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# Aspirin plus Clopidogrel as Secondary Prevention after Stroke or Transient Ischemic Attack: A Systematic Review and Meta-Analysis

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**Key Words**
Stroke · Transient ischemic attack · Antiplatelet therapy · Secondary prevention · Meta-analysis

**Abstract**
***Background:*** Antiplatelet agents are the mainstay for secondary prevention of non-cardioembolic stroke. This systematic review examined the safety and efficacy of short-, middle-, and long-term aspirin in combination with clopidogrel as secondary prevention of stroke or transient ischemic attack (TIA) of presumed arterial origin. ***Methods:*** PubMed, EmBase, and CENTRAL were searched up to May 2014. Randomized controlled trials (RCTs) that compared aspirin plus clopidogrel versus aspirin or clopidogrel as secondary prevention of stroke or TIA of arterial origin were included. The analyses were stratified into short-term (≤3 months), middle-term (>3 months and <1 year), and long-term (≥1 year). Outcomes were compared using risk ratio (RR) and 95% confidence interval (95% CI). ***Results:*** Eight RCTs (20,728 patients) were included in the overall analysis. Compared with aspirin or clopidogrel alone, the complete analysis of all the data indicated that the combination therapy significantly reduced the risk of stroke recurrence (RR, 0.82; 95% CI 0.70–0.96, p = 0.01) and major vascular events (RR, 0.84; 95% CI 0.73–0.96, p < 0.01). But the risk of hemorrhagic stroke (RR, 1.59; 95% CI 1.08–2.33, p = 0.02) and major bleeding (RR, 1.83; 95% CI 1.37–2.45, p < 0.01) was increased. No RCT studied middle-term combination therapy. The analyses were therefore stratified into only two subgroups, short- and long-term treatment. Stratified analysis of short-term treatment showed that relative to monotherapy, the drug combination reduced the risk of stroke recurrence (RR, 0.69; 95% CI 0.59–0.81, p < 0.01) and did not increase the risk of hemorrhagic stroke (RR, 1.23; 95% CI 0.50–3.04, p = 0.65) and major bleeding events (RR, 2.17; 95% CI 0.18–25.71, p = 0.54). Short-term combination therapy was associated with a significantly lower risk of major vascular events (RR, 0.70; 95% CI 0.69 to 0.82, p < 0.01). Stratified analysis of long-term treatment revealed that the combination treatment did not decrease the risk of stroke recurrence (RR, 0.92; 95% CI 0.83–1.03, p = 0.15), but was associated with a significantly higher risk of hemorrhagic stroke (RR, 1.67; 95% CI 1.10–2.56, p = 0.02) and major bleeding events (RR, 1.90; 95% CI 1.46–2.48, p < 0.01). Long-term combination therapy failed to reduce the risk of major vascular events (RR, 0.92; 95% CI 0.84–1.03, p = 0.09). ***Conclusions:*** Compared with monotherapy, short-term aspirin in combination with clopidogrel is more effective as secondary prevention of stroke or TIA without increasing the risk of hemorrhagic stroke and major bleeding events. Long-term combination therapy does not reduce the risk of stroke recurrence, and is associated with increased major bleeding

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events. The clinical applicability of the findings of this systematic review, however, needs to be confirmed in future clinical trials.
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## Introduction

Stroke is a leading cause of death globally [1]. Patients surviving a stroke or transient ischemic attack (TIA) are at an increased risk for subsequent stroke [2]. Without secondary prevention measures, patients after a stroke or TIA face an annual risk of 4–16% of developing serious vascular events [3–5].

Antiplatelet agents are the mainstay for secondary prevention of non-cardioembolic stroke. Aspirin, an inhibitor of cyclooxygenase hence preventing thromboxane A2 synthesis, is routinely prescribed and prevents 13~19% of vascular events in secondary prevention trials [3, 6]. Clopidogrel, a P2Y12-receptor antagonist, inhibits platelet aggregation synergistically with aspirin [7–9]. The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) study showed that aspirin plus clopidogrel is more effective than aspirin alone in reducing the risk of subsequent stroke without increasing the risk of bleeding events in patients already having an episode of minor stroke or TIA [10]. It is worth noting that the results cannot be immediately applicable to patients with moderate-to-severe stroke for whom an early secondary prevention is certainly needed [11].

However, several other high-quality trials failed to show a clear benefit of aspirin plus clopidogrel as secondary prevention [12–15]. Previous guidelines did not recommend clopidogrel plus aspirin for secondary prevention of stroke or TIA [16–18]. The latest AHA/ASA guideline cautiously recommends the combination of aspirin and clopidogrel for minor ischemic stroke or TIA within 24 h [19]. In this systematic review, we aimed at comparing the efficacy and safety of short-, middle-, and long-term combination treatment of clopidogrel plus aspirin versus aspirin or clopidogrel alone as secondary prevention of stroke and TIA of presumed arterial origin.

## Methods

We searched eligible studies using online databases including PubMed, EmBase, the Cochrane Central Register of Controlled Trials (CENTRAL) with the last search updated on May 2014. The search used the following terms and combinations: 'clopidogrel', 'aspirin' or 'acetylsalicylic acid', 'stroke' or 'cerebrovascular disorder' or 'transient ischemic attack' or 'cerebral infarction' or 'brain ischemia'. No language or date restriction was applied. A manual examination of the references in selected articles and pertinent reviews was also performed. The search was limited to randomized clinical trials (RCTs) conducted in adult human subjects. Only published studies with full-text articles were included.

All the following criteria must be met for inclusion in the analysis: (1) study design: randomized controlled trials, (2) patients were treated with aspirin and clopidogrel versus aspirin or clopidogrel alone, and (3) patients had prior stroke or TIA of arterial origin. The exclusion criteria included: (1) an equivocal treatment allocation process; (2) statistically significant imbalance in major baseline characteristics among the study groups; (3) use of other platelet aggregation inhibitors. For studies that produced multiple publications, only the data from the most recent or most complete publication were included in the analysis.

