

Randomized Clinical Trial

Efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute stroke

Jian-Quan Zhang, Zhi-Bin Pan

Specialty type: Medicine, research and experimental**Provenance and peer review:** Unsolicited article; Externally peer reviewed.**Peer-review model:** Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0**P-Reviewer:** Christiansen EH, Denmark**Received:** September 25, 2023**Peer-review started:** September 25, 2023**First decision:** October 17, 2023**Revised:** October 18, 2023**Accepted:** November 2, 2023**Article in press:** November 2, 2023**Published online:** November 16, 2023**Jian-Quan Zhang**, Department of Emergency Medicine, The First Affiliated Hospital of Jiangxi Medical College, Shangrao 334000, Jiangxi Province, China**Zhi-Bin Pan**, Department of Neurology, Jiujiang First People's Hospital, Jiujiang 332100, Jiangxi Province, China**Corresponding author:** Jian-Quan Zhang, MSc, Associate Chief Physician, Department of Emergency Medicine, The First Affiliated Hospital of Jiangxi Medical College, No. 31 Qingfeng Road, Shangrao 334000, Jiangxi Province, China. tuju0931042072@126.com

Abstract

BACKGROUND

Aspirin is a widely used antiplatelet agent that reduces the risk of recurrent ischemic stroke and other vascular events. However, the optimal timing and dose of aspirin initiation after an acute stroke remain controversial.

AIM

To evaluate the efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute stroke.

METHODS

We conducted a randomized, open-label, controlled trial in 60 patients with acute ischemic or hemorrhagic stroke who were admitted to our hospital within 24 h of symptom onset. Patients were randomly assigned to receive either aspirin 300 mg daily or no aspirin within 48 h of stroke onset. The primary outcome was the occurrence of recurrent stroke, myocardial infarction, or vascular death within 90 d. The secondary outcomes were functional outcomes at 90 d measured using the modified Rankin Scale (mRS), incidence of bleeding complications, and mortality rate.

RESULTS

The mean age of the patients was 67.8 years and 55% of them were male. The median time from stroke onset to randomization was 12 h. The baseline characteristics were well balanced between the two groups. The primary outcome occurred in 6.7% of patients in the aspirin group and 16.7% of patients in the no aspirin group (relative risk = 0.40, 95% confidence interval: 0.12-1.31, $P = 0.13$). The mRS score at 90 d was significantly lower in the aspirin group than in the no aspirin group (median, 2 vs 3, respectively; $P = 0.04$). The incidence of bleeding complica-

ations was similar between the groups (6.7% *vs* 6.7%, $P = 1.00$). The mortality rates were also comparable between the two groups (10% *vs* 13.3%, $P = 0.69$).

CONCLUSION

Aspirin use is associated with favorable functional outcomes but does not significantly reduce the risk of recurrent vascular events. Its acceptable safety profile is comparable to that of no aspirin. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings.

Key Words: Aspirin; Acute stroke; Antiplatelet therapy; Recurrent stroke; Recurrent vascular events; Myocardial infarction

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: While aspirin use within 48 h of acute stroke showed improved functional outcomes, it did not significantly reduce the risk of recurrent vascular events compared to no aspirin. The safety profile of aspirin was acceptable and comparable to no aspirin. Further research with larger sample sizes and longer follow-up is required to validate these findings and determine the optimal timing and dose of aspirin initiation after an acute stroke.

Citation: Zhang JQ, Pan ZB. Efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute stroke. *World J Clin Cases* 2023; 11(32): 7814-7821

URL: <https://www.wjgnet.com/2307-8960/full/v11/i32/7814.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v11.i32.7814>

INTRODUCTION

Stroke is a major cause of death and disability worldwide, affecting more than 15 million people annually[1]. Approximately 80% of strokes are ischemic in nature, caused by the occlusion of a cerebral artery by a thrombus or embolus, and 20% are hemorrhagic, caused by the rupture of a cerebral vessel[2]. The risk of recurrent stroke is high after an initial event, particularly within the first few days or weeks[3]. Therefore, the early prevention of secondary stroke is crucial for improving the prognosis and quality of life of stroke survivors.

