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Safety and efficacy of low-dose aspirin in ischemic stroke patients with different G6PD conditions

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Abstract

Background and purpose: Aspirin is the first recommended antiplatelet agent to prevention secondary stroke, but its safety and efficacy in stroke patients with glucose-6-phosphate dehydrogenase deficiency remain unclear. We sought to evaluate its safety and efficacy in ischemic stroke patients with and without glucose-6-phosphate dehydrogenase deficiency.

Methods: Patients with ischemic stroke receiving aspirin (100 mg/day) for three months were recruited for a multi-center, prospective, cohort study. Blood glucose-6-phosphate dehydrogenase activity was examined after stroke. Safety outcomes including acute hemolysis, moderate-to-severe bleeding, and death (vascular, all-cause), and efficacy outcome indicated as stroke recurrence were evaluated at three months. Risk factors associated with moderate-to-severe bleeding and all-cause death were determined using multivariate or Cox regression analysis.

Results: Among the included 1121 patients, 81 of 130 glucose-6-phosphate dehydrogenase deficient and 576 of 991 glucose-6-phosphate dehydrogenase normal patients received aspirin for three months. Acute hemolysis was observed in one of the glucose-6-phosphate dehydrogenase deficient and in none of the glucose-6-phosphate dehydrogenase normal patients ($p = 0.876$). The rates of moderate-to-severe bleeding were 2.5% and 0.3% ($p = 0.045$), and the percentages of all-cause death were 6.2% and 1.4% ($p = 0.008$) in the glucose-6-phosphate dehydrogenase deficient and glucose-6-phosphate dehydrogenase normal patients. Stroke recurrence rate was similar in the two groups (2.5% vs. 1.7%; $p = 0.608$). Glucose-6-phosphate dehydrogenase deficiency was significantly associated with increased risk of moderate-to-severe bleeding (adjust $p = 0.048$) and all-cause death during aspirin use (adjust $p = 0.008$).

Conclusions: Long-term low-dose aspirin therapy might relate to worse safety outcomes in patients with glucose-6-phosphate dehydrogenase deficiency and large clinical trials are needed to further confirm these findings.

Keywords

Aspirin, G6PD deficiency, ischemic stroke, safety, efficacy

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Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme deficiency in human, affecting more than 400 million people worldwide.[1,2] The global prevalence of G6PD deficiency is estimated to be 4.9%, and Asia is one of the highest epidemic areas.[1] G6PD catalyzes the rate-determining step in the pentose phosphate pathway and produces nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) to fuel glutathione recycling. The glutathione pathway is paramount to antioxidant defense, and G6PD-deficient cells do not cope well with oxidative damage.[1,3,4] The most common clinical manifestations are neonatal jaundice and acute hemolytic anemia, which in most patients is triggered by an exogenous agent.[1] Aspirin is a common oxidizing agent,[1,3] which has been widely used for long-term stroke prevention worldwide.[5,6] However, its safety and efficacy in stroke patients with G6PD deficiency have not reached an agreement. It has reported that high-dose aspirin (>400 mg/day) induced hemolysis in patients with G6PD deficiency,[7–12] although other has found that G6PD-deficient patients did not develop hemolysis with a three-month aspirin therapy at 250 mg per day after ischemic heart disease.[13] Bleeding is a common but severe complication after aspirin treatment, which may lead to a poor stroke outcome.[6] A family history of G6PD deficiency has been associated with an increased risk of antepartum hemorrhage.[14] These findings suggest that safety of aspirin appears to be worse in ischemic stroke patients with G6PD deficiency, and its efficacy needs to be further investigated. In this study, we aimed to compare the safety and efficacy outcomes of low-dose aspirin (100 mg/day) therapy in patients with and without G6PD deficiency at three months after ischemic stroke, in order to evaluate the influence of G6PD deficiency on aspirin treatment for secondary stroke prevention.