Two independent researchers (Q.Z. and M.Z.) assessed the study quality using the Jadad scale [20], and extracted the following data: trial name, intervention dose, number of patients, age, gender distribution, stroke type, onset-to-treatment Interval, and duration of dual treatment. After the complete analysis of all the data, the analysis was stratified into two subgroups on a pre-planned basis. Long-term combination therapy was defined as treatment with aspirin and clopidogrel lasting for at least 1 year, as described earlier [21]. Middle-term combination therapy was defined as dual treatment duration between 3 months and 1 year. Short-term combination therapy was defined as dual treatment with a duration of ≤3 months. The primary outcome was stroke recurrence (all types; ischemic or hemorrhagic, fatal or nonfatal). The secondary outcomes included major vascular events and major bleeding (moderate and severe bleeding). Definition of vascular events followed that in the primary studies, where TIA and ischemic stroke were mostly defined as neurologic deficit attributable to focal brain ischemia lasting for less and more than 24 h, respectively. Ischemic stroke was typically supported by brain imaging results. Major vascular events included stroke, myocardial infarction (MI), and vascular death. If there was a disagreement, additional researchers (C.W.) reviewed the original articles, and resolved the disagreement.

The relative risk (RR) and 95% confidence interval (95% CI) were estimated for each study. The Q-statistics and the $I^2$ index were used to assess the presence and quantify the extent of heterogeneity ($p \leq 0.10$ or $I^2 \geq 50\%$ was considered significant heterogeneity). The fixed-effects model was used when there was no statistically significant heterogeneity; otherwise, the random-effects model was used. The significance of the pooled RR was determined by using a Z-test, and $p < 0.05$ was considered statistically significant. All tests were 2-sided. A sensitivity analysis was performed by excluding one trial at a time, starting from those with a lower quality score, and by excluding studies using different comparator. Funnel plot method was used to screen for potential reporting bias. The data were analyzed using the Review Manager Software 5.2 (Cochrane Collaboration, Oxford, UK).

## Results

Eight RCTs involving 20,728 patients fulfilled the inclusion criteria (fig. 1) [10, 12–15, 22–24]. A total of 18 studies were excluded: four were excluded because they

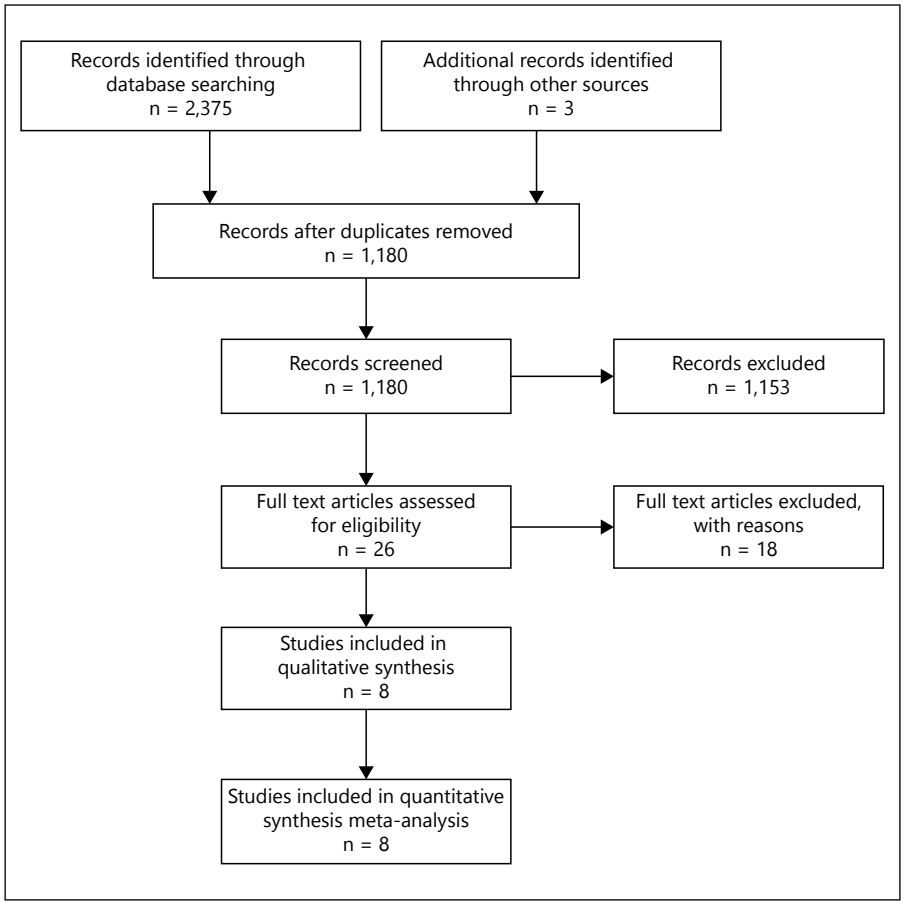


**Fig. 1.** Flow diagram of study selection.

were not RCTs [25–28], three were excluded because the comparator was not aspirin or clopidogrel alone [29–31], seven were excluded for lack of specific data [9, 32–37], two were excluded since the trials were ongoing [38, 39], and two were excluded due to redundancy [40, 41]: the original study reported both primary and secondary prevention, and the subsequent report [14] focused on results in patients with previous TIA or ischemic stroke. The baseline characteristics of included studies are summarized in table 1. In the Bal Dit Sollier study [22], there were four groups, and only patients with stroke or TIA from the aspirin plus clopidogrel group and the aspirin group were included in this analysis. The Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial used clopidogrel as a comparator. The remaining 6 trials used aspirin as a comparator. For the Secondary Prevention of Small Subcortical Strokes (SPS3) study, the precise data about the incidence of hemorrhagic stroke (primary intracerebral hemorrhages) were obtained from a meta-analysis co-authored by the principal investigators of the SPS3 trial [42]. The follow-up of these studies ranged from 7 days to 3.4 years. The duration of the combination therapy was 7 days to 3 months in 5 trials [10, 13, 22–24], and more than 1 year in the remaining 3 trials [12, 14, 15]. No RCT studied middle-term combination therapy between 3 months and 1 year. The analyses were therefore only stratified into two subgroups, short- and long-term combination therapy.

