Observational Study

Medicine®

OPEN

Cerebral microbleeds in patients with ischemic cerebrovascular disease taking aspirin or clopidogrel

Lihong Ge, MD[a], Xuehui Ouyang, BS[c], Chao Ban, MS[a], Haixia Yu, MS[a], Qiong Wu, MD[a], Hui Wu, MD[a], Junguo Liang, MD[b,*]

Abstract

Cerebral microbleeds (CMBs) may be markers of intracerebral bleeding risk in patients receiving antithrombotic drugs. This study aimed to analyze CMBs and white matter hyperintensities (WMHs) in patients taking aspirin or clopidogrel.

This retrospective study included patients with ischemic cardiovascular disease administered 75 mg/day aspirin (n = 150) or clopidogrel (n = 150, matched for age and gender) for >1 year (Affiliated Hospital of Inner Mongolia Medical University, China, from July, 2010 to July, 2015). Patients underwent T2-weighted imaging, T1-weighted imaging, diffusion-weighted imaging (DWI) and enhanced T2*-weighted angiography (ESWAN) imaging (3.0-Tesla scanner). Baseline vascular risk factors for CMBs and macroscopic bleeding (MB) were evaluated using univariate and multivariate analyses.

The aspirin and clopidogrel groups did not differ significantly in baseline characteristics or prevalences of CMBs or MB. The odds of MB were higher in patients with CMBs than in patients without CMBs in both the aspirin (odds ratio, 95% confidence interval: 4.09, 1.93–8.68; $P < .001$) and clopidogrel (6.42, 2.83–14.57; $P < .001$) groups. The odds of WMHs were also higher in patients with CMBs in both the aspirin (3.28, 1.60–6.71; $P = .001$) and clopidogrel (4.09, 1.91–8.75; $P < .001$) groups. Patients receiving treatment for >5 years showed elevated risk of CMBs in the aspirin (0.17; 0.09–0.36; $P < .001$) and clopidogrel (0.15, 0.07–0.33; $P < .001$) groups as well as higher odds of MB in the aspirin (0.34, 0.16–0.71; $P = .004$) and clopidogrel (0.37, 0.17–0.80; $P = .010$) groups.

The WMHs and MB were associated with CMBs in patients taking aspirin or clopidogrel for >1 year, and long-term use increased the risks of CMB and bleeding.

Abbreviations: CMBs = cerebral microbleeds, CVD = cerebrovascular disease, DWI = diffusion-weighted imaging, ESWAN = enhanced T2*-weighted angiography, GRE = gradient-recalled-echo, MRI = magnetic resonance imaging, TIA = transient ischemic attack, WMHs = white matter hyperintensities.

Keywords: aspirin, cerebral microbleed, *clopidogrel*, enhanced T2*-weighted magnetic resonance imaging, white matter hyperintensity

1. Introduction

Cerebral microbleeds (CMBs) are focal deposits of hemosiderin breakdown products that occur due to earlier leakages of blood from small vessels in the brain.[1] The CMBs can be detected as small, round, homogenous, low-intensity lesions by magnetic resonance imaging (MRI) using T2*-weighted gradient-recalled-echo (GRE) and T2*-weighted angiography (SWAN) sequences.[2–4] The incidence of CMBs is around 4 to 5% in the healthy population but can exceed 50% in patients with cerebrovascular disease (CVD), and these lesions are thought to be subclinical markers of the risk of stroke and dementia.[1] In addition to their association with future macroscopic hemorrhage and stroke,[5–8] CMBs have also been associated with ischemic stroke, increasing age, male sex, low serum triglycerides, Alzheimer's disease, trauma, inflammatory conditions, and genetic disorders.[9–16]

Aspirin and clopidogrel are antiplatelet agents widely used in the primary and secondary prevention of thrombotic CVD or cardiovascular disease, including acute coronary syndrome.[17] However, there is an evidence that antiplatelet agents are associated with an increased risk of intracerebral hemorrhage.[18–20] Interestingly, the prevalence of CMBs has been reported to be higher in patients treated with antiplatelet drugs compared with nonusers.[21] Furthermore, a systematic review of published and unpublished data concluded that antiplatelet drug use was associated with an increased prevalence of CMBs in patients with intracerebral hemorrhage, ischemic stroke or transient ischemic attack (TIA).[22] In addition, CMBs were more prevalent in antiplatelet drug users with intracerebral hemorrhage than in matched antiplatelet drug users without intracerebral hemorrhage or in patients with intracerebral hemorrhage unrelated to antiplatelet drugs, suggesting that CMBs are associated with antiplatelet-related intracerebral hemorrhage.[23] This was supported by the observation that, in patients with ischemic stroke

Editor: Salvatore De Rosa.

LG and XO contributed equally to this work.

The authors have no conflicts of interest to disclose.

[a] Department of Magnetic Resonance, [b] Department of Thoracic Surgery, the Affiliated Hospital of Inner Mongolia Medical University, [c] Department of Magnetic Resonance, Inner Mongolia Autonomous Region People's Hospital, Hohhot, China.

[*] Correspondence: Junguo Liang, Department of Thoracic Surgery, the Affiliated Hospital of Inner Mongolia Medical University, 1 Channel North Road, Huimin District Hohhot 010050, China (e-mail: lchest@126.com).