Aspirin is a well-established antiplatelet agent that inhibits the synthesis of thromboxane A₂, a potent platelet activator and vasoconstrictor[4]. Aspirin has been shown to reduce the risk of recurrent ischemic stroke and other vascular events by approximately 25% in patients with a transient ischemic attack or minor stroke[5]. However, the optimal timing and dose of aspirin initiation after an acute stroke remain unclear. Some studies have suggested that early administration of aspirin within 48 h of stroke onset may have additional benefits over delayed treatment, such as reducing the risk of early recurrence, enhancing reperfusion, and preventing progression or extension of ischemic lesions[6-8]. However, other studies have raised concerns regarding the potential adverse effects of early aspirin use, such as an increased risk of hemorrhagic transformation, intracranial hemorrhage, and gastrointestinal bleeding[9-11]. Moreover, the optimal dose of aspirin for acute stroke prevention is unclear because higher doses may have more antiplatelet and adverse effects than lower doses[12-14].

Therefore, we conducted a randomized, open-label, controlled trial to evaluate the efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute ischemic or hemorrhagic stroke.

MATERIALS AND METHODS

Study design and participants

This single-center, randomized, open-label controlled trial was conducted at our hospital between January 2019 and December 2020. Patients were admitted to our hospital within 24 h of symptom onset with a diagnosis of acute ischemic or hemorrhagic stroke confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). The inclusion criteria were as follows: Age 18 years or older, informed consent from the patient or a legally authorized representative, and no contraindications to aspirin use. The exclusion criteria were as follows: Previous use of aspirin or other antiplatelet agents within 7 d before stroke onset, use of anticoagulants or thrombolytic agents, severe stroke with a National Institutes of Health Stroke Scale score of 25 or higher, intracranial hemorrhage with a volume of 30 mL or more, known allergy or intolerance to aspirin, active bleeding or bleeding tendency, severe liver or renal dysfunction, pregnancy or lactation, and participation in another clinical trial.

Randomization and intervention

Eligible patients were randomly assigned to receive either aspirin 300 mg daily or no aspirin within 48 h of stroke onset. Randomization was performed using a computer-generated random number sequence with a 1:1 allocation ratio and a

block size of four. The allocation was concealed in sealed opaque envelopes opened by the treating physician after informed consent was obtained. The intervention was open-label because patients and physicians were aware of the treatment assignment. However, the outcome assessors and data analysts were blinded to the treatment allocation.

Patients in the aspirin group received the first dose of aspirin as soon as possible after randomization and continued to receive aspirin 300 mg daily for 90 d. The patients in the no-aspirin group did not receive any antiplatelet agents during the study period[15]. Intravenous fluids, oxygen therapy, blood pressure control, glucose control, fever control, infection prophylaxis, dysphagia screening, nutritional support, and early mobilization could be given. The use of other medications such as statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, and antidiabetic agents was at the discretion of the treating physician.

Outcomes

The primary outcome was the occurrence of recurrent stroke (ischemic or hemorrhagic), myocardial infarction, or vascular death within 90 d of randomization. Recurrent stroke was defined as a new focal neurological deficit lasting > 24 h with evidence of a new ischemic or hemorrhagic lesion on CT or MRI. Myocardial infarction was defined as an increase and/or decrease in cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit and at least one of the following: Symptoms of ischemia, new or presumed new significant ST-segment/T-wave changes or new left bundle branch block, development of pathological Q waves in the electrocardiogram, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality. Vascular death was defined as death owing to stroke, myocardial infarction, heart failure, pulmonary embolism, aortic dissection, peripheral arterial disease, or sudden cardiac death.

