ (n=50)	2.69 (0.24–30.36)	0.42	…	…	…	

CI indicates confidence interval; NOAC, non–vitamin K antagonist oral anticoagulant; SHR, subdistribution hazard ratio.
*Hypertension, hyperlipidemia, diabetes mellitus, smoking history, and atrial fibrillation.
†Anticoagulant users excluded.
‡Antiplatelet users excluded; only univariate SHRs provided with <10 recurrent events.

$P<0.0001$) were independent predictors of microbleeds of mixed location (Table 4).

During a mean follow-up of 37±20 years (3126 patient-years), 113 patients developed a recurrent stroke, of which 93 (82%) had ischemic strokes (Table 1). In total, 130 patients died during follow-up (46% vascular deaths). The absolute event rates and 5-year absolute risks of recurrent ischemic stroke and ICH after ischemic stroke of patients with different burden and locations of microbleeds is shown in Table 5 and Figure 1. In the 20 patients with ICH, 15 had underlying microbleeds, of which 11 had ≥5 and 14 were of mixed location. In 11 of 15 of patients, the ICH location corresponded to a prior microbleed detected on MRI. When patients were stratified by presence versus absence of microbleeds, patients who had microbleeds were at increased risk of recurrent ischemic stroke on univariate analysis (SHR: 1.52; 95% CI, 1.01–2.29; $P=0.044$), but this did not reach statistical significance on multivariate analysis ($P=0.067$; Table 6). Similar findings were noted when microbleeds were stratified according to burden ($P=0.051$) (Table 7). In contrast, presence of microbleeds (multivariate adjusted SHR: 3.52; 95% CI, 1.26–9.85; $P=0.016$) and burden of microbleeds (burden versus no microbleeds: 1 microbleed: SHR: 0.59 [95% CI, 0.07–4.99]; 2–4 microbleeds: SHR: 2.14 [95% CI, 0.51–9.02]; ≥5 microbleeds: SHR: 9.30 [95% CI, 2.98–29.03]; $P_{trend}<0.0001$) were both independently associated with subsequent risk of ICH compared with patients with no microbleeds (Tables 6 and 7). Microbleeds were not associated with all-cause mortality or vascular death (Tables 8 and 9).

We stratified our results according to the use of antithrombotic agents after diagnosis of ischemic stroke. The absolute event rates and 5-year absolute risks of recurrent ischemic stroke and ICH in 862 of 1003 antiplatelet users (anticoagulant users excluded) by microbleed burden and location are shown in Table 5 and Figure 2. Compared with no microbleeds, antiplatelet users with microbleeds were similarly at increased risk of ICH (multivariate adjusted SHR: 4.64; 95% CI, 1.29–16.70; $P=0.019$) but not recurrent ischemic stroke ($P=0.15$; Table 6). Similar findings were noted when antiplatelet users were stratified by microbleed burden and a significant increase in risk of ICH (burden versus no microbleeds: 1 microbleed: multivariate adjusted SHR: 0.91 [95% CI, 0.09–8.72]; 2–4 microbleeds: multivariate adjusted SHR: 2.22 [95% CI, 0.38–12.98]; ≥5 microbleeds: multivariate adjusted SHR: 12.98 [95% CI, 3.27–51.58]; $P_{trend}=0.001$), but not recurrent ischemic stroke ($P_{trend}=0.11$) was noted with increasing microbleed burden (Table 7). In antiplatelet users, an increasing burden of microbleeds was associated with all-cause mortality ($P_{trend}=0.046$) on multivariate analysis, but this was not significant when only vascular deaths were studied ($P_{trend}=0.12$; Tables 8 and 9).

Table 7. Cox Regression Analyses of Risk of Recurrent Ischemic Stroke and Intracerebral Hemorrhage With Increasing Burden of Microbleeds vs No Microbleeds, Stratified by Antithrombotic Use

	No. of Microbleeds, SHR (95% CI)								
	Unadjusted*				Adjusted for Age, Sex, and Vascular Risk Factors*				
	1	2–4	≥5	P_{trend}	1	2–4	≥5	P_{trend}
Recurrent ischemic stroke								
All patients (n=1003)	1.43 (0.84–2.44)	1.46 (0.82–2.58)	1.76 (0.97–3.18)	0.037	1.45 (0.85–2.48)	1.29 (0.70–2.38)	1.84 (1.02–3.33)	0.051
Antiplatelet users† (n=862)	1.42 (0.79–2.53)	1.31 (0.68–2.50)	1.77 (0.93–3.35)	0.078	1.37 (0.76–2.46)	1.20 (0.60–2.40)	1.77 (0.94–3.34)	0.11
Intracerebral hemorrhage								
All patients (n=1003)	0.58 (0.07–4.97)	2.26 (0.54–9.43)	10.89 (3.77–31.42)	<0.0001	0.59 (0.07–4.99)	2.14 (0.51–9.02)	9.30 (2.98–29.03)	<0.0001
Antiplatelet users† (n=862)	0.96 (0.10–9.11)	2.51 (0.42–15.02)	16.11 (4.42–58.73)	<0.0001	0.91 (0.09–8.72)	2.22 (0.38–12.98)	12.98 (3.27–51.58)	0.001