Medicine (2019) 98:9(e14685)

Received: 17 July 2018 / Received in final form: 26 January 2019 / Accepted: 30 January 2019

http://dx.doi.org/10.1097/MD.0000000000014685

treated with antithrombotic agents, an increased number of CMBs was associated with elevated risks of subsequent intracerebral hemorrhage and death from intracerebral hemorrhage.[24] The presence of CMBs may also be a risk factor for intracerebral hemorrhage related to warfarin, an antithrombotic agent with a different mechanism of action to aspirin and clopidogrel.[25] Indeed, warfarin use was found to enhance the prevalence of CMBs in patients with intracerebral hemorrhage but not ischemic stroke.[22,26] However, some studies have concluded that antiplatelet drug therapy has no effect on the frequency of CMBs,[25–27] while others have suggested that the effect is mediated only on deep CMBs and not lobar CMBs.[28]

White matter hyperintensities (WMHs) are lesions detectable by MRI that are generally regarded as indicators of cerebral small vessel disease.[29] The WMHs are associated with an elevated risk of stroke, dementia, and death[30] as well as poorer functional recovery after ischemic stroke.[29] Several studies have identified an association between WMHs and CMBs in healthy subjects as well as in subjects with primary or recurrent stroke.[9,31–34] However, the characteristics of the association between WHMs and CMBs in patients receiving aspirin and clopidogrel have yet to be compared in detail.

The aim of this study was to examine the associations of CMBs with WMH characteristics and intracerebral bleeding events in patients with stroke or TIA receiving aspirin or clopidogrel.

2. Materials and methods

2.1. Patients

This was a retrospective study. Patients with ischemic CVD treated at the Affiliated Hospital of Inner Mongolia Medical University, China, between July 2010 and July 2015 were included in this study. The inclusion criteria were: First, diagnosed with stroke or TIA. Second, had received treatment with aspirin (75 mg/day) or *clopidogrel* (75 mg/day) for more than 1 year. The exclusion criteria were: First, had received previous anticoagulant or thrombolytic therapy. Second, had received aspirin combined with *clopidogrel*.Third, cerebral amyloid angiopathy. Fourth, motion artifacts in the MRI examinations. Fifth, incomplete data. Patients receiving aspirin (aspirin group) and clopidogrel (clopidogrel group) were matched for gender and age. The study was approved by the Ethics Committee of Inner Mongolia Medical University. Due to the retrospective nature of the analysis, informed consent from the patients was waived.

2.2. MRI examination

The MRI examinations of the brain were performed on a 3.0-Tesla MR scanner (SignaHDx, GE Healthcare, Chicago, IL). All patients underwent an MRI series comprising T1-weighted fluid-attenuated inversion recovery (FLAIR) imaging (repetition time, 1976 ms; echo time, 25.2 ms; inversion time, 860.0 ms; section thickness, 5 mm; field of view, 24×18 cm; matrix, 320×224; NEX, 1.0). In addition, T2*-weighted fast spin-echo/propeller imaging (repetition time, 4700 ms; echo time, 114.0 ms; section thickness, 5 mm; field of view, 24×24 cm; matrix, 320×320; NEX, 1.0) and diffusion-weighted imaging (DWI) (b = 1000; repetition time, 4450 ms; echo time, 76.6 ms; section thickness, 5 mm; field of view, 24×24 cm; matrix, 128×128; NEX, 2.0) were performed. An enhanced T2*-weighted angiography (ESWAN) scan was obtained using the following settings: repetition time, 53.3 ms; echo time, 5.1 ms; flip angle, 20°; field of view, 24×24; slice thickness, 1.8; slice spacing, 0 mm; matrix, 448×352. The phase-sensitive images obtained with ESWAN were processed using Functool software, which was part of Advantage Workstation 4.3 (GE Healthcare). The CMBs were identified as low signals in the T2*-weighted MRI. These events cannot be demonstrated by conventional MRI or CT scans.

The MRI images were independently evaluated by 2 authors (HXY and CHB) who were blinded to the patients' clinical profiles. The number of microbleeds and the grading score for WMH were determined by consensus. Lesions within the sulcal areas and areas of symmetrical hypodensity in the globus pallidus, which were likely to represent adjacent pial blood vessels and calcification, respectively, were excluded. The degree of CMBs was classified using a scoring system[35] with 4 grades: absent (0), mild (1–5), moderate (5–10), and severe (>10). The severity of WMH on T2*-weighted images was classified as punctate foci, foci starting to show confluence, or large confluent areas, as previously described.[36]

We evaluated vascular risk factors according to Orken et al.[26] Hypertension was considered to be present when a patient had received antihypertensive treatment before admission or when hypertension was diagnosed during a hospital stay with systolic and diastolic blood pressures of at least 140 and 90 mm Hg, respectively, on multiple occasions. Diabetes mellitus (DM) was diagnostically defined as a history of DM with or without current hypoglycemic treatment or 2 fasting plasma glucose levels of 126 mg/dL or higher. A diagnosis of hyperlipidemia was made if the fasting serum total cholesterol level was > 220 mg/dL or the patient was currently undergoing cholesterol-lowering therapy. A history of smoking was noted when a subject was either a current smoker or an ex-smoker who had quit smoking less than 5 years before admission. Addiction to alcohol was considered as a risk factor if current consumption reached 300 g/week.