*Stroke Recurrence*

Compared with aspirin or clopidogrel alone, data pooled from all eight trials indicated that the combination of aspirin and clopidogrel was associated with a significantly lower risk of stroke recurrence of all types (RR, 0.82; 95% CI 0.70–0.96, p = 0.01) (fig. 2). There was a significant statistical heterogeneity (p = 0.08, $I^2$ = 45.0%). With respect to reduction of ischemic stroke (both fatal and nonfatal), there was a significant trend in favor of aspirin and clopidogrel (RR, 0.80; 95% CI 0.73–0.88, p < 0.01) (fig. 3). However, the risk of hemorrhagic stroke was significantly increased in combination therapy (RR, 1.59; 95% CI 1.08–2.33, p = 0.02) (fig. 4).

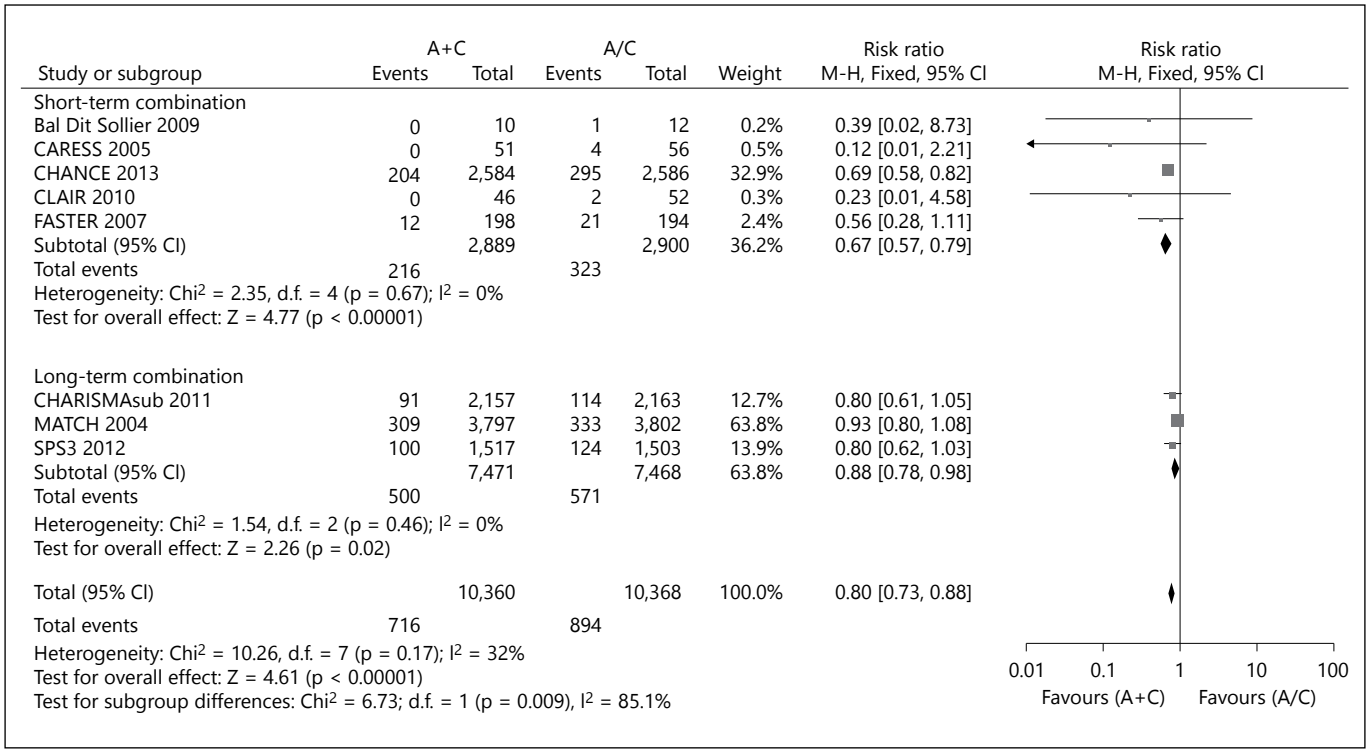


**Fig. 2.** Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on stroke.

**Table 1.** Characteristics of included trials

| Study | Treatment (A+C) daily dose | Comparator (A/C) daily dose | Participants, n | Age, years | Female, % | Type | Onset-to-treatment interval | Dual treatment duration | Jadad score |
|---|---|---|---|---|---|---|---|---|---|
| Bal Dit Sollier 2009 | A 325 mg + C 75 mg | A 300 mg | 22 | 69 | 27.3 | stroke, TIA | >8 days | 10 days | 3 |
| CARESS 2005 | A 75 mg + C 75 mg | A 75 mg | 107 | 65 | 30.8 | stroke, TIA | <5 months | 7 days | 5 |
| CHANCE 2013 | A 75 mg + C 75 mg* | A 75 mg | 5,170 | 62 | 33.8 | minor stroke, TIA | <24 h | 21 days | 5 |
| CHARISMA 2011 | A 75–100 mg + C 75 mg | A 75–100 mg | 1,331 | 65 | 36.8 | stroke, TIA | <5 years | 2.1 years | 5 |
| CLAIR 2010 | A 75–160 mg + C 75 mg | A 75–160 mg | 98 | 58 | 22.4 | stroke, TIA | <7 days | 7 days | 5 |
| FASTER 2007 | A 81 mg + C 75 mg | A 75 mg | 392 | 68 | 47.2 | minor stroke, TIA | <24 h | 90 days | 5 |
| MATCH 2004 | A 75 mg + C 75 mg | C 75 mg | 7,599 | 66 | 37.1 | stroke, TIA | <3 months | 1.5 years | 5 |
| SPS3 2012 | A 325 mg + C 75 mg | A 325 mg | 3,020 | 63 | 37 | lacunar stroke | <180 days | 3.4 years | 5 |