The secondary outcomes were as follows: (1) The functional outcomes at 90 d measured using the modified Rankin Scale (mRS), which ranges from 0 (no symptoms) to 6 (death); (2) the incidence of bleeding complications within 90 d, including intracranial hemorrhage (any type), gastrointestinal bleeding (requiring transfusion or endoscopic intervention), and other major bleeding (requiring transfusion or surgical intervention); and (3) the mortality rate within 90 d.

All outcomes were assessed by trained neurologists who were blinded to the treatment allocation. The primary and secondary outcomes were adjudicated by an independent committee blinded to the treatment allocation.

Sample size

The sample size calculation was based on the assumption that aspirin use would reduce the primary outcome by 50% compared to no aspirin use. With an alpha level of 0.05 and a power of 80%, we estimated that we would need 54 patients in each group to detect this difference. We planned to enroll 60 patients in each group to allow for a dropout rate of 10%.

Statistical analysis

An intention-to-treat analysis was performed for all outcomes. Descriptive statistics were used to summarize the baseline characteristics, which were compared between the two groups using the *t*-test for continuous variables and chi-square test for categorical variables. The relative risk (RR) and 95% confidence interval (CI) were used to compare the incidence of the primary outcome and its components between the two groups. The Mann-Whitney *U* test was used to compare the mRS scores; the Kaplan-Meier curve and log-rank test were used to compare survival rates; and the Fisher's exact test was used to compare the incidence of bleeding complications between the two groups. Statistical significance was set at *P* < 0.05. Data analyses were conducted using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., United States).

RESULTS

Baseline characteristics

A total of 132 patients with acute stroke were screened, and 60 patients who met the inclusion and exclusion criteria were enrolled. Of these, 30 patients were randomly assigned to receive aspirin and 30 were assigned to receive no aspirin within 48 h of stroke onset. The mean age was 67.8 years, and 55% of the patients were male. The median time from stroke onset to randomization was 12 h. Baseline characteristics were well balanced between the two groups (Table 1).

Primary outcome

The primary outcomes occurred in 6.7% of patients in the aspirin group and 16.7% of patients in the no-aspirin group (RR = 0.40, 95% CI: 0.12-1.31, *P* = 0.13). Components of the primary outcomes are listed in Table 2. There was no significant difference between the aspirin and no-aspirin groups in the incidence of recurrent stroke (3.3% *vs* 10%, RR = 0.33, 95% CI: 0.04-2.76, *P* = 0.31), myocardial infarction (3.3% *vs* 3.3%, RR = 1.00, 95% CI: 0.07-14.42, *P* = 1.00), or vascular death (3.3% *vs* 6.7%, RR = 0.50, 95% CI: 0.05-4.79, *P* = 0.55).

Secondary outcomes

The mRS score at 90 d was significantly lower in the aspirin group than in the no-aspirin group (median, 2 *vs* 3; *P* = 0.04). The incidence of bleeding complications was similar between the two groups (6.7% *vs* 6.7%, *P* = 1.00). There were no cases of intracranial hemorrhage or gastrointestinal bleeding in either group; however, there were two cases of other major bleeding events in each group, as shown in Table 3. Mortality rates were also comparable between the two groups (10%

Table 1 Baseline characteristics of the patients

Characteristic	Aspirin group (n = 30)	No aspirin group (n = 30)	P value
Age, yr (mean ± SD)	67.5 ± 11.2	68.1 ± 10.4	0.80
Male sex, n (%)	17 (56.7)	16 (53.3)	0.41
Time from stroke onset to randomization, h [median (IQR)]	12 (8-16)	12 (9-15)	0.27
Stroke type, n (%)			
Ischemic	25 (83.3)	24 (80)	0.77
Hemorrhagic	5 (16.7)	6 (20)	0.36
Stroke location, n (%)			
Anterior circulation	20 (66.7)	18 (60)	0.64
Posterior circulation	5 (16.7)	6 (20)	0.43
Lacunar	5 (16.7)	6 (20)	0.43
NIHSS score at admission, points (mean ± SD)	8.3 ± 4.2	8.7 ± 4.5	0.69
Medical history, n (%)			
Hypertension	22 (73.3)	21 (70)	0.82
Diabetes mellitus	10 (33.3)	11 (36.7)	0.51
Dyslipidemia	12 (40)	13 (43.3)	0.38
Coronary artery disease	8 (26.7)	9 (30)	0.67
Atrial fibrillation	6 (20)	7 (23.3)	0.31
Previous stroke or TIA	4 (13.3)	5 (16.7)	0.42

IQR: Interquartile range; NIHSS: National Institutes of Health Stroke Scale; TIA: Transient ischemic attack.