2.3. Statistical analysis

Data were analyzed using SPSS for Windows version 16.0 (SPSS Inc, Chicago, IL). Continuous variables are expressed as the means ± standard deviation (SD) and were compared between groups by Student *t* test. Categorical variables are expressed as frequencies and percentages and were compared between groups by the Chi-squared test or Fisher's exact test. Multivariate logistic stepwise regression analysis was used for subgroup analysis, with calculations of odds ratios (ORs) and 95% confidence intervals (CIs). Univariate logistic regression analysis was used to analyze the factors associated with CMBs and macroscopic bleeding, with calculations of ORs and 95% CIs. Variables with $P < .05$ were included in the multivariate enter analyses. Continuous variables were converted into categorical variables. Statistical significance was established using a conventional $P < .05$ level.

3. Results

3.1. Baseline characteristics of the study participants

A total of 370 patients (180 in the aspirin group, 190 in the clopidogrel group) were enrolled and 150 patients in each group were matched for gender and age. The baseline characteristics of patients before and after matching are summarized in Table 1. No patients had acute coronary syndrome. No significant differences were found in age, gender, nationality or prevalences of hypertension, coronary artery disease, DM, hyperlipidemia, smoking, alcohol addiction, previous stroke or previous coronary angioplasty between the aspirin-treated patients and *clopidogrel*-treated patients (Table 1), suggesting that the 2 groups were well

Table 1

Baseline characteristics of patients.

Characteristic	Before matching			After matching		
	Aspirin (n = 180)	Clopidogrel (n = 190)	*P*	Aspirin (n = 150)	Clopidogrel (n = 150)	*P*
Age, y, mean ± SD	65.4 ± 8.9	64.3 ± 8.6	.26	65.9 ± 9.0	66.4 ± 8.5	.16
Gender, n (%)			.64			.73
Male	102 (57%)	103 (54%)		87 (58%)	84 (56%)	
Female	78 (43%)	87 (46%)		63 (42%)	66 (44%)	
Nationality, n (%)			.30			.35
Han	131 (73%)	129 (68%)		116 (77%)	109 (73%)	
Others	49 (27%)	61 (32%)		34 (23%)	41 (27%)	
Hypertension, n (%)	103 (57%)	101 (53%)	.43	88 (59%)	84 (56%)	.64
Coronary artery disease, n (%)	34 (19%)	33 (17%)	.70	19 (13%)	23 (15%)	.51
Diabetes mellitus, n (%)	49 (27%)	49 (26%)	.76	34 (23%)	45 (30%)	.15
Hyperlipidemia, n (%)	82 (46%)	81 (43%)	.57	67 (45%)	72 (48%)	.56
Smoking, n (%)	83 (46%)	80 (42%)	.44	68 (45%)	60 (40%)	.35
Alcohol addiction, n (%)	87 (48%)	82 (43%)	.32	72 (48%)	61 (41%)	.20
Previous stroke, n (%)	63 (35%)	72 (38%)	.56	48 (32%)	58 (39%)	.23
Previous coronary angioplasty, n (%)	24 (13%)	31 (16%)	.42	9 (6%)	11 (7%)	.64
White matter hyperintensities, n (%)			.78			.42
Punctate foci	54 (30%)	56 (29%)		39 (26%)	36 (24%)	
Foci starting to show confluence	54 (30%)	53 (28%)		39 (26%)	33 (22%)	
Large confluent areas	25 (14%)	31 (16%)		10 (7%)	11 (7%)	
Cerebral microbleeds, n (%)			.83			.09
Mild	29 (16%)	29 (15%)		14 (9%)	9 (20%)	
Moderate	49 (27%)	46 (24%)		34 (23%)	26 (57%)	
Severe	27 (15%)	31 (16%)		12 (8%)	11 (24%)	
Macroscopic bleeding, n (%)	57 (32%)	55 (29%)	.57	42 (28%)	35 (23%)	.36
Duration of treatment, n (%)			.57			.56
≤ 5 years	97 (54%)	108 (57%)		82 (55%)	88 (59%)	
>5 years	83 (46%)	82 (43%)		68 (45%)	62 (41%)	

SD = standard deviation.

matched for all clinical characteristics and potential confounding factors. In addition, there were no significant differences between the 2 groups in the prevalences of CMBs and macroscopic intracerebral bleeding (Table 1).

3.2. Association of macroscopic bleeding with the presence of CMBs

Nearly half the patients with CMBs in both the aspirin group (45%) and *clopidogrel group* (47%) had macroscopic bleeding (Table 2). The frequency of hemorrhagic complications was higher in patients with CMBs than in patients without CMBs in both the aspirin group (27/60 [45%] vs 15/90 [17%]; OR, 4.09; 95% CI, 1.93–8.68; $P < .001$) and clopidogrel group (22/46 [47%] vs 13/104 [13%]; OR, 6.42; 95% CI, 2.83–14.57; $P < .001$) (Table 2).

3.3. Association of WMHs with the presence of CMBs

The prevalence of WMHs was higher in patients with CMBs than in patients without CMBs in both the aspirin group (45/60 [75%] vs 43/90 [48%]; OR, 3.28; 95% CI, 1.60–6.71; $P = .001$) and the

Table 2

The presence of WMHs and macroscopic bleeding in patients with and without CMBs.