* Clopidogrel (C) at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin (A) at a dose of 75 mg per day for the first 21 days; the placebo plus aspirin (75 mg per day for 90 days). All participants received open-label aspirin at a clinician-determined dose of 75–300 mg on day 1.

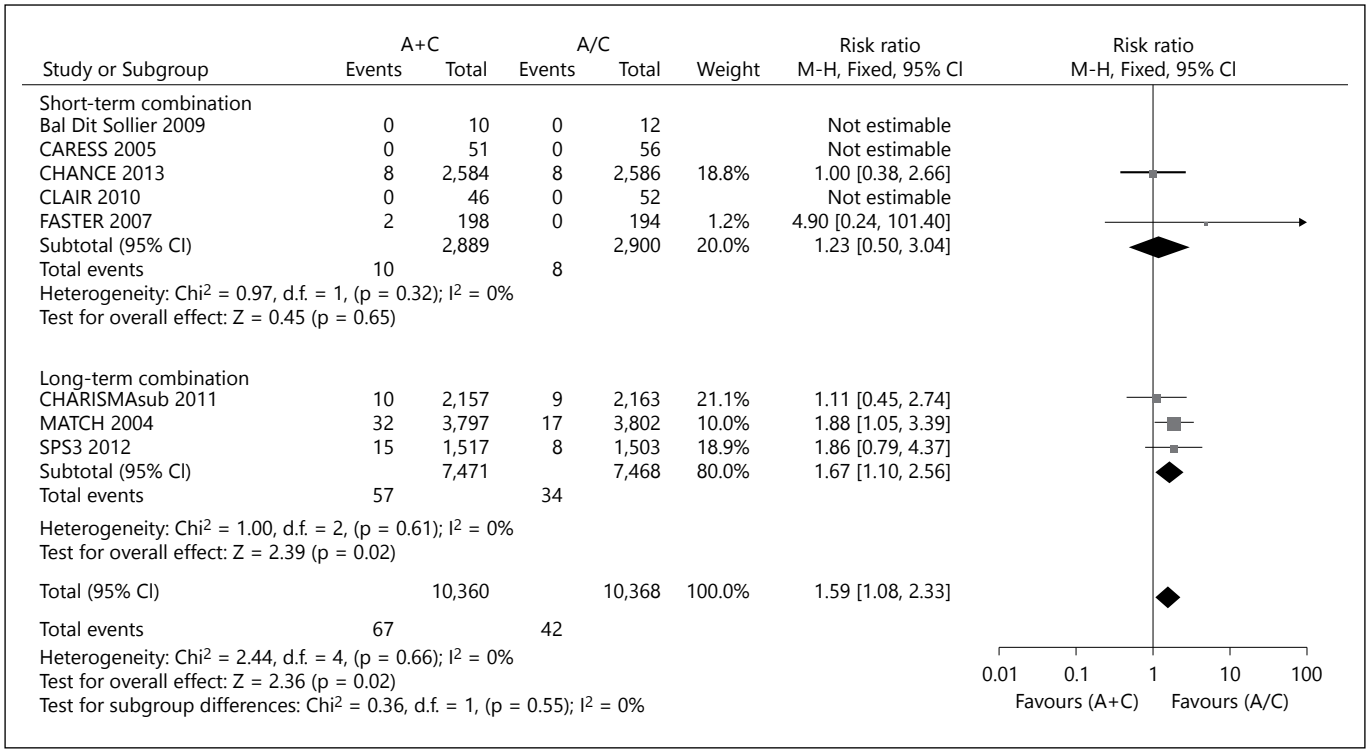


**Fig. 3.** Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on ischemic stroke.

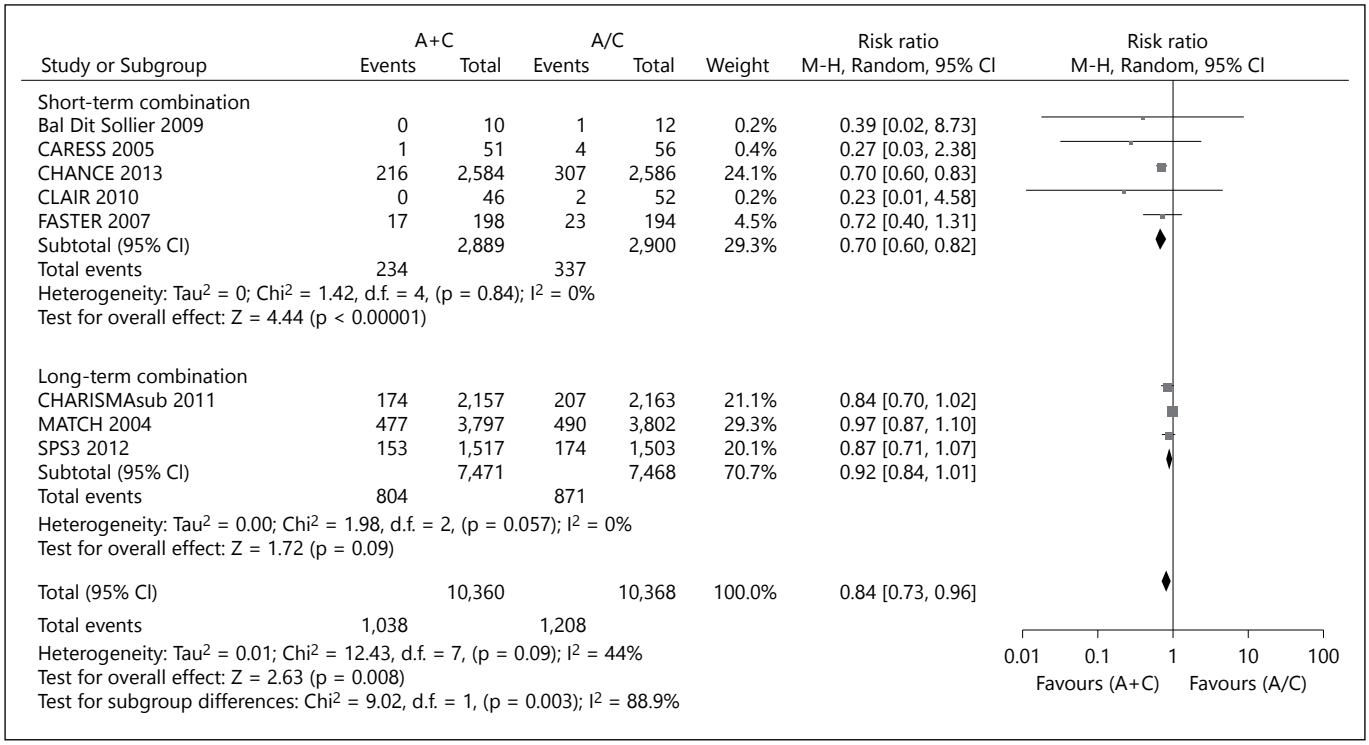


**Fig. 4.** Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on hemorrhagic stroke.

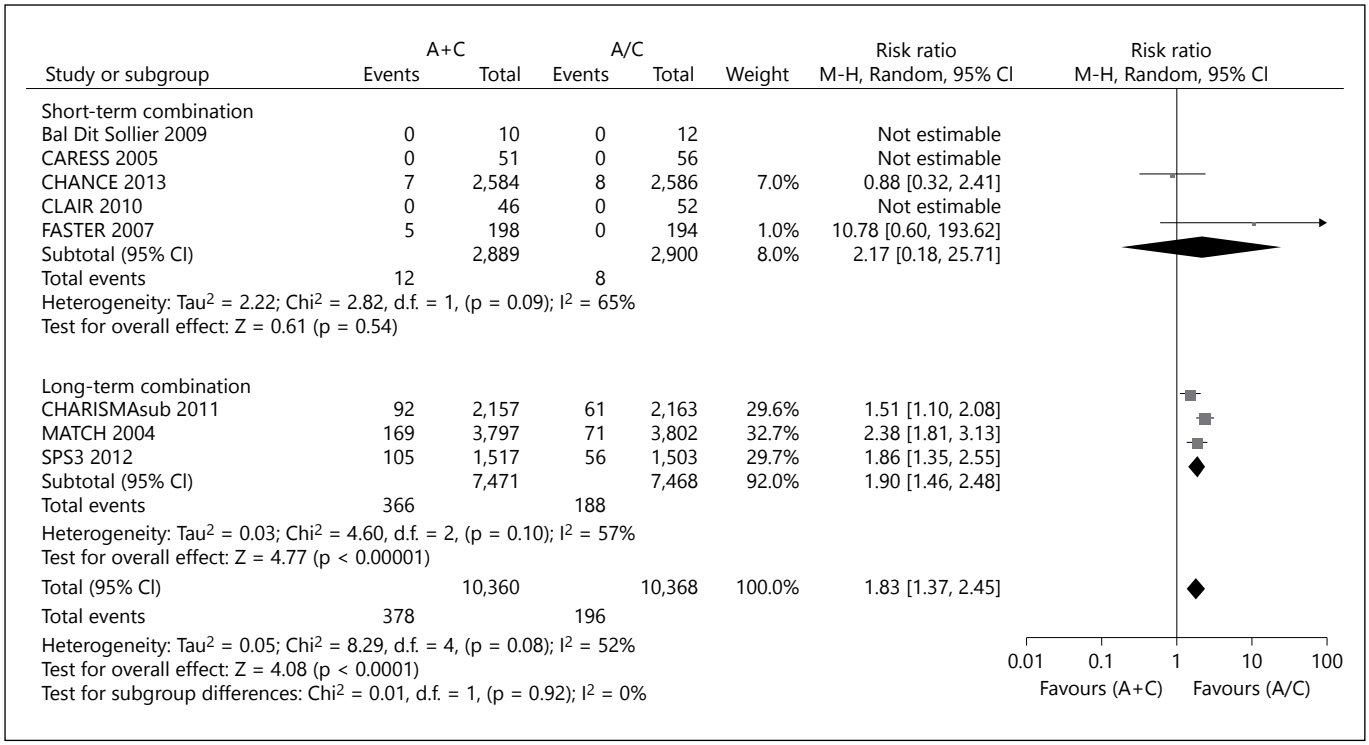


**Fig. 5.** Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on stroke, MI, or vascular death.

The stratified analysis of short-term combination therapy included 5 RCTs, and revealed that, compared with aspirin monotherapy, combination therapy significantly decreased the risk of stroke recurrence (RR, 0.69; 95% CI 0.59–0.81, p < 0.01) (fig. 2). The combination therapy also reduced the risk of ischemic stroke (RR, 0.67; 95% CI 0.57–0.79, p < 0.01) (fig. 3). Hemorrhagic stroke was not affected (RR, 1.23; 95% CI 0.50–3.04, p = 0.65) (fig. 4).