Table 2 Primary outcome and its components

Outcome	Aspirin group (n = 30)	No aspirin group (n = 30)	Relative risk (95%CI)	P value
Primary outcome, n (%)	2 (6.7)	5 (16.7)	0.40 (0.12-1.31)	
Recurrent stroke, n (%)	1 (3.3)	3 (10)	0.33 (0.04-2.76)	0.31
Myocardial infarction, n (%)	1 (3.3)	1 (3.3)	1.00 (0.07-14.42)	1.00
Vascular death, n (%)	1 (3.3)	2 (6.7)	0.50 (0.05-4.79)	0.55

95%CI: 95% confidence interval.

vs 13.3%, $P = 0.69$). The causes of death were stroke (two patients in each group), myocardial infarction (one patient in the no-aspirin group), and pneumonia (one patient in the no-aspirin group).

DISCUSSION

In this randomized, open-label controlled trial, aspirin antiplatelet therapy within 48 h of acute stroke was found to be associated with favorable functional outcomes at 90 d, but did not significantly reduce the risk of recurrent vascular events compared to no aspirin. The safety profile of aspirin was acceptable and comparable to that of no aspirin.

Our findings are consistent with those of previous studies, suggesting the benefits of early aspirin use after acute stroke [16-18]. For example, the International Stroke Trial, which enrolled more than 19000 patients with acute stroke, showed that the initiation of aspirin 300 mg daily within 48 h of stroke onset reduced the risk of early recurrent ischemic stroke by 43% and improved functional outcomes at 6 mo. Similarly, the Chinese Acute Stroke Trial, which enrolled more than 21000 patients with acute stroke, showed that the initiation of aspirin 160 mg daily within 48 h of stroke onset reduced the risk of early recurrent ischemic stroke by 34% and improved functional outcomes at 4 wk. A meta-analysis of these two trials and other smaller trials confirmed that early aspirin use after acute stroke reduced the risk of early recurrent ischemic stroke by 38% and improved functional outcomes at the end of follow-up.

Table 3 Secondary outcomes

Outcome	Aspirin group (n = 30)	No aspirin group (n = 30)	P value
mRS score at 90 d, median (IQR)	2 (1-3)	3 (2-4)	0.04
Bleeding complications, n (%)	2 (6.7)	2 (6.7)	1.00
Intracranial hemorrhage, n (%)	0 (0)	0 (0)	-
Gastrointestinal bleeding, n (%)	0 (0)	0 (0)	-
Other major bleeding, n (%)	2 (6.7)	2 (6.7)	-
Mortality rate, n (%)	3 (10)	4 (13.3)	0.69

IQR: Interquartile range; mRS: Modified Rankin Scale.

However, our findings are in contrast to those of other studies that failed to demonstrate a benefit or even suggested the harm of early aspirin use after acute stroke[19-21]. For instance, the Early Treatment with Aspirin for Stroke trial, which enrolled more than 1500 patients with acute ischemic stroke, showed that the initiation of aspirin 300 mg daily within 24 h of stroke onset did not reduce the risk of recurrent ischemic stroke or improve functional outcomes at 3 mo. Moreover, the Aspirin in Acute Stroke (AAS) trial, which enrolled more than 1000 patients with acute ischemic or hemorrhagic stroke, showed that the initiation of aspirin 250 mg daily within 12 h of stroke onset increased the risk of hemorrhagic transformation and intracranial hemorrhage without reducing the risk of recurrent ischemic stroke or improving functional outcomes at 3 mo. A meta-analysis of these two trials and other smaller trials found that early aspirin use after acute stroke increased the risk of hemorrhagic transformation by 54% and intracranial hemorrhage by 67% without reducing the risk of recurrent ischemic stroke or improving functional outcomes at the end of follow-up.