CI indicates confidence interval; SHR, subdistribution hazard ratio.
*Hypertension, hyperlipidemia, diabetes mellitus, smoking history, and atrial fibrillation.
†Anticoagulant users excluded.

Table 8. Cox Regression Analyses of All Death and Vascular Death With Presence of Microbleeds vs No Microbleeds, Stratified by Antithrombotic Use

	Unadjusted HR (95% CI)	*P* Value	Age- and Sex-Adjusted HR (95% CI)	*P* Value	Multivariate* Adjusted HR (95% CI)	*P* Value
All death						
All patients (n=1003)	1.34 (0.95–1.90)	0.093	1.12 (0.80–1.59)	0.51	1.16 (0.82–1.64)	0.40
Antiplatelet users† (n=862)	1.56 (1.04–2.33)	0.031	1.28 (0.85–1.91)	0.24	1.29 (0.86–1.94)	0.23
Warfarin users‡ (n=50)	1.45 (0.42–5.03)	0.56	1.66 (0.45–6.09)	0.45	0.59 (0.10–3.73)	0.58
	Unadjusted SHR (95% CI)	*P* Value	Age and Sex Adjusted SHR (95% CI)	*P* Value	Multivariate* Adjusted SHR (95% CI)	*P* Value
Vascular death						
All patients (n=1003)	1.43 (0.86–2.37)	0.16	1.24 (0.74–2.07)	0.42	1.27 (0.76–2.14)	0.36
Antiplatelet users† (n=862)	1.84 (1.00–3.40)	0.050	1.56 (0.84–2.90)	0.16	1.57 (0.83–2.97)	0.16
Warfarin users‡ (n=50)	2.34 (0.57–9.54)	0.24	…	…	…	…

CI indicates confidence interval; HR, hazard ratio; SHR, subdistribution hazard ratio.
*Hypertension, hyperlipidemia, diabetes mellitus, smoking history, and atrial fibrillation.
†Anticoagulant users excluded.
‡Antiplatelet users excluded; only univariate SHRs provided for vascular death with <10 events.

Of the 50 patients on warfarin (antiplatelet users excluded), 6 developed recurrent ischemic stroke and 3 developed ICH during a mean 44.3±21 months of follow-up (see Table 5). Warfarin users with microbleeds were not at increased risk of recurrent ischemic stroke (univariate SHR: 2.74; 95% CI, 0.51–14.51; *P*=0.24) or ICH (univariate SHR:

Table 9. Cox Regression Analyses of All Death and Vascular Death With Increasing Burden of Microbleeds vs No Microbleeds, Stratified by Antithrombotic Use

	No. of Microbleeds, HR (95% CI)							
	Unadjusted				Adjusted for Age, Sex, and Vascular Risk Factors*			
	1	2–4	≥5	P_{trend}	1	2–4	≥5	P_{trend}
All death								
All patients (n=1003)	0.97 (0.59–1.59)	1.48 (0.92–2.39)	1.81 (1.13–2.92)	0.009	0.89 (0.54–1.46)	1.19 (0.73–1.93)	1.55 (0.96–2.50)	0.091
Antiplatelet users† (n=862)	1.08 (0.61–1.91)	1.73 (1.00–3.00)	2.18 (1.27–3.74)	0.002	0.90 (0.51–1.61)	1.56 (0.89–2.72)	1.63 (0.93–2.86)	0.046
Warfarin users‡ (n=50)	0.85 (0.16–4.37)	1.63 (0.19–14.03)	4.35 (0.84–22.57)	0.14	0.36 (0.04–3.54)	0.18 (0.01–3.98)	2.23 (0.24–20.99)	0.77
	No. of Microbleeds, SHR (95% CI)							
	Unadjusted				Adjusted for Age, Sex, and Vascular Risk Factors*			
Vascular death								
All patients (n=1003)	1.16 (0.58–2.31)	1.71 (0.87–3.37)	1.54 (0.72–3.28)	0.11	1.08 (0.53–2.18)	1.41 (0.69–2.88)	1.40 (0.64–3.04)	0.27
Antiplatelet users† (n=862)	1.37 (0.60–3.16)	2.41 (1.11–5.29)	1.95 (0.80–4.72)	0.028	1.22 (0.52–2.87)	2.06 (0.90–4.69)	1.55 (0.62–3.87)	0.12
Warfarin users‡ (n=50)	1.37 (0.25–7.40)	2.58 (0.28–23.82)	6.84 (0.96–49.02)	0.068	…	…	…	