The stratified analysis of long-term combination therapy, which included 3 RCTs, failed to show significant reduction in stroke recurrence with combination therapy (RR, 0.92; 95% CI 0.83–1.03, p = 0.15) (fig. 2). The risk for ischemic stroke, however, was lower in patients receiving combination therapy (RR, 0.88; 95% CI 0.78–0.98, p = 0.02) (fig. 3). Additionally, there was a significantly higher risk of hemorrhagic stroke (RR, 1.67; 95% CI 1.10–2.56, p = 0.02) (fig. 4). There was no significant difference in heterogeneity in any of the aforementioned stratified analysis (p > 0.10, $I^2$ < 50%).

*Secondary Outcomes*

Available data from 8 studies indicated a significant reduction in major vascular events during follow up (RR, 0.84; 95% CI 0.73–0.96, p < 0.01) (fig. 5). The incidence of major bleeding was significantly higher in patients receiving clopidogrel plus aspirin than those receiving aspirin alone (RR, 1.83; 95% CI 1.37–2.45, p < 0.01) (fig. 6). There was a significant difference in heterogeneity in major vascular events (p = 0.09, $I^2$ = 44%) and major bleeding (p = 0.08, $I^2$ = 52%).

Compared with aspirin alone, short-term combination therapy was associated with a significantly lower risk of major vascular events (RR, 0.70; 95% CI 0.60–0.82, p < 0.01) (fig. 5). There was no significant difference in heterogeneity (p = 0.84, $I^2$ = 0). The analysis did not identify significant difference in major bleeding (RR, 2.17; 95% CI 0.18–25.71, p = 0.54) (fig. 5). A significant heterogeneity was observed (p = 0.09, $I^2$ = 65%).

The stratified analysis of the long-term combination therapy failed to reveal significant difference in major vascular events (RR, 0.92; 95% CI 0.84–1.03, p = 0.09) (fig. 5). There was no significant difference in heterogeneity (p = 0.37, $I^2$ = 0). The analysis revealed a higher incidence of major bleeding upon long-term dual therapy (RR, 1.90; 95% CI 1.46–2.48, p < 0.01) (fig. 6). There was a significant difference in heterogeneity in major bleeding (p = 0.1, $I^2$ = 57%). However, exclusion of the MATCH

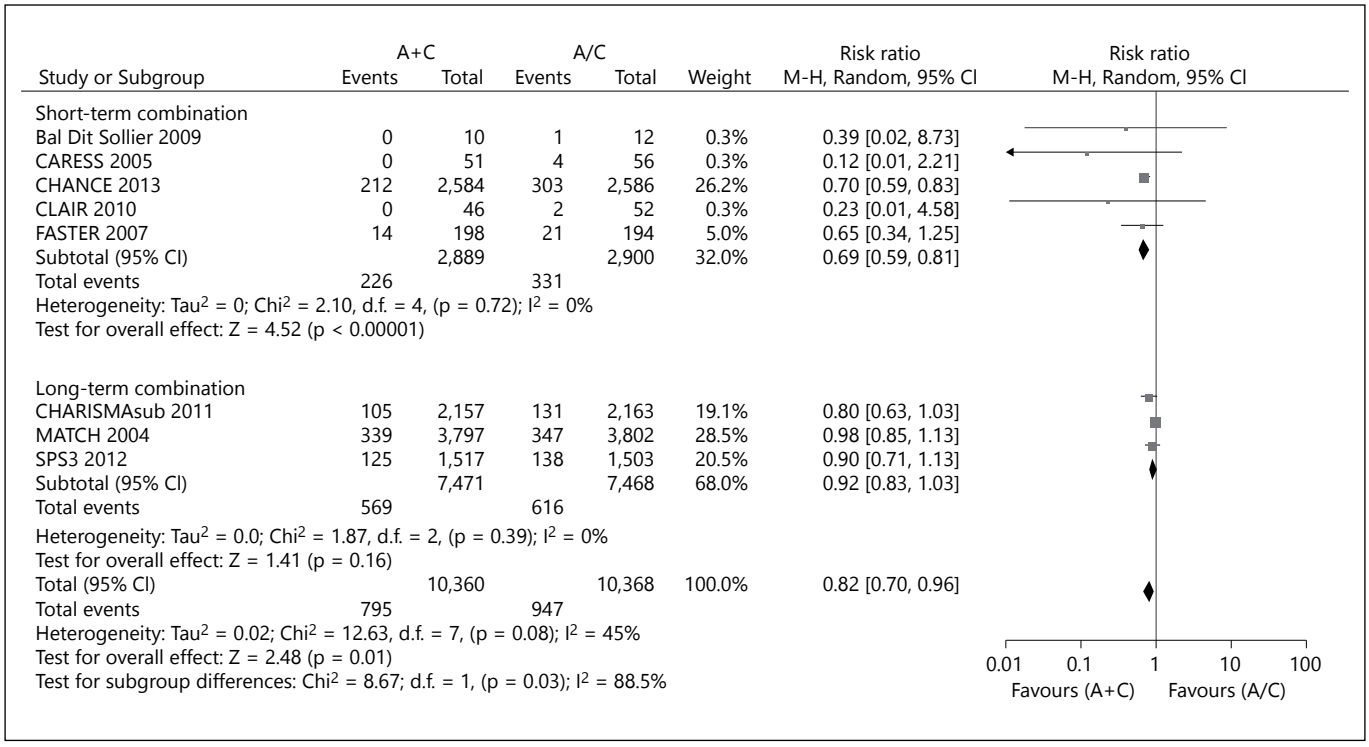


**Fig. 6.** Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on major bleeding.

trial (using clopidogrel as the comparator) did not change the conclusion with regards to major bleeding (RR, 1.68; 95% CI 1.34–2.10, $p < 0.01$) and there was no heterogeneity ($p = 0.37$, $I^2 = 0$).