Variable	CMBs (+)	CMBs (-)	OR	95% CI	*P*
Aspirin					
n	60	90			
WMHs, n (%)	45 (75%)	43 (48%)	3.28	1.60–6.71	.001
Punctate foci	15 (25%)	24 (27%)	0.97	0.43–1.94	.82
Beginning confluence of foci	21 (35%)	18 (20%)	2.15	1.03–4.52	.04
Large confluent areas	9 (15%)	1 (1%)	15.71	1.93–127.55	.001
Macroscopic bleeding, n (%)	27 (45%)	15 (17%)	4.09	1.93–8.68	<.001
Clopidogrel					
n	46	104			
WMHs, n (%)	36 (78%)	44 (42%)	4.09	1.91–8.75	<.001
Punctate foci	13 (28%)	23 (22%)	0.52	0.21–1.27	.42
Beginning confluence of foci	16 (35%)	17 (16%)	1.27	0.52–3.11	.01
Large confluent areas	7 (15%)	4 (4%)	2.41	0.65–9.02	.01
Macroscopic bleeding, n (%)	22 (47%)	13 (13%)	6.42	2.83–14.57	<.001

CI = confidence interval, CMBs = cerebral microbleeds, OR = odds ratio, WMHs = white matter hyperintensities.

clopidogrel group (36/46 [78%] vs 44/104 [42%]; OR, 4.09; 95% CI, 1.91–8.75; $P<.001$) (Table 2). Interestingly, the presence of CMBs was significantly associated with more advanced WMH lesions (i.e. large confluent areas), as shown in Table 2.

3.4. Association of CMBs and macroscopic bleeding with the duration of treatment with aspirin or clopidogrel

Notably, compared with patients receiving short-term treatment (≤ 5 years), the risk of CMBs in patients receiving long-term treatment (>5 years) was higher in both the aspirin group (42/68 [61%] vs 18/82 [22%]; OR, 0.17; 95% CI, 0.09–0.36; $P<.001$) and clopidogrel group (33/62 [53%] vs 13/88 [15%]; OR, 0.15; 95% CI, 0.07–0.33; $P<.001$) (Table 3). The risk of macroscopic bleeding was also elevated in patients receiving long-term treatment with aspirin (27/68 [40%] vs 15/82 [18%]; OR, 0.34; 95% CI, 0.16–0.71; $P=.004$) or clopidogrel (21/62 [34%] vs 14/88 [16%]; OR, 0.37; 95% CI, 0.17–0.80; $P=.01$) (Table 3).

3.5. Multivariate analyses of CMBs according to aspirin and clopidogrel

Table 4 showed that age ≥70 years (OR, 2.27, 95% CI, 1.14–4.52, $P=.02$), hypertension (OR, 3.19, 95% CI, 1.89–5.39, $P<.001$), DM (OR, 2.91, 95% CI, 1.61–5.27, $P<.001$), WMHs (OR, 2.04, 95% CI, 1.09–3.79, $P=.03$), and ≤5 years of treatment (OR, 0.48, 95% CI, 0.27–0.85, $P=.01$) were independently associated with MCBs. Treatment (aspirin vs clopidogrel) was not associated in the univariate analysis ($P=.63$).

3.6. Multivariate analyses of macroscopic bleeding according to aspirin and clopidogrel

Table 5 showed that age 60 to 70 years (OR, 2.20, 95% CI, 1.07–4.52, $P=.03$), male gender (OR, 0.53, 95% CI, 0.15–0.94, $P=.04$), hypertension (OR, 2.68, 95% CI, 1.55–4.63, $P<.001$), hyperlipidemia (OR, 2.06, 95% CI, 1.18–3.60, $P=.01$), alcohol addiction (OR, 3.72, 95% CI, 1.40–9.88, $P=.008$), and DM (OR, 3.82, 95% CI, 2.10–6.96, $P<.001$) were independently associated with MCBs. Treatment (aspirin vs clopidogrel) was not associated in the univariate analysis ($P=.88$).

4. Discussion

A notable finding of the present study was that CMBs occurred in 40.0% of patients taking aspirin for at least 1 year and 30.7% of patients taking clopidogrel for at least 1 year, with statistical analysis revealing no significant difference between groups. In both the groups, the frequencies of WMHs and macroscopic bleeding were higher in patients with CMBs than in those without CMBs. Furthermore, patients treated with either antiplatelet

Table 3

Analysis of the association of cerebral microbleeds and macroscopic bleeding with the duration of treatment.

Variable	≤5 years	>5 years	OR	95% CI	P
Aspirin					
N	82	68			
Cerebral microbleeds, n (%)	18 (22%)	42 (61%)	0.17	0.09–0.36	<.001
Macroscopic bleeding, n (%)	15 (18%)	27 (40%)	0.34	0.16–0.71	.004
Clopidogrel					
N	88	62			
Cerebral microbleeds, n (%)	13 (15%)	33 (53%)	0.15	0.07–0.33	<.001
Macroscopic bleeding, n (%)	14 (16%)	21 (34%)	0.37	0.17–0.80	.01

CI = confidence interval, OR = odds ratio.

Table 4

Univariate and multivariate logistic regression analyses for cerebral microbleeds.