CI indicates confidence interval; HR, hazard ratio; SHR, subdistribution hazard ratio.
*Hypertension, hyperlipidemia, diabetes mellitus, smoking history, and atrial fibrillation.
†Anticoagulant users excluded.
‡Antiplatelet users excluded.

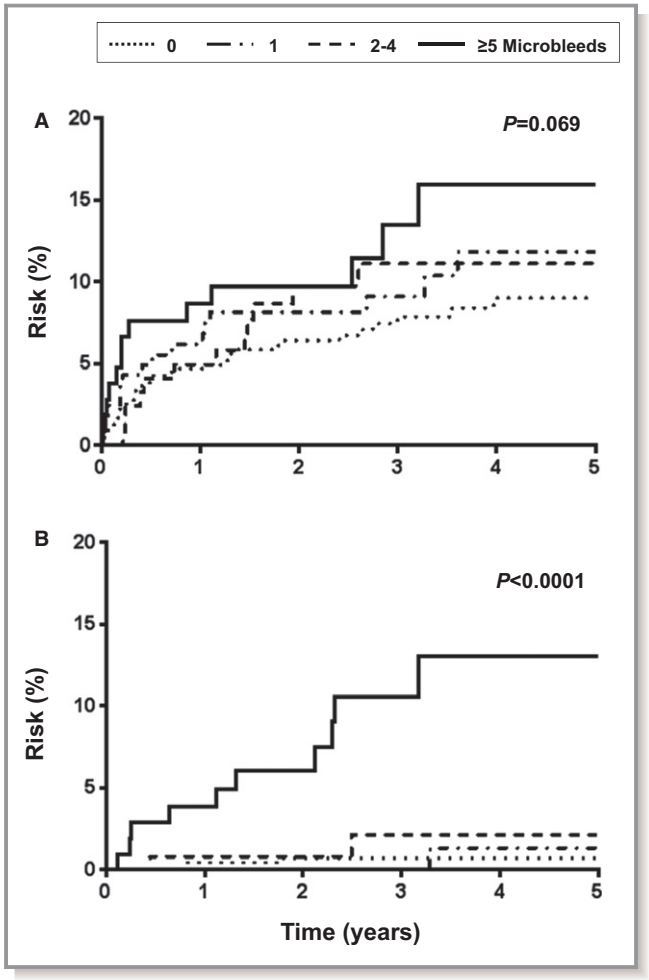

Figure 2. Risk of recurrent ischemic stroke (A) and intracerebral hemorrhage (B) in ischemic stroke patients on antiplatelet agents with increasing cerebral microbleed burden. Statistical significance of differences in risk determined by log rank test.

2.69; 95% CI, 0.24–30.36; P=0.42; Table 6). Thirty-five patients were on non–vitamin K antagonist oral anticoagulants, 5 of whom developed recurrent ischemic stroke (2/5 with no microbleeds, 1/5 with 1 microbleed, and 2/5 with 2–4 microbleeds; 1/5 had microbleeds of mixed location); however, none of the 13 patients with microbleeds (3/13 with 1 microbleed, 6/13 with 2–4 microbleeds, and 4/13 with ≥5 microbleeds; 8/13 had microbleeds of mixed location) developed an ICH with mean 26.4±13.5 months of follow-up.

In a multivariate analysis including age, sex, vascular risk factors, postevent antithrombotic use, microbleed burden, microbleed location, and other neuroimaging markers of SVD, only having ≥5 microbleeds (SHR: 6.08; 95% CI, 1.11–33.21; P=0.037) was identified as an independent predictor of ICH (Table 10). In contrast, age, hyperlipidemia, smoking history, and atrial fibrillation (all P<0.05) were identified as independent predictors of recurrent ischemic stroke, but neuroimaging markers of SVD were not (Table 11).