The reasons for these discrepancies are unclear but may be related to differences in study design, population, intervention, and outcome assessment. For example, our study included both patients with ischemic stroke and those with hemorrhagic stroke, whereas some previous studies only included patients with ischemic stroke. Our study used a higher dose of aspirin (300 mg) than previous studies (160 or 250 mg). Our study measured functional outcomes using the mRS score, whereas previous studies used other scales, such as the Barthel Index or the Glasgow Outcome Scale. Our study had a longer follow-up period (90 d) than previous studies (4 wk or 2 mo). Therefore, it is possible that our study captured more benefits and less harm from early aspirin use after acute stroke than previous studies.

The mechanisms by which early aspirin use may improve functional outcomes after acute stroke are not fully understood but may involve several pathways. Aspirin may contribute to improved outcomes in the following ways: (1) Prevention of platelet aggregation and thrombus formation in ruptured atherosclerotic plaques or cardiac emboli, thereby reducing the risk of early recurrent ischemic stroke; (2) enhancement of cerebral blood flow and reperfusion by inhibiting thromboxane A₂-mediated vasoconstriction and promotion of nitric oxide-mediated vasodilation; (3) attenuation of inflammation and oxidative stress by inhibiting cyclooxygenase-2-mediated prostaglandin E₂ synthesis and nuclear factor-kappa B activation; and (4) modulation of neurogenesis and neuroplasticity by stimulating the expression of brain-derived neurotrophic factors and synaptic remodeling.

The safety profile of early aspirin use after acute stroke was acceptable and comparable to that of no aspirin use. No cases of intracranial hemorrhage or gastrointestinal bleeding were observed in either group. This may be due to the careful selection of patients with no contraindications to aspirin, such as those with severe stroke, large intracranial hemorrhage, active bleeding, or a bleeding tendency. Moreover, we used a moderate dose of aspirin (300 mg), which may have less adverse effects than higher doses (500 mg or more)[22-24]. However, other major bleeding events in both groups were observed, including hematuria, epistaxis, and hemoptysis. These bleeding complications may be related to other factors such as hypertension, infection, trauma, or coagulation disorders. Therefore, we suggest that early aspirin use after acute stroke should be carefully monitored for any signs or symptoms of bleeding and discontinued if necessary.

Our study had several limitations. First, our sample size was small and our study was underpowered to detect a significant difference in the primary outcome between the two groups. Therefore, we cannot exclude the possibility of a type II error or false-negative result. Second, our study was open-label and not placebo-controlled, which may have introduced bias and confounding factors into the intervention and outcome assessments. However, we attempted to minimize these potential sources of bias using concealed randomization, blinded outcome assessment, and independent outcome adjudication. Third, this was a single-center study conducted in a specific population, which may have limited the generalizability and external validity of our findings. Therefore, our results should be interpreted with caution and confirmed in larger, multicenter, double-blind placebo-controlled trials with different populations.

CONCLUSION

In conclusion, aspirin antiplatelet therapy within 48 h of acute stroke is associated with favorable functional outcomes at 90 d, but does not significantly reduce the risk of recurrent vascular events compared with that of no-aspirin therapy. The safety profile of aspirin is acceptable and comparable to that of aspirin. Further studies with larger sample sizes and

longer follow-up periods are required to confirm our findings.

ARTICLE HIGHLIGHTS

Research background

The optimal timing and dose of aspirin initiation after an acute stroke are still debated. This study aimed to evaluate the efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute stroke. A randomized controlled trial was conducted. The primary outcome was the occurrence of recurrent stroke, myocardial infarction, or vascular death within 90 d. Secondary outcomes comprised functional outcomes, bleeding complications, and mortality rates. Results showed favorable functional outcomes with aspirin use, but no significant reduction in recurrent vascular events. Larger studies with longer follow-up periods are needed for further confirmation.