	Univariate logistic regression			Multivariate logistic regression		
Variable	P	OR	95% CI	P	OR	95% CI
Age						
60–70 years vs 60 years	.001	2.46	1.44–4.18	.35	1.37	0.71–2.63
≥70 years vs 60 years	.27	1.36	0.78–2.36	.02	2.27	1.14–4.52
Nationality (Han vs others)	.25	0.76	0.48–1.21			
Previous coronary angioplasty (yes vs no)	.01	2.21	1.24–3.94	.59	0.66	0.15–2.94
Coronary artery disease (yes vs no)	.004	2.19	1.28–3.74	.58	1.47	0.38–5.68
Gender (male vs female)	.001	2.13	1.38–3.29	.94	0.97	0.45–2.10
Previous stroke (yes vs no)	<.001	2.89	1.86–4.49	.73	1.11	0.61–2.02
Hypertension (yes vs no)	<.001	2.93	1.88–4.58	<.001	3.19	1.89–5.39
Hyperlipidemia (yes vs no)	<.001	3.24	2.10–5.02	.001	2.44	1.44–4.16
Alcohol addiction (yes vs no)	<.001	2.62	1.70–4.03	.24	1.66	0.72–3.83
Smoking (yes vs no)	<.001	2.42	1.58–3.72	.97	1.01	0.49–2.10
Diabetes mellitus (yes vs no)	<.001	3.72	2.30–6.03	<.001	2.91	1.61–5.27
White matter hyperintensities (yes vs no)	<.001	4.85	3.05–7.73	.03	2.04	1.09–3.79
Treatment (aspirin vs clopidogrel)	.11	0.71	0.47–1.08			
Duration of treatment (≤5 years vs >5 years)	.03	0.63	0.41–0.97	.01	0.48	0.28–0.85

CI = confidence interval, OR = odds ratio.

Table 5

Univariate and multivariate logistic regression analyses for macroscopic bleeding.

	Univariate logistic regression			Multivariate logistic regression		
Variable	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**
Age						
60–70 years vs 60 years	.004	2.30	1.31–4.05	.03	2.20	1.07–4.52
≥70 years vs 60 years	.33	1.35	0.74–2.44	.39	1.36	0.67–2.75
Nationality (Han vs. others)	.75	0.92	0.57–1.51			
Previous coronary angioplasty (yes vs no)	.001	2.61	1.46–4.68	.30	2.53	0.44–14.60
Coronary artery disease (yes vs no)	.01	2.02	1.17–3.49	.44	0.53	0.10–2.68
Gender (male vs female)	.02	1.69	1.07–2.67	.04	0.37	0.15–0.94
Previous stroke (yes vs no)	<.001	3.51	2.21–5.58	.33	1.36	0.74–2.51
Hypertension (yes vs no)	<.001	2.87	1.77–4.64	<.001	2.68	1.55–4.63
Hyperlipidemia (yes vs no)	<.001	2.96	1.87–4.68	.01	2.06	1.18–3.60
Alcohol addiction (yes vs no)	<.001	2.83	1.79–4.48	.01	3.72	1.40–9.88
Smoking (yes vs no)	<.001	2.38	1.51–3.75	.87	1.07	0.49–2.31
Diabetes mellitus (yes vs no)	<.001	5.14	3.13–8.45	<.001	3.82	2.10–6.96
White matter hyperintensities (yes vs no)	<.001	3.79	2.32–6.18	.36	1.37	0.70–2.67
Treatment (aspirin vs clopidogrel)	.57	0.88	0.56–1.37			
Duration of treatment (≤5 years vs >5 years)	.81	1.06	0.68–1.65			

CI = confidence interval, OR = odds ratio.

agent for >5 years showed elevated risk of both CMBs and macroscopic bleeding. Taken together, our novel data indicate that the presence of CMBs in patients with CVD is associated with elevated risks of both WMHs and macroscopic bleeding. Treatment (aspirin vs clopidogrel) had no impact on the occurrence of CMBs or macroscopic bleeding.

There is some debate regarding whether antiplatelet drug use increases the risk of CMBs. Some previous studies have suggested that the prevalence of CMBs may be elevated in patients treated with antiplatelet drugs in comparison with nonusers, particularly those with intracerebral hemorrhage, ischemic stroke or TIA.[21,22,37] However, not all investigations have observed an influence of antiplatelet agents on the frequency of CMBs,[25–27] and some have concluded that the effect was mediated only on deep CMBs and not lobar CMBs.[28] The present study was not designed to assess whether therapy with aspirin or clopidogrel for at least 1 year was associated with an enhanced risk of CMBs compared with nonusers. However, the prevalences of CMBs in the aspirin group (40.0%) and clopidogrel group (30.7%) were broadly in keeping with other studies of patients with CVD receiving therapy with antiplatelet agents. For example, a meta-analysis determined that the incidence of CMBs in patients taking antiplatelet drugs was 66.7% (range, 33.3–93.3%; pooled from 12 studies) in those with intracerebral hemorrhage and 32.1% (range, 14.3–52.9%; pooled from 11 studies) in those with cerebral infarct or TIA.[22] Some reports have suggested that CMB risk may be elevated by aspirin use in comparison to use of other inhibitors of platelet aggregation.[18,21,38] However, in the present study, there was no significant difference in the prevalence of CMBs between the aspirin group and clopidogrel group, and the multivariate analyses showed that there were no differences between aspirin and clopidogrel. This is in line with previous studies that showed no difference in bleeding recurrence between those 2 drugs,[39,40] but this is controversial.[41] Further clinical investigations are merited to definitively establish whether or not aspirin is associated with a heightened risk of CMBs compared with clopidogrel or other inhibitors of platelet aggregation.