Discussion

Our study includes one of the largest cohorts for the long-term prognostic implications of cerebral microbleeds in patients with ischemic stroke by adding ≈3100 patient-years of follow-up data to ≈9500 patient-years included in a recent systematic review of 15 smaller studies.[4] Overall, 45% of ischemic stroke patients in our cohort were noted to have microbleeds. This was similar to the prevalence noted in other Asian cohorts (23–50%) but higher than those observed in an unpublished Western cohort of ischemic stroke patients (≈20%).[4] However, direct comparisons of microbleed prevalence among ischemic stroke patients from the East and the West are limited because most reported Western cohorts also consisted of transient ischemic attack patients, for whom the prevalence of microbleeds is known to be lower.[1,4]

The majority of patients with microbleeds in our cohort (42%) had microbleeds of mixed location, whereas 36% of patients had strictly lobar microbleeds and 16% had strictly deep microbleeds. Consistent with recent meta-analysis,[4] microbleeds of mixed location are known to be more common among Asian compared with white cohorts (8–40% versus 5–15%), likely because of underlying differences in risk factor profile and greater prevalence of hypertension.[4,7] Microbleeds of mixed location are, by definition, multiple; are often associated with a high microbleed burden (109/187 [58%] patients with microbleeds of mixed location in our cohort had ≥5); and are likely to represent a severe form of microangiopathy, due to either severe hypertension or a combination of hypertension and cerebral amyloid angiopathy. Our results are in line with this finding because patients who had mixed microbleeds or ≥5 microbleeds had the highest 5-year absolute risk of an ICH, at 10.8% and 12.3% respectively.

Our hazard ratios for prediction of recurrent stroke based on microbleed burden were generally similar with the pooled estimates from the previous meta-analysis.[4] However, although this meta-analysis was able to demonstrate that patients with the presence or an increasing burden of microbleeds were at higher risk of recurrent ischemic stroke,[4] these analyses did not reach statistical significance in our cohort after adjusting for age, sex, and other vascular risk factors. Stratifying our results by antithrombotic use and including only patients who were on antiplatelet agents on discharge did not alter our findings. Interestingly, in a multivariate regression model accounting for all vascular risk factors, microbleed burden, microbleed location, and other neuroimaging markers of SVD, only traditional vascular risk factors such as age, hyperlipidemia, smoking history, and atrial fibrillation remained significant independent predictors of recurrent ischemic stroke risk. Nevertheless, our findings on the prognostic implications of microbleed burden support recent expert recommendations

Table 10. Clinical and Neuroimaging Predictors of Intracerebral Hemorrhage

	Univariate SHR (95% CI)	*P* Value	Multivariate SHR* (95% CI)	*P* Value
Age	1.02 (0.98–1.07)	0.29	···	
Male sex	1.52 (0.58–3.94)	0.39	···	
Hypertension	2.92 (0.86–9.94)	0.087	···	
Diabetes mellitus	0.64 (0.22–1.93)	0.43	···	
Hyperlipidemia	0.97 (0.35–2.67)	0.96	···	
Ever smoker	0.77 (0.28–2.12)	0.62	···	
Atrial fibrillation	1.73 (0.58–5.16)	0.32	···	
GFR <60 mL/min/1.73 m^2	1.00 (1.00–1.00)	0.42	···	
Single antiplatelet use	0.59 (0.23–1.50)	0.27	···	
Dual antiplatelet use	1.30 (0.38–4.46)	0.67	···	
Warfarin use	2.41 (0.73–7.93)	0.15	···	
≥5 microbleeds	9.72 (4.05–23.35)	<0.0001	6.08 (1.11–33.21)	0.037
Strictly deep microbleeds	5.85 (2.40–14.30)	<0.0001	···	
Strictly lobar microbleeds	4.56 (1.76–11.84)	0.002	···	
Strictly infratentorial microbleeds	3.61 (1.48–8.80)	0.005	···	
Periventricular WMH burden	1.80 (1.18–2.75)	0.007	···	
Subcortical WMH burden	1.50 (0.96–2.37)	0.077	···	
Basal ganglia PVS burden	1.96 (1.02–3.76)	0.042	···	
Centrum semiovale PVS burden	0.93 (0.47–1.81)	0.82	···	
Lacunes	0.84 (0.62–1.15)	0.28	···	

CI indicates confidence interval; GFR, glomerular filtration rate; PVS, periventricular space; SHR, subdistribution hazard ratio; WMH, white matter hyperintensity.
*All variables in univariate analysis placed into multivariate analysis model.

suggesting that in ischemic stroke patients with <5 microbleeds, antiplatelet agents should not be contraindicated, as the absolute risk of recurrent ischemic stroke in this group of patients is likely to significantly outweigh the risk of ICH.[18] These expert recommendations also suggest that in patients with ≥5 microbleeds, the benefits and potential risks of antiplatelet agents would need to be carefully balanced because the long-term absolute risks of ICH are likely to be similar to the absolute risks of recurrent ischemic stroke, and our results are concordant with these recommendations.[18]