Research motivation

The optimal timing and dose of aspirin initiation after acute stroke are still debated, highlighting the need for further investigation. This study aimed to evaluate the efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute stroke. Understanding the impact of aspirin use on functional outcomes and recurrent vascular events is crucial for informing clinical decision-making and optimizing patient care. Larger studies with longer follow-up periods will provide more conclusive evidence in this field and guide future management strategies for acute stroke patients.

Research objectives

The primary aim was to assess the occurrence of recurrent stroke, myocardial infarction, or vascular death within 90 days. Secondary objectives included evaluating functional outcomes at 90 d using the modified Rankin Scale, determining the incidence of bleeding complications, and comparing mortality rates between the aspirin and no aspirin groups. By addressing these objectives, the study aimed to provide valuable insights into the use of aspirin in acute stroke management.

Research methods

A randomized, open-label, controlled trial was conducted involving 60 patients with acute ischemic or hemorrhagic stroke admitted within 24 h of symptom onset. Patients were randomly assigned to receive either a daily dose of 300 mg aspirin or no aspirin within 48 h of stroke onset. The primary outcome measured was the occurrence of recurrent stroke, myocardial infarction, or vascular death within 90 d. Secondary outcomes included functional outcomes at 90 d using the modified Rankin Scale (mRS), the incidence of bleeding complications, and mortality rate. Baseline characteristics were balanced between the two groups, and statistical analyses were performed to assess the relative risk and significance of the outcomes.

Research results

Among the 60 patients included, those in the aspirin group showed favorable functional outcomes compared to the no aspirin group, as indicated by significantly lower modified Rankin Scale (mRS) scores at 90 d. However, there was no significant reduction in the occurrence of recurrent stroke, myocardial infarction, or vascular death between the two groups. The incidence of bleeding complications and mortality rates were comparable between the aspirin and no aspirin groups. Further studies with larger sample sizes and longer follow-up periods are necessary to validate these findings.

Research conclusions

Aspirin use within 48 h of symptom onset in acute stroke patients is associated with improved functional outcomes. However, there is no significant reduction in the risk of recurrent stroke, myocardial infarction, or vascular death compared to not using aspirin. The safety profile of aspirin is similar to that of no aspirin in terms of bleeding complications and mortality rates. To validate these results, further research with larger sample sizes and longer follow-up periods is necessary.

Research perspectives

The study results highlight the need for further investigation into the optimal timing and dose of aspirin initiation after acute stroke. Future studies should consider larger sample sizes and longer follow-up periods to confirm the findings regarding functional outcomes and the risk reduction of recurrent vascular events. Additionally, exploring alternative antiplatelet therapies or combination treatments may provide valuable insights into improving outcomes in acute stroke management. Overall, ongoing research is necessary to refine the use of aspirin and optimize its benefits in the context of acute stroke.

FOOTNOTES

Author contributions: Zhang JQ proposed the concept of this study; Zhang JQ and Pan ZB contributed to data collection; Zhang JQ

contributed to formal analysis; Pan ZB participated in the survey; Zhang JQ contributed to the methods; Zhang JQ guided the research; Zhang JQ and Pan ZB validated this study; Zhang JQ and Pan ZB contributed to the visualization of this study; Zhang JQ prepared the first draft; Zhang JQ and Pan ZB jointly reviewed and edited the manuscript.

Institutional review board statement: This study obtained the ethical review and approval of the First Affiliated Hospital of Jiangxi Medical College.

Clinical trial registration statement: This study has been registered at the Clinical Research Registry at www.researchregistry.com. The registration identification number is (researchregistry9015).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare that there are no conflicts of interest to disclose.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Jian-Quan Zhang [0009-0004-2225-5810](https://orcid.org/0009-0004-2225-5810).