We observed that the presence of CMBs was significantly associated with the prevalence and severity of WMHs. Consistent with our observations, numerous other studies have reported an association between the severity of WMHs and CMBs, both in healthy subjects and in patients with stroke.[9–11,31–34,42–44] The relationship between the distribution of CMBs and WMH has also been explored, with previous investigations reporting associations of WMHs with deep, lobar and diffuse (i.e. both deep and lobar) CMBs.[11,43,45] Interestingly, a recent study concluded that although the presence of CMBs was independently associated with the severity of periventricular WMHs, the relationship with deep WMHs was found only in patients with hypertension.[46]

An important finding of our study was that the presence of CMBs was strongly associated with intracerebral bleeding. This is in agreement with previous research indicating that the number of CMBs in patients with ischemic stroke treated with antithrombotic agents was related to increased risks of both intracerebral hemorrhage and death from intracerebral hemorrhage.[24] Another report found that, compared with controls, patients with ischemic CVD treated with aspirin for >1 year had higher frequencies of both CMBs (40% vs 12%) and intracerebral hemorrhage (28% vs 1%).[47] Furthermore, in patients taking an antiplatelet drug, CMBs were detected more frequently in those with intracerebral hemorrhage than in those without intracerebral hemorrhage, implying that CMBs are associated with antiplatelet-related intracerebral hemorrhage.[23] The CMBs may also be a risk factor for intracerebral hemorrhage related to warfarin, another antithrombotic agent.[22,25,26] Interestingly, incident intracerebral hemorrhage was reported to be associated with higher numbers of total, deep and paraventricular WMHs,[48] supporting the relationship between CMBs, WMHs, and macroscopic bleeding observed in our study.

The present study also determined that CMBs and intracerebral bleeding were strongly associated with the duration of antiplatelet therapy. A previous investigation also found that the frequency of CMBs was higher in patients with ischemic CVD treated with aspirin for >5 years than in those treated for ≤ 5 years.[47] A relationship between duration of aspirin therapy (>10 years vs ≤ 10 years) and deep or infratentorial microbleeds was also reported, but this effect became nonsignificant after adjustment for hypertension and other factors.[49] In elderly subjects, aspirin use for >5 years did not

enhance the risk of CMBs.[50] In addition, a study showed that the bleeding events tend to concentrate around the therapeutic switch, but the present study did not include patients who switched treatment.[51] Furthermore, the present study did not examine the resistance to aspirin or clopidogrel. Additional study is needed to confirm whether the duration of antiplatelet therapy affects the risk of CMBs. Resistance markers such as platelet reactivity, pharmacometabolomics, and microRNAs should also be examined.[51–54]

This study has some limitations. First, this is a retrospective study and so is prone to information bias and selection bias. Also, since the study was not prospective in design, strong evidence regarding the associations between CMBs and clinical outcomes such as intracerebral hemorrhage and mortality could not be obtained. Second, this was a single-center study, so the generalizability of the findings is not known. Third, although the sample size was not particularly small, the study may have been underpowered to detect certain differences between groups. Fourth, unknown confounding factors not included in the analysis may have influenced the results. Fifth, the distributions of CMBs and WMHs and their associations were not explored. Sixth, the exact time at bleeding event occurrence could not be determined; this will be examined in a future prospective trial. Finally, hypertension might influence the results and future studies should be conducted independently in hypertensive and non-hypertensive subjects. In addition, there was no difference between aspirin and clopidogrel. As a retrospective analysis, there was no data about optimal treatment or compliance.

In conclusion, our data indicate that the presence of CMBs in patients taking aspirin or clopidogrel with ischemic CVD is associated with elevated risks of both WMHs and macroscopic bleeding. Furthermore, the duration of antiplatelet therapy may also influence the prevalences of CMBs and macroscopic hemorrhage.

Author contributions

Conceptualization: Lihong Ge, Haixia Yu, Junguo Liang.
Data curation: Lihong Ge, Xuehui Ouyang, Chao Ban, Haixia Yu.
Formal analysis: Lihong Ge, Xuehui Ouyang, Chao Ban, Haixia Yu.
Investigation: Chao Ban, Haixia Yu.
Methodology: Lihong Ge, Chao Ban, Haixia Yu, Qiong Wu.
Project administration: Lihong Ge, Qiong Wu.
Resources: Qiong Wu, Hui Wu.
Software: Xuehui Ouyang, Hui Wu.
Supervision: Hui Wu.
Validation: Hui Wu.
Writing – original draft: Lihong Ge, Xuehui Ouyang.
Writing – review & editing: Lihong Ge, Xuehui Ouyang, Chao Ban, Hui Wu, Junguo Liang.