Visual inspection of funnel plots indicated an asymmetry in main outcomes (fig. 7). The Bal Dit Sollier study was of relatively low quality and small sample size. We therefore conducted a sensitivity analysis by excluding this study, which did not change the conclusion.

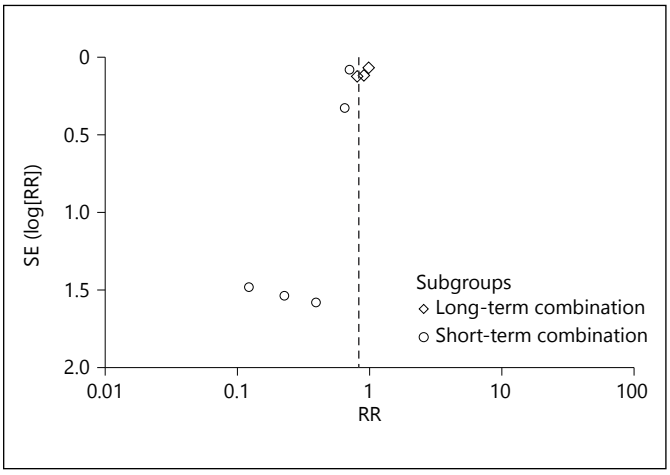


**Fig. 7.** Funnel plot of included studies for stroke.

## Discussion

The current study included eight RCTs involving 20,728 patients. The complete analysis of all the pooled data showed aspirin plus clopidogrel could significantly reduce the risk of overall stroke (regardless of stroke type) and major vascular events. However, the risk of hemorrhagic stroke and major bleeding was significantly increased in combination therapy. A stratified analysis of short-term combination therapy (≤3 months) indicated that compared to aspirin alone, aspirin plus clopidogrel could significantly reduce the risk of stroke recurrence and major vascular events. The combination therapy did not increase the risk of hemorrhagic stroke and major bleeding. In the stratified analysis of long-term combination therapy (≥1 year), the combination therapy did not affect stroke recurrence and major vascular events, but increased the risk of hemorrhagic stroke and major bleeding. These

findings are generally consistent with recent systematic reviews [21, 42, 43].

The benefit of platelet aggregation inhibitors as secondary prevention of non-cardiogenic stroke or TIA has been well established. Recent systematic reviews indicated that early combination antiplatelet therapy is more effective in reducing the risk of stroke in patients with acute stroke or TIA compared with monotherapy [44, 45]. Dipyridamole plus aspirin reduces the risk of stroke recurrence [46], and is recommended by major guidelines for secondary prevention of stroke in patients with stroke or TIA [16, 17, 19].

The MATCH, SPS3 and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trials indicated that long-term therapy with aspirin plus clopidogrel is not effective in secondary prevention of stroke in patients with TIA and ischemic stroke [12, 14, 15]. The SPS3 trial examined dual treatment with aspirin (325 mg/day) and clopidogrel (75 mg/day) in patients with subcortical lacunar ischemic stroke [15], and failed to show significant reduction in the risk of stroke recurrence, and was terminated due to an increased rate of major hemorrhage. Arguably, whether the dose of aspirin (325 mg/day) is appropriate for long-term treatment remains an issue. All patients in SPS3 and most patients in MATCH had lacunar infarcts, which are generally considered to result from hyaline arteriolosclerosis and endothelial dysfunction in small penetrating cerebral arteries [26, 47, 48]. The use of antiplatelet therapy in patients with subcortical lacunar ischemic stroke, therefore, is theoretically problematic. In the MATCH trial, the Kaplan-Meier survival curves showed that the risk of intracranial hemorrhage for each treatment group did not diverge until at 3–4 months after randomization, with a noticeably increased risk of intracerebral hemorrhage for the combination therapy. Therefore, the use of the combination therapy beyond three months may incur an increased risk of intracerebral bleeding.

The FASTER (Fast Assessment of Stroke and TIA to prevent Early Recurrence) trial was conducted in patients with ischemic stroke or TIA within 24 h of symptom onset, and failed to show significant reduction in the risk of recurrent stoke and major vascular events in the dual antiplatelet group [13]. The CLAIR (clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis) and CARESS (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis) trials included patients with large artery stenosis, and suggested that the combination therapy of aspirin plus clopidogrel is more effective in reducing embolization than aspirin alone [23, 24].

Stratified analysis of short-term combination therapy has revealed that the CHANCE is the only properly powered study. The CHANCE trial showed that the short-term combination therapy reduced the risk of stroke without increasing the risk of bleeding events [10]. The CHANCE trial enrolled patients in the first 24 h after a minor stroke or TIA. The trial used a short course (21 days) of combined aspirin and clopidogrel, and therefore was likely to generate more apparent benefit. The trial was conducted entirely in China, where the level of healthcare, secondary prevention practices, and distribution of stroke subtypes differ from those of other countries. In addition, Chinese patients show distinct vascular pathology from Caucasian patients and thus the conclusions from the CHANCE may not be immediately applicable to Caucasian patients or patients of other ethnic descents. Patients in the CHANCE were also younger compared to the average stroke population and had less severe neurological deficits. Therefore, caution is advised when the CHANCE data is used for older patients with worse deficits who may not benefit from dual antiplatelet therapy because of the increased occurrence of hemorrhagic complications.

The meta-analysis in the current study is based on group data and not individual patient data, and is thus limited in many aspects, including the time from the event, blood pressure control, time on treatment, and stroke etiology. Furthermore, the included studies vary in terms of study sample, onset-to-treatment interval, stroke type, treatment course, comparator, and flow-up duration. Moreover, only published data were included, which may lead to a reporting bias by overestimating the effect of dual therapy. Our visual inspection of the funnel plots revealed an asymmetry, which indicates the likelihood of publication bias. The asymmetry of funnel plot may be also due to an insufficient number of trials, small-study effect and significant statistical heterogeneity. Obtaining and including data from unpublished trials may offer a way to avoid such bias, but it would be a very challenging endeavor to gain access to data from unpublished studies. In addition, the data from the CHARISMA were derived from a subgroup of patients with stroke, and thus may introduce random error.