S-Editor: Lin C

L-Editor: Wang TQ

P-Editor: Yu HG

REFERENCES

- 1 Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson L, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C; Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014; **383**: 245-254 [PMID: [24449944](https://pubmed.ncbi.nlm.nih.gov/24449944/) DOI: [10.1016/s0140-6736\(13\)61953-4](https://doi.org/10.1016/s0140-6736(13)61953-4)]
- 2 Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet* 2008; **371**: 1612-1623 [PMID: [18468545](https://pubmed.ncbi.nlm.nih.gov/18468545/) DOI: [10.1016/S0140-6736\(08\)60694-7](https://doi.org/10.1016/S0140-6736(08)60694-7)]
- 3 Coull AJ, Lovett JK, Rothwell PM; Oxford Vascular Study. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ* 2004; **328**: 326 [PMID: [14744823](https://pubmed.ncbi.nlm.nih.gov/14744823/) DOI: [10.1136/bmj.37991.635266.44](https://doi.org/10.1136/bmj.37991.635266.44)]
- 4 Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005; **353**: 2373-2383 [PMID: [16319386](https://pubmed.ncbi.nlm.nih.gov/16319386/) DOI: [10.1056/NEJMr052717](https://doi.org/10.1056/NEJMr052717)]
- 5 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**: 71-86 [PMID: [11786451](https://pubmed.ncbi.nlm.nih.gov/11786451/) DOI: [10.1136/bmj.324.7329.71](https://doi.org/10.1136/bmj.324.7329.71)]
- 6 The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet* 1997; **349**: 1569-1581 [PMID: [9174558](https://pubmed.ncbi.nlm.nih.gov/9174558/) DOI: [10.1016/S0140-6736\(97\)04011-7](https://doi.org/10.1016/S0140-6736(97)04011-7)]
- 7 Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS, Xie JX, Warlow C, Peto R. Indications for early aspirin use in acute ischaemic stroke: A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. *Stroke* 2000; **31**: 1240-1249 [PMID: [10835439](https://pubmed.ncbi.nlm.nih.gov/10835439/) DOI: [10.1161/01.str.31.6.1240](https://doi.org/10.1161/01.str.31.6.1240)]
- 8 Sandercock PA, Counsell C, Gubitz GJ, Tseng MC. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev* 2008; CD000029 [PMID: [18646056](https://pubmed.ncbi.nlm.nih.gov/18646056/) DOI: [10.1002/14651858.CD000029.pub2](https://doi.org/10.1002/14651858.CD000029.pub2)]
- 9 Xia C, Wang X, Lindley RI, Delcourt C, Chen X, Zhou Z, Guo R, Carcel C, Malavera A, Calic Z, Mair G, Wardlaw JM, Robinson TG, Anderson CS. Early decompressive hemicraniectomy in thrombolysed acute ischemic stroke patients from the international ENCHANTED trial. *Sci Rep* 2021; **11**: 16495 [PMID: [34389772](https://pubmed.ncbi.nlm.nih.gov/34389772/) DOI: [10.1038/s41598-021-96087-z](https://doi.org/10.1038/s41598-021-96087-z)]
- 10 Sandercock PA, van den Belt AG, Lindley RI, Slattery J. Antithrombotic therapy in acute ischaemic stroke: an overview of the completed randomised trials. *J Neurol Neurosurg Psychiatry* 1993; **56**: 17-25 [PMID: [8429318](https://pubmed.ncbi.nlm.nih.gov/8429318/) DOI: [10.1136/jnnp.56.1.17](https://doi.org/10.1136/jnnp.56.1.17)]
- 11 Wong KS, Chen C, Ng PW, Tsoi TH, Li HL, Fong WC, Yeung J, Wong CK, Yip KK, Gao H, Wong HB; FISS-tris Study Investigators. Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. *Lancet Neurol* 2007; **6**: 407-413 [PMID: [17434095](https://pubmed.ncbi.nlm.nih.gov/17434095/) DOI: [10.1016/S1474-4422\(07\)70079-0](https://doi.org/10.1016/S1474-4422(07)70079-0)]
- 12 Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry* 1991; **54**: 1044-1054 [PMID: [1783914](https://pubmed.ncbi.nlm.nih.gov/1783914/) DOI: [10.1136/jnnp.54.12.1044](https://doi.org/10.1136/jnnp.54.12.1044)]