References

[1] Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 2009;8:2.165–174.
[2] Yates PA, Villemagne VL, Ellis KA, et al. Cerebral microbleeds: a review of clinical, genetic, and neuroimaging associations. Front Neurol 2014;4:205.
[3] Vernooij MW, Ikram MA, Wielopolski PA, et al. Cerebral microbleeds: accelerated 3D T2*-weighted GRE MR imaging versus conventional 2D T2*-weighted GRE MR imaging for detection. Radiology 2008;248:1.272–277.
[4] Boeckh-Behrens T, Lutz J, Lummel N, et al. Susceptibility-weighted angiography (SWAN) of cerebral veins and arteries compared to TOF-MRA. Eur J Radiol 2012;81:6.1238–1245.
[5] Jeon SB, Kang DW, Cho AH, et al. Initial microbleeds at MR imaging can predict recurrent intracerebral hemorrhage. J Neurol 2007;254:4.508–512.
[6] Greenberg SM, Eng JA, Ning M, et al. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke 2004;35:6.1415–1420.
[7] Nishikawa T, Ueba T, Kajiwara M, et al. Cerebral microbleeds predict first-ever symptomatic cerebrovascular events. Clin Neurol Neurosurg 2009;111:10.825–828.
[8] Senior K. Microbleeds may predict cerebral bleeding after stroke. Lancet 2002;359:9308.769.
[9] Gao T, Wang Y, Zhang Z. Silent cerebral microbleeds on susceptibility-weighted imaging of patients with ischemic stroke and leukoaraiosis. Neurol Res 2008;30:3.272–276.
[10] Pettersen JA, Sathiyamoorthy G, Gao FQ, et al. Microbleed topography, leukoaraiosis, and cognition in probable Alzheimer disease from the Sunnybrook dementia study. Arch Neurol 2008;65:6.790–795.
[11] Poels MM, Vernooij MW, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. Stroke 2010;41(10 Suppl.):S103–106.
[12] Sveinbjornsdottir S, Sigurdsson S, Aspelund T, et al. Cerebral microbleeds in the population based AGES-Reykjavik study: prevalence and location. J Neurol Neurosurg Psychiatry 2008;79:9.1002–1006.
[13] Blitstein MK, Tung GA. MRI of cerebral microhemorrhages. AJR Am J Roentgenol 2007;189:3.720–725.
[14] Dichgans M, Holtmannspotter M, Herzog J, et al. Cerebral microbleeds in CADASIL: a gradient-echo magnetic resonance imaging and autopsy study. Stroke 2002;33:1.67–71.
[15] Jeerakathil T, Wolf PA, Beiser A, et al. Cerebral microbleeds: prevalence and associations with cardiovascular risk factors in the Framingham Study. Stroke 2004;35:8.1831–1835.
[16] Wieberdink RG, Poels MM, Vernooij MW, et al. Serum lipid levels and the risk of intracerebral hemorrhage: the Rotterdam Study. Arterioscler Thromb Vasc Biol 2011;31:12.2982–2989.
[17] Huo YZY, Han Y, Yan H, et al. Cardiovascular diseases in China – the Blue Book. Myocardial infarction (part two). Cardiol Plus 2017;2:1.46–55.
[18] Gorelick PB. Cerebral microbleeds: evidence of heightened risk associated with aspirin use. Arch Neurol 2009;66:6.691–93.
[19] Antithrombotic Trialists C, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:9678.1849–1860.
[20] Naidech AM, Bendok BR, Garg RK, et al. Reduced platelet activity is associated with more intraventricular hemorrhage. Neurosurgery 2009;65:4.684–688. discussion 688.
[21] Vernooij MW, Haag MD, van der Lugt A, et al. Use of antithrombotic drugs and the presence of cerebral microbleeds: the Rotterdam Scan Study. Arch Neurol 2009;66:6.714–720.
[22] Lovelock CE, Cordonnier C, Naka H, et al. Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies. Stroke 2010;41:6.1222–1228.
[23] Gregoire SM, Jager HR, Yousry TA, et al. Brain microbleeds as a potential risk factor for antiplatelet-related intracerebral haemorrhage: hospital-based, case-control study. J Neurol Neurosurg Psychiatry 2010;81:6.679–84.
[24] Soo YO, Yang SR, Lam WW, et al. Risk vs benefit of anti-thrombotic therapy in ischaemic stroke patients with cerebral microbleeds. J Neurol 2008;255:11.1679–686.
[25] Ueno H, Naka H, Ohshita T, et al. Association between cerebral microbleeds on T2*-weighted MR images and recurrent hemorrhagic stroke in patients treated with warfarin following ischemic stroke. AJNR Am J Neuroradiol 2008;29:8.1483–1486.
[26] Orken DN, Kenangil G, Uysal E, et al. Cerebral microbleeds in ischemic stroke patients on warfarin treatment. Stroke 2009;40:11.3638–3640.
[27] Nishikawa T, Ueba T, Kajiwara M, et al. Cerebral microbleeds in patients with intracerebral hemorrhage are associated with previous cerebrovascular diseases and white matter hyperintensity, but not with regular use of antiplatelet agents. Neurol Med Chir (Tokyo) 2009;49:8.333–338. discussion 338-339.
[28] Romero JR, Preis SR, Beiser A, et al. Risk factors, stroke prevention treatments, and prevalence of cerebral microbleeds in the Framingham Heart Study. Stroke 2014;45:5.1492–1494.