Methods

Study design and participants

The prospective and multicenter observational study, recruiting acute ischemic stroke patients presenting of symptoms within seven days, was conducted in four clinical centers in South China (Supplementary Figure S1) between March 2015 and November 2017. The inclusion criteria were (1) age ≥18 years; (2) evidence of cerebral infarction on computed tomography or magnetic resonance imaging; and (3) consecutive use of low-dose aspirin (100 mg/day) for more than three months after stroke onset. The exclusion criteria mainly included (1) hemorrhagic stroke or other pathological brain disease; (2) a modified Rankin Scale (mRS) score ≥2 before stroke onset; (3) comorbidity with other hemolytic diseases, including thalassemia; (4) baseline hemoglobin level < 90 g/L; (5) use of medications contraindicated to G6PD deficiency[3]; (6) aspirin treatment within one month before enrollment; (7) clopidogrel-aspirin therapy then clopidogrel alone; (8) any anticoagulant therapy; (9) severe organ dysfunction or malignancy with an expected survival duration less than three months. The study was approved by local ethics committees for clinical scientific research and animal ethics at each clinical center. Written informed consent was obtained from each participant.

Diagnosis of G6PD deficiency

The qualitative G6PD level was examined on the second day after admission. G6PD deficiency was defined by the level of blood G6PD activity (<1300 U/L) or the ratio of G6PD/6-phosphogluconate dehydrogenase (<1.0) using standard quantitative approaches, which detect NADPH production from nicotinamide adenine dinucleotide phosphate (NADP).[1]

Data collection and outcome measures

The baseline characteristics, medical history, neurological deficits, infarct volumes, bleeding and coagulation function as well as antiplatelet regimen were collected. The participants were followed up at three months through face-to-face visits to the local hospital or by telephone for those who were unable to or refused to return to the hospital. Antiplatelet treatments and concomitant medications (especially those contraindicated for G6PD deficiency) were recorded. Participants with aspirin alone or those with clopidogrel-aspirin for 21 days[15] then aspirin alone for three months were included in the analyses. The data that support the findings of this study are available from the corresponding author upon reasonable request.

The safety outcomes included acute hemolysis, moderate-to-severe bleeding, and death (vascular, all-cause) at three months. Acute hemolysis was defined as the presentation of fatigue, back pain, jaundice, dark urine as well as laboratory parameters indicating a >10% decrease in the hemoglobin level and serum bilirubin level >24 μmol/L.[13,16] Bleeding was defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.[17] Moderate hemorrhage was defined as bleeding that required a blood transfusion but did not lead to a hemodynamic compromise requiring intervention. Severe hemorrhage was defined as a fatal or intracranial hemorrhage or other hemorrhage causing a hemodynamic compromise for which blood or fluid replacement, inotropic support, or surgical intervention were required.[17]

Vascular death was defined as death due to stroke (ischemic or hemorrhagic), systemic hemorrhage, myocardial infarction, congestive heart failure, pulmonary embolism, sudden death, or arrhythmia.[15] The efficacy outcome was defined as new stroke events (ischemic or hemorrhagic) at three months. Stroke event was defined as rapid onset of focal neurological deficits of presumably vascular origin with a duration of $\geq$24 h.[18]

Statistical analysis

The sample size calculation is presented in Supplementary File S1. Categorical variables are presented as proportion and continuous variables are presented as median and interquartile range (IQR). Differences of baseline characteristics and outcomes between the G6PD-deficient and G6PD-normal groups were compared using Chi-square test for categorical variables or Wilcoxon rank-sum test for continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) for associations of G6PD deficiency with safety and efficacy outcomes were determined using Cox models. Risk factors for moderate-to-severe bleeding were identified using multivariable regression logistic model and those for all-cause death were determined using Cox regression model. All statistical analyses were conducted using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

Results

A total of 1121 patients with acute ischemic stroke were included in the study, of which 130 (11.6%) were identified as G6PD-deficient and 991 (88.4%) as G6PD-normal (Figure 1). Ninety-five patients (5 with G6PD deficiency and 90 with normal G6PD) were excluded because of loss to follow-up or unknown antiplatelet treatments at three months. Aspirin (100 mg/day) was used for three months in 81 (64.8%) patients with G6PD deficiency and 576 (63.9%) with normal G6PD.

Baseline characteristics

The basic clinical characteristics are shown in Table 1. Patients with G6PD deficiency had higher proportions of stroke history (24.7% vs. 13.5%, $p=0.008$) and atrial fibrillation (8.6% vs. 2.4%, $p=0.008$) yet a lower rate of hyperlipidemia (18.5% vs. 34.9%, $p=0.003$) compared with those with normal G6PD. The median baseline prothrombin time was longer in patients with G6PD deficiency compared to those with normal G6PD (11.4 vs. 11.2 s, $p=0.029$). No significant differences were found between the two groups in other baseline parameters including age, sex, previous history of hypertension, diabetes, coronary heart disease, smoking, drinking, infarct volumes, National Institute of Health Stroke Scale (NIHSS) scores, pulmonary infection, hospitalization duration, and antiplatelet treatment (all $p>0.05$).