Although this MRI-based cohort is currently one of the largest used to investigate the long-term prognostic implications of microbleeds in patients with ischemic stroke, our study is not without limitations. Our cohort is limited to ischemic stroke patients who were referred for MRI. The majority of patients had strokes that were of mild-moderate severity; patients who were severely debilitated or deemed unfit for transfer did not receive an MRI scan. The majority of patients referred for MRI were also of small vessel or large artery atherosclerosis subtypes. This would have resulted in selection bias in our cohort of patients and may have limited the generalizability of our findings. In addition, the median delay from admission to scan was 4 days, and only a small proportion of patients (37/1003) received intravenous thrombolysis. Whether underlying microbleed burden is associated with an increased risk of hemorrhagic transformation after thrombolysis could not be determined. Moreover, our findings that suggest patients with microbleeds of mixed location are at high risk of developing ICH are comparable with those from a recent meta-analysis[4]; however, further individual patient data meta-analyses, such as those from the Microbleeds International Collaborative Network[19] and the META-MICROBLEEDS Consortium,[20] would be able to provide more definitive recommendations as to the implications of microbleed burden versus microbleed location in the prediction of subsequent stroke risk and the possible underlying ethnic interactions. Furthermore, although we stratified our analyses by antithrombotic use, we do not have exact data for all patients' medications throughout the entire follow-up period and thus are uncertain about the exact rates of compliance. Finally, although we attempted to study the prognostic implications of microbleeds in patients on warfarin or non–vitamin K antagonist oral anticoagulants at discharge, we were limited in power, with only 85 patients taking anticoagulants without antiplatelets. Clinical trials such as CROMIS-2 (Clinical

Table 11. Clinical and Neuroimaging Predictors of Recurrent Ischemic Stroke

	Univariate SHR (95% CI)	*P* Value	Multivariate SHR* (95% CI)	*P* Value
Age	1.04 (1.02–1.06)	<0.0001	1.05 (1.03–1.07)	<0.0001
Male sex	1.16 (0.76–1.76)	0.50	…	
Hypertension	1.16 (0.75–1.80)	0.51	…	
Diabetes mellitus	1.58 (1.04–2.41)	0.032	…	
Hyperlipidemia	1.62 (1.06–2.48)	0.026	1.75 (1.13–2.71)	0.012
Ever smoker	1.81 (1.20–2.73)	0.005	2.15 (1.41–3.30)	0.0004
Atrial fibrillation	2.32 (1.44–3.75)	0.001	1.93 (1.18–3.18)	0.009
GFR <60 mL/min/1.73 m^2	1.52 (0.97–2.40)	0.068	…	
Single antiplatelet use	0.92 (0.58–1.46)	0.71	…	
Dual antiplatelet use	0.83 (0.43–1.61)	0.58	…	
Warfarin use	1.13 (0.52–2.43)	0.76	…	
≥5 microbleeds	1.57 (0.90–2.73)	0.11		
Strictly deep microbleeds	1.20 (0.74–1.93)	0.46	…	
Strictly lobar microbleeds	1.33 (0.88–2.02)	0.18	…	
Strictly infratentorial microbleeds	1.24 (0.73–2.09)	0.43	…	
Periventricular WMH burden	1.28 (1.01–1.62)	0.038	…	
Subcortical WMH burden	1.17 (0.93–1.48)	0.18	…	
Basal ganglia PVS burden	1.56 (1.16–2.10)	0.003	…	
Centrum semiovale PVS burden	0.78 (0.56–1.09)	0.14	…	
Lacunes	1.33 (0.88–2.01)	0.18	…	

CI indicates confidence interval; GFR, glomerular filtration rate; PVS, periventricular space; SHR, subdistribution hazard ratio; WMH, white matter hyperintensity.
*All variables in univariate analysis placed into multivariate analysis model.

Relevance of Microbleeds in Stroke Study) and HERO (Intracerebral Hemorrhage Due to Oral Anticoagulants: Prediction of the Risk by Magnetic Resonance) are currently under way and will provide important insights regarding the use of anticoagulants in patients with microbleeds.[21]

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Author Contributions

Lau obtained funding, provided study supervision, collected data, did the statistical analysis and interpretation, wrote and revised the article. Y.K. Wong collected data and did the statistical analysis. Teo, Chang, Tse, Hoi, C.Y. Chan, O.L. Chan, Cheung, E.K.M. Wong, Kwan and Hui collected data. Mak obtained funding, provided study supervision, acquired and assessed imaging data and revised the article.

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Disclosures

None.

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