[29] Etherton MR, Wu O, Rost NS. Recent advances in leukoaraiosis: white matter structural integrity and functional outcomes after acute ischemic stroke. Curr Cardiol Rep 2016;18:12.123.
[30] Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010;341:c3666.
[31] Fan YH, Mok VC, Lam WW, et al. Cerebral microbleeds and white matter changes in patients hospitalized with lacunar infarcts. J Neurol 2004;251:5.537–41.
[32] Kato H, Izumiyama M, Izumiyama K, et al. Silent cerebral microbleeds on T2*-weighted MRI: correlation with stroke subtype, stroke recurrence, and leukoaraiosis. Stroke 2002;33:6.1536–1540.
[33] Chowdhury MH, Nagai A, Bokura H, et al. Age-related changes in white matter lesions, hippocampal atrophy, and cerebral microbleeds in healthy subjects without major cerebrovascular risk factors. J Stroke Cerebrovasc Dis 2011;20:4.302–309.
[34] Yamada S, Saiki M, Satow T, et al. Periventricular and deep white matter leukoaraiosis have a closer association with cerebral microbleeds than age. Eur J Neurol 2012;19:1.98–04.
[35] Lee SH, Bae HJ, Yoon BW, et al. Low concentration of serum total cholesterol is associated with multifocal signal loss lesions on gradient-echo magnetic resonance imaging: analysis of risk factors for multifocal signal loss lesions. Stroke 2002;33:12.2845–2849.
[36] Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987;149:2.351–356.
[37] Liu S, Li C. Antiplatelet drug use and cerebral microbleeds: a meta-analysis of published studies. J Stroke Cerebrovasc Dis 2015;24:10.2236–2244.
[38] Huang Y, Cheng Y, Wu J, et al. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study. Lancet Neurol 2008;7:6.494–499.
[39] McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;119:8.624–638.
[40] Tamura T, Sakaeda T, Kadoyama K, et al. Aspirin- and clopidogrel-associated bleeding complications: data mining of the public version of the FDA adverse event reporting system, AERS. Int J Med Sci 2012;9:6.441–446.
[41] Naka H, Nomura E, Kitamura J, et al. Antiplatelet therapy as a risk factor for microbleeds in intracerebral hemorrhage patients: analysis using specific antiplatelet agents. J Stroke Cerebrovasc Dis 2013;22:6.834–840.
[42] Takashima Y, Mori T, Hashimoto M, et al. Clinical correlating factors and cognitive function in community-dwelling healthy subjects with cerebral microbleeds. J Stroke Cerebrovasc Dis 2011;20:2.105–110.
[43] Poels MM, Ikram MA, van der Lugt A, et al. Incidence of cerebral microbleeds in the general population: the Rotterdam Scan Study. Stroke 2011;42:3.656–661.
[44] Tsushima Y, Aoki J, Endo K. Brain microhemorrhages detected on T2*-weighted gradient-echo MR images. AJNR Am J Neuroradiol 2003;24:1.88–96.
[45] Yakushiji Y, Yokota C, Yamada N, et al. Clinical characteristics by topographical distribution of brain microbleeds, with a particular emphasis on diffuse microbleeds. J Stroke Cerebrovasc Dis 2011;20: 3.214–221.
[46] Gao Z, Wang W, Wang Z, et al. Cerebral microbleeds are associated with deep white matter hyperintensities, but only in hypertensive patients. PLoS One 2014;9:3e91637.
[47] Ge L, Niu G, Han X, et al. Aspirin treatment increases the risk of cerebral microbleeds. Can J Neurol Sci 2011;38:6.863–868.
[48] Kaffashian S, Tzourio C, Zhu YC, et al. Differential effect of white-matter lesions and covert brain infarcts on the risk of ischemic stroke and intracerebral hemorrhage. Stroke 2016;47:7.1923–1925.
[49] Yamashiro K, Tanaka R, Okuma Y, et al. Associations of durations of antiplatelet use and vascular risk factors with the presence of cerebral microbleeds. J Stroke Cerebrovasc Dis 2014;23:3.433–440.
[50] Kim CK, Kwon HT, Kwon HM. No significant association of aspirin use with cerebral microbleeds in the asymptomatic elderly. J Neurol Sci 2012;319:1-2.56–58.
[51] Caiazzo G, De Rosa S, Torella D, et al. Administration of a loading dose has no additive effect on platelet aggregation during the switch from ongoing clopidogrel treatment to ticagrelor in patients with acute coronary syndrome. Circ Cardiovasc Interv 2014;7:1.104–12.
[52] Giustino G, Redfors B, Kirtane AJ, et al. Platelet reactivity and risk of ischemic stroke after coronary drug-eluting stent implantation: from the ADAPT-DES study. JACC Cardiovasc Interv 2018;11:13.1277–286.
[53] Amin AM, Sheau Chin L, Teh CH, et al. Pharmacometabolomics analysis of plasma to phenotype clopidogrel high on treatment platelets reactivity in coronary artery disease patients. Eur J Pharm Sci 2018;117: 351–61.
[54] Carino A, De Rosa S, Sorrentino S, et al. Modulation of circulating microRNAs levels during the switch from clopidogrel to ticagrelor. Biomed Res Int 2016;2016:3968206.