Safety outcomes

Acute hemolysis was observed in 1 (1.2%) of the 81 G6PD-deficient patients and in none of the G6PD-normal patients with aspirin treatment ($p=0.876$; Table 2). Patients with G6PD deficiency showed a

Figure 1. Flowchart showing patient selection.

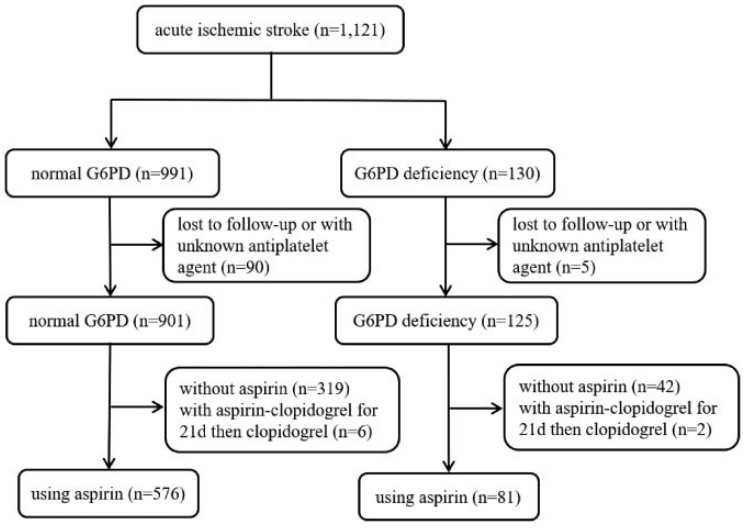


Table 1. Patient baseline characteristics.

Characteristics	G6PD-deficient ($n = 81$)	G6PD-normal ($n = 576$)
Age, median (IQR), y	65 (54–76)	63 (54–71)
Male, % (*n*)	66.7 (54)	73.3 (422)
Medical history, % (*n*)		
Previous stroke/TIA	24.7 (20)	13.5 (78)
Hypertension	75.3 (61)	72.4 (417)
Diabetes	27.2 (22)	30.4 (175)
Hyperlipidemia	18.5 (15)	34.9 (201)
Coronary heart disease	13.6 (11)	8.7 (50)
Atrial fibrillation	8.6 (7)	2.4 (14)
Smoking, % (*n*)	42.0 (34)	42.7 (246)
Drinking, % (*n*)	23.5 (19)	18.6 (107)
NIHSS score, median (IQR)	5 (3, 9)	5 (3, 9)
Infarct volume, median (IQR)	3.1 (1.2–17.3)	3.4 (1.3–13.9)
PT, median (IQR), s	11.4 (10.9–12.2)	11.2 (10.6–11.8)
APTT, median (IQR), s	29.8 (27.0–33.9)	29.9 (26.5–33.1)
Pulmonary infection, % (*n*)	16.0 (13)	9.5 (55)
Time from symptom to hospitalization, median (IQR), d	2 (1–4)	2 (1–4)
Hospitalization duration, median (IQR), d	10 (7–15)	10 (7–13)
Antiplatelet treatment, % (*n*)		
Aspirin alone	71.6 (58)	74.5 (429)
Clopidogrel-aspirin for 21 days then aspirin	28.4 (23)	25.5 (147)

APTT: activated partial thromboplastin time; G6PD: glucose-6-phosphate dehydrogenase; IQR: interquartile range; NIHSS: National Institute of Health Stroke Scale; PT: prothrombin time; TIA: transient ischemic attack.

higher rate of moderate-to-severe bleeding, as compared with their G6PD-normal counterparts (OR 7.45, 95% CI 1.05–52.91, $p = 0.045$; Table 2). The incidences of mild bleeding ($p = 0.506$) or any bleeding ($p = 0.506$) event did not significantly differ between the two groups. Death from vascular causes was found in three (3.7%) of the G6PD-deficient patients and five (0.9%) of the G6PD-normal patients (OR 4.41, 95% CI 1.05–18.44, $p = 0.042$; Table 2). Death from all causes occurred in five (6.2%) of the G6PD-deficient patients compared with eight (1.4%) of the G6PD-normal patients (OR 4.58, 95% CI 1.50–14.00, $p = 0.008$). At three months, 76 (93.8%) of the 81 G6PD-deficient patients and 568 (98.6%) of the 576 G6PD-normal patients survived ($p = 0.003$; Figure 2).