- 13 **Dutch TIA Trial Study Group**, van Gijn J, Algra A, Kappelle J, Koudstaal PJ, van Latum A. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. *N Engl J Med* 1991; **325**: 1261-1266 [PMID: 1922220 DOI: 10.1056/NEJM199110313251801]
- 14 **Diener HC**, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; **364**: 331-337 [PMID: 15276392 DOI: 10.1016/S0140-6736(04)16721-4]
- 15 **Powers WJ**, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2019; **50**: e344-e418 [PMID: 31662037 DOI: 10.1161/STR.0000000000000211]
- 16 **Barer D**. Interpretation of IST and CAST stroke trials. International Stroke Trial. Chinese Acute Stroke Trial. *Lancet* 1997; **350**: 440; author reply 443-440; author reply 444 [PMID: 9259671 DOI: 10.1016/s0140-6736(97)26032-0]
- 17 **Bousser MG**, Amarenco P, Chamorro A, Fisher M, Ford I, Fox KM, Hennerici MG, Mattle HP, Rothwell PM, de Cordoüe A, Fratacci MD; PERFORM Study Investigators. Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial. *Lancet* 2011; **377**: 2013-2022 [PMID: 21616527 DOI: 10.1016/S0140-6736(11)60600-4]
- 18 **Zuern CS**, Lindemann S, Gawaz M. Platelet function and response to aspirin: gender-specific features and implications for female thrombotic risk and management. *Semin Thromb Hemost* 2009; **35**: 295-306 [PMID: 19452405 DOI: 10.1055/s-0029-1222608]
- 19 **Chen C**, Wang X, Chen X, Ouyang M, Sun L, Arima H, Robinson T, Lindley RI, Chalmers J, Li G, Song L, Anderson CS; ENCHANTED Investigators. Disparities between Asian and Non-Asian Thrombolysed Acute Ischemic Stroke Patients in the Enhanced Control of Hypertension and Thrombolysis Stroke Trial. *Cerebrovasc Dis* 2021; **50**: 560-566 [PMID: 34153968 DOI: 10.1159/000516487]
- 20 **van Walraven C**, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, Koudstaal PJ, Chang Y, Hellemons B. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA* 2002; **288**: 2441-2448 [PMID: 12435257 DOI: 10.1001/jama.288.19.2441]
- 21 **Wang Q**, Chen C, Chen XY, Han JH, Soo Y, Leung TW, Mok V, Wong KS. Low-molecular-weight heparin and early neurologic deterioration in acute stroke caused by large artery occlusive disease. *Arch Neurol* 2012; **69**: 1454-1460 [PMID: 22893265 DOI: 10.1001/archneurol.2012.1633]
- 22 **Niu PP**, Guo ZN, Jin H, Xing YQ, Yang Y. Antiplatelet regimens in the long-term secondary prevention of transient ischaemic attack and ischaemic stroke: an updated network meta-analysis. *BMJ Open* 2016; **6**: e009013 [PMID: 26988347 DOI: 10.1136/bmjopen-2015-009013]
- 23 **Dawson J**, Béjot Y, Christensen LM, De Marchis GM, Dichgans M, Hagberg G, Heldner MR, Milionis H, Li L, Pezzella FR, Taylor Rowan M, Tiu C, Webb A. European Stroke Organisation (ESO) guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack. *Eur Stroke J* 2022; **7**: I-II [PMID: 36082250 DOI: 10.1177/23969873221100032]
- 24 **Diener HC**, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ. Management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke (MATCH): study design and baseline data. *Cerebrovasc Dis* 2004; **17**: 253-261 [PMID: 14981346 DOI: 10.1159/000076962]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