In conclusion, the current study showed that the dual antiplatelet therapy with aspirin and clopidogrel reduces the risk of stroke recurrence and major vascular events, but increases the risk of hemorrhagic stroke and major bleeding. Short-term combination therapy (≤3 months)

offers protection against stroke recurrence and major vascular events without increasing the risk of hemorrhagic stroke and major bleeding events in patients with prior stroke or TIA of arterial origin. Long-term combination therapy (≥1 year), on the other hand, does not reduce the risk of stroke recurrence and major vascular events, and is associated with increased hemorrhagic stroke and major bleeding events. This systematic review suggests the benefit of dual antiplatelet with aspirin and clopidogrel may be greatest in the short term for secondary prevention of non-cardioembolic ischemic stroke or TIA. The opinion is similar to the recommendations of the new guideline for the prevention of stroke and TIA from the AHA/ASA [19]. Further well-designed, longer follow-up clinical trials are needed to confirm possible short-term beneficial effects of aspirin plus clopidogrel as secondary prevention in non-Chinese patients with stroke and TIA. The results from long-term follow-up of CHANCE, ongoing POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) [39] and COMPRESS (Combination of Clopidogrel and Aspirin for Prevention of Early Recurrence in Acute Atherothrombotic Stroke) [38] trials may provide more conclusive evidence on the use of dual antiplatelet therapy for stroke patients of other ethnic descents than Chinese and for elderly stroke patients.


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## Disclosure Statement

None.

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# Erratum

In the article by Zhang et al., entitled 'Aspirin plus Clopidogrel as Secondary Prevention after Stroke or Transient Ischemic Attack: A Systematic Review and Meta-Analysis' [Cerebrovasc Dis 2015;39:13–22, DOI: 10.1159/000369778] there are several errors in the published version. The corrections are as follows:

1. In the original article there is a mix-up of figures. The correct figs. 2–6 with the corresponding legends are printed below.
2. In fig. 5 'Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on stroke, MI, or vascular death', 19th line, '(p = 0.057)' should be '(p = 0.37)'.
3. On p. 18, left column, 12th line, 'p = 0.15' should be 'p = 0.16'.
4. On p. 18, right column, 13th line, '(fig. 5)' should be '(fig. 6)'.
5. On p. 18, right column, 18th line, '0.84–1.03' should be'0.84–1.01'.

| Study or Subgroup | A+C Events | A+C Total | A/C Events | A/C Total | Weight | Risk ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Short-term combination | | | | | | |
| Bal Dit Sollier 2009 | 0 | 10 | 1 | 12 | 0.3% | 0.39 [0.02, 8.73] |
| CARESS 2005 | 0 | 51 | 4 | 56 | 0.3% | 0.12 [0.01, 2.21] |
| CHANCE 2013 | 212 | 2,584 | 303 | 2,586 | 26.2% | 0.70 [0.59, 0.83] |
| CLAIR 2010 | 0 | 46 | 2 | 52 | 0.3% | 0.23 [0.01, 4.58] |
| FASTER 2007 | 14 | 198 | 21 | 194 | 5.0% | 0.65 [0.34, 1.25] |
| Subtotal (95% CI) | | 2,889 | | 2,900 | 32.0% | 0.69 [0.59, 0.81] |
| Total events | 226 | | 331 | | | |
| Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.10$, d.f. = 4, (p = 0.72); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 4.52 (p < 0.00001) | | | | | | |
| Long-term combination | | | | | | |
| CHARISMAsub 2011 | 105 | 2,157 | 131 | 2,163 | 19.1% | 0.80 [0.63, 1.03] |
| MATCH 2004 | 339 | 3,797 | 347 | 3,802 | 28.5% | 0.98 [0.85, 1.13] |
| SPS3 2012 | 125 | 1,517 | 138 | 1,503 | 20.5% | 0.90 [0.71, 1.13] |
| Subtotal (95% CI) | | 7,471 | | 7,468 | 68.0% | 0.92 [0.83, 1.03] |
| Total events | 569 | | 616 | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.87$, d.f. = 2, (p = 0.39); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 1.41 (p = 0.16) | | | | | | |
| Total (95% CI) | | 10,360 | | 10,368 | 100.0% | 0.82 [0.70, 0.96] |
| Total events | 795 | | 947 | | | |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 12.63$, d.f. = 7, (p = 0.08); $I^2 = 45\%$ | | | | | | |
| Test for overall effect: Z = 2.48 (p = 0.01) | | | | | | |
| Test for subgroup differences: $Chi^2 = 8.67$; d.f. = 1, (p = 0.03); $I^2 = 88.5\%$ | | | | | | |

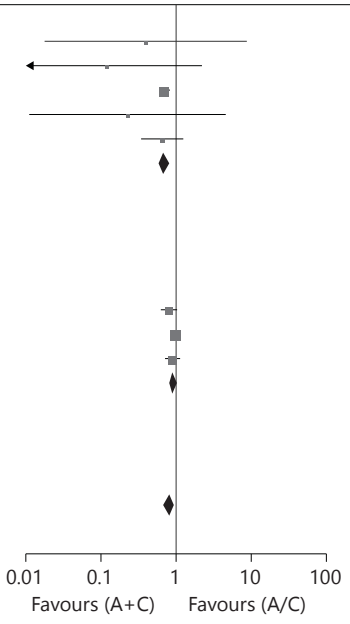


**Fig. 2.** Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on stroke.