Efficacy outcomes

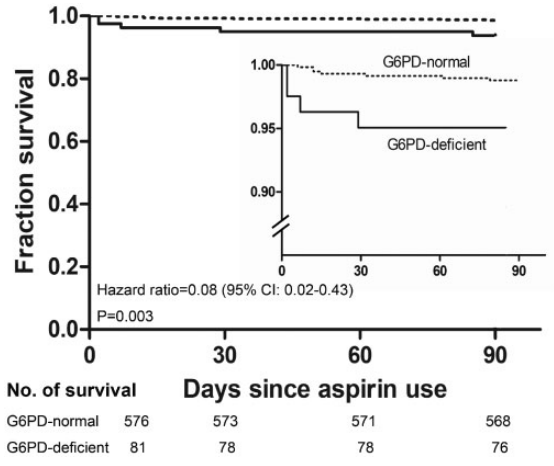
Recurrence of stroke (ischemic or hemorrhagic) occurred in 2 (2.5%) of the 81 G6PD-deficient patients and 10 (1.7%) of the 576 G6PD-normal patients at three months (OR 1.49, 95% CI 0.33–1.79, $p = 0.608$; Table 2).

Table 2. Safety and efficacy outcomes at three months.

Outcomes	G6PD-deficient ($n=81$)		G6PD-normal ($n=576$)		Odds ratio (95% CI)
	n	%	*N*	%	
Acute hemolysis	1	1.2	0	0.0	. . .
Bleeding[a]					
Mild	0	0.0	8	1.4	0.04 (0–495.24)
Moderate-severe	2	2.5	2	0.3	7.45 (1.05–52.91)
Any	4	4.9	16	2.8	1.87 (0.62–5.59)
Death					
Vascular	3	3.7	5	0.9	4.41 (1.05–18.44)
All-cause	5	6.2	8	1.4	4.58 (1.50–14.00)
Stroke recurrence	2	2.5	10	1.7	1.49 (0.33–6.79)

[a]Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria as follows: severe bleeding was defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention; moderate bleeding as bleeding that required transfusion of blood but did not lead to hemodynamic compromise requiring intervention; and mild bleeding as bleeding not requiring transfusion and not causing hemodynamic compromise (e.g. subcutaneous bleeding, mild hematomas, and oozing from puncture sites, not including gingival bleeding).
CI: confidence interval; G6PD: glucose-6-phosphate dehydrogenase.

Figure 2. Patient survival rate at three months. The inset shows the same set of data on an enlarged segment of the y axis.



Associations between G6PD deficiency and safety outcomes

Multivariable regression analysis showed that G6PD-deficient patients with aspirin therapy had a higher risk of moderate-to-severe bleeding by adjusting for age, sex, previous stroke or transient ischemic attack (TIA), hypertension, atrial fibrillation, hyperlipidemia, NIHSS scores, baseline coagulation function, and dual antiplatelet regimen when compared to the G6PD-normal patients (OR 7.36, 95% CI 1.02–53.03, adjusted $p=0.048$; Table 3). Death from all causes was significantly associated with G6PD deficiency, previous coronary artery disease, and NIHSS scores (all adjusted $p<0.05$), but not age, sex, stroke history, hypertension, atrial fibrillation, hyperlipidemia, diabetes, baseline prothrombin time, and pulmonary infection in Cox regression analysis (all adjusted $p>0.05$; Table 4).

Non-aspirin group

In patients without aspirin, the baseline characteristics were well balanced between G6PD-deficient ($n=319$) and G6PD-normal individuals ($n=42$; all $p>0.05$; Table S1 online-only Data Supplement). None of the patients in either group developed acute hemolysis at three months. The differences in bleeding (mild, moderate-to-severe, any) and death (vascular, all-cause) between the G6PD-deficient and G6PD-normal groups were not significant (all $p>0.05$). The rates of stroke recurrence (ischemic or hemorrhagic) were 0% in the G6PD-deficient group and 2.5% in the G6PD-normal group ($p=0.503$; Table S2 online-only Data Supplement).

Table 3. Univariable and multivariable regression analysis of risk factors for moderate-to-severe bleeding at three months.

Variables	Univariable Odds ratio (95% CI)	Multivariable[a] Odds ratio (95% CI)
Age	0.97 (0.90, 1.05)	...
Gender	1.00 (0, 1.00)	...
G6PD deficiency	7.27 (1.01, 52.31)	7.36 (1.02, 53.03)
Previous stroke/TIA	1.00 (0, 1.00)	...
Hypertension	1.00 (0, 1.00)	...
Atrial fibrillation	1.00 (0, 1.00)	...
Hyperlipidemia	0.93 (0.17–5.08)	...
NIHSS score	1.12 (0.97, 1.30)	...
PT	1.03 (0.81, 1.30)	...
APTT	1.00 (0.82, 1.23)	...
INR	1.53 (0.10, 24.44)	...
Fib	0.75 (0.28, 2.01)	...
Clopidogrel-aspirin for 21 d	0.96 (0.10, 9.24)	...

[a]Models are built using stepwise regression with variables which entered the model at the 0.10 significant level and removed at the 0.05 significant level.
APTT: activated partial thromboplastin time; Fib: fibrinogen; CI: confidence interval; G6PD: glucose-6-phosphate dehydrogenase; INR: international normalized ration; NIHSS: National Institute of Health Stroke Scale; PT: prothrombin time; TIA: transient ischemic attack.

Discussion

We have found that G6PD deficiency was a risk predictor for moderate-to-severe bleeding and all-cause death at three months in ischemic stroke patients treated with low-dose aspirin. Aspirin could still induce acute hemolysis among G6PD-deficient patients after acute stage of stroke. However, stroke recurrence was similar in patients with aspirin therapy regardless of G6PD condition. These findings suggest that G6PD deficiency might be associated with worse safety outcomes in those using long-term low-dose aspirin, but it needs to be confirmed by large randomized controlled clinical trials.

Although aspirin has been considered as a potential hemolytic agent contraindicated to G6PD-deficient patients,[5–10,19] evidence of case studies on myocardial infarction has demonstrated that low-dose aspirin use (100 mg/day) did not cause hemolysis in patients with G6PD-deficiency in long-term duration.[16,20–23] Therefore, low-dose aspirin (100 mg/day) use in G6PD-deficient patients has been proposed.[23] However, we observed acute hemolysis presenting itself as jaundice, back pain, and dark urine in 1 out of 81 G6PD-deficient patients receiving aspirin (100 mg/day) for two months without other medications using contraindicated to G6PD deficiency, infections, or consuming fava bean. The 83-year-old patient had a marked decrease in hemoglobin level from 152.0 g/L to 119.0 g/L, erythrocytes counts from 5.40×10^{12}/L to 4.17×10^{12}/L, and an increase in total bilirubin level from 48.4 to 88.1 μmol/L (Supplementary Table S3). His residual G6PD enzyme activity was detected at a level of 3%. Residual G6PD enzyme activity and drug metabolism affect the risk of hemolysis.[19,24] Considering the discrepancies regarding ages and residual G6PD activity in the cases as previously reported,[16,20–23] hemolysis crisis in our patient is supposed to relate to a lower residual G6PD activity and an elder age.

It looks like that the risk of hemolysis is low induced by aspirin in patients with G6PD deficiency. However, neither enough attention has been paid to this issue in previous studies. Apart from symptomatic hemolysis with jaundice, back pain, and dark urine, drug-induced hemolysis on G6PD deficiency can also be asymptomatic, indicated as decline in hemoglobin levels.[25,26] In our population, we further evaluated hemoglobin decrease after using aspirin between the two groups,

Table 4. Cox regression analysis of risk factors for all-cause death at three months.

Variables	Cox regression[a] Odds ratio (95% CI)
Age	...
Sex	...
G6PD deficiency	5.60 (1.70, 18.46)
Previous stroke/TIA	...
Atrial fibrillation	...
Hypertension	...
Diabetes	...
Coronary artery disease	3.78 (1.24, 11.55)
Hyperlipidemia	...
PT	...
Pulmonary infection	...
NIHSS score	1.35 (1.23, 1.48)

[a]Models were built using stepwise regression with variables entered the model at the 0.10 significant level and removed at the 0.05 significant level. CI: confidence interval; G6PD: glucose-6-phosphate dehydrogenase; NIHSS: National Institute of Health Stroke Scale; PT: prothrombin time; TIA: transient ischemic attack.

and found that G6PD-deficient patients demonstrated a higher percentage of hemoglobin decrease of $\geq$25 g/L or 25% (15.0% vs. 3.3%, $p = 0.006$). Lower hemoglobin level is suggested to be associated with a worse stroke outcome.[27,28] Collectively, these findings call into the attention regarding the hemolytic risk of low-dose aspirin therapy in G6PD-deficient patients.

To our best knowledge, this is the first time that the association between long-term aspirin use and bleeding in G6PD-deficient stroke patients has been confirmed in a large cohort. Family history of G6PD deficiency has been shown to be associated with an increased risk of antepartum hemorrhage among neonates in Qatar where G6PD deficiency is highly prevalent.[14] A G6PD-deficient neonate was found to develop adrenal hemorrhage several days after birth.[29] However, G6PD deficiency did not increase risks of spontaneous intracranial hemorrhage,[30] or risks of intracranial hemorrhage transformation in patients with intravenous thrombolysis.[31] Our study demonstrated that G6PD-deficient patients with aspirin therapy had a significant higher risk of moderate-to-severe bleeding. The dual administration of aspirin and clopidogrel for 21 days was balanced between the two groups, which excluded the potentially confounding effects of dual antiplatelet therapy on bleeding. All of the patients developing bleeding did not have atrial fibrillation and intracranial hemorrhage, which could also exclude the complication of intracranial hemorrhagic transformation after cardioembolic infarct. Deficiency of the G6PD enzyme causes excessive oxidative stress in endothelial cells, and contributes to the pathophysiology of vasoculopathy.[4,32] G6PD deficiency also decreases endothelial nitric oxide bioavailability, and thereby contributes to vascular dysfunction.[33] The involvement of abnormal reactive oxygen species and nitric oxide metabolisms in the onset and progression of vascular pathology might increase the risk of bleeding after aspirin therapy in patients with G6PD deficiency.

Another important finding is that a higher incidence of all-cause death at three months was observed in G6PD-deficient patients taking aspirin in our study. The G6PD-deficient group was also found to have more vascular death than the G6PD-normal group. Multivariable analyses shown that all-cause death was associated with G6PD deficiency, NIHSS scores, coronary artery disease, and pulmonary infection. However, as reported in baseline characteristics (Table 1), the severity of neurological deficits and the occurrence of pulmonary infection were balanced between the two groups. Although G6PD-deficient patients have a higher percentage of coronary artery disease, the OR value of G6PD deficiency contributed to all-cause death was the highest among these factors in multivariable analyses. These indicated that G6PD deficiency was a significant risk factor for death in patients receiving low-dose aspirin.

In this study, the prevalence of G6PD deficiency among ischemic stroke patients (11.6%) is higher than those of epidemiological studies showing a mean prevalence of 4.29% (ranging 0–17.4%).[34] This leads to speculate whether G6PD deficiency possibly increases a risk of stroke. G6PD deficiency is significantly related to an increased risk for cerebral vasculopathy and ischemic events in sickle cell anemia individuals.[35,36] Conversely, other studies have reported that G6PD deficiency does not contribute to stroke risk.[37–39] Therefore, the association between G6PD deficiency and stroke still remains controversial. Given the fact that our participants were recruited from regions with high prevalence of G6PD deficiency (e.g. 13.6–14.1% in the "Zhuang" nationality of Guangxi Province[34]), our results cannot imply the casual impacts of G6PD deficiency on stroke risk.

There are several limitations of this study. One major limitation is a small number of events at three months. Consequently, risk factors associated with hemolysis could not be determined and the power to

estimate the effects of covariates associated with bleeding and death was poor. Nevertheless, this study features a relatively larger sample size among studies on the effects of aspirin use in G6PD-deficient patients, even though the prevalence of G6PD deficiency ranges from 4 to 10% worldwide.[1,2] Another limitation is the study design and data collection. Confounding variables, including concomitant medications and diseases, are inevitable because of the observational nature of the study and may have affected the outcome measurements to some extent. However, all participants were requested to refrain from using other medications contraindicated for G6PD deficiency. As the current-related literature comprises case reports and observational studies, we are conducting a randomized controlled trial to further elucidate the safety and efficacy of low-dose aspirin in ischemic stroke patients with G6PD deficiency (NCT04088513) to further determine the relationship between G6PD deficiency and outcomes with aspirin treatment.

In conclusion, G6PD deficiency may be a potential risk factor for moderate-to-severe bleeding and all-cause death at three months in ischemic stroke patients treated with low-dose aspirin, and the ongoing randomized controlled trial will further make clear the influence of G6PD conditions on aspirin treatment.

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Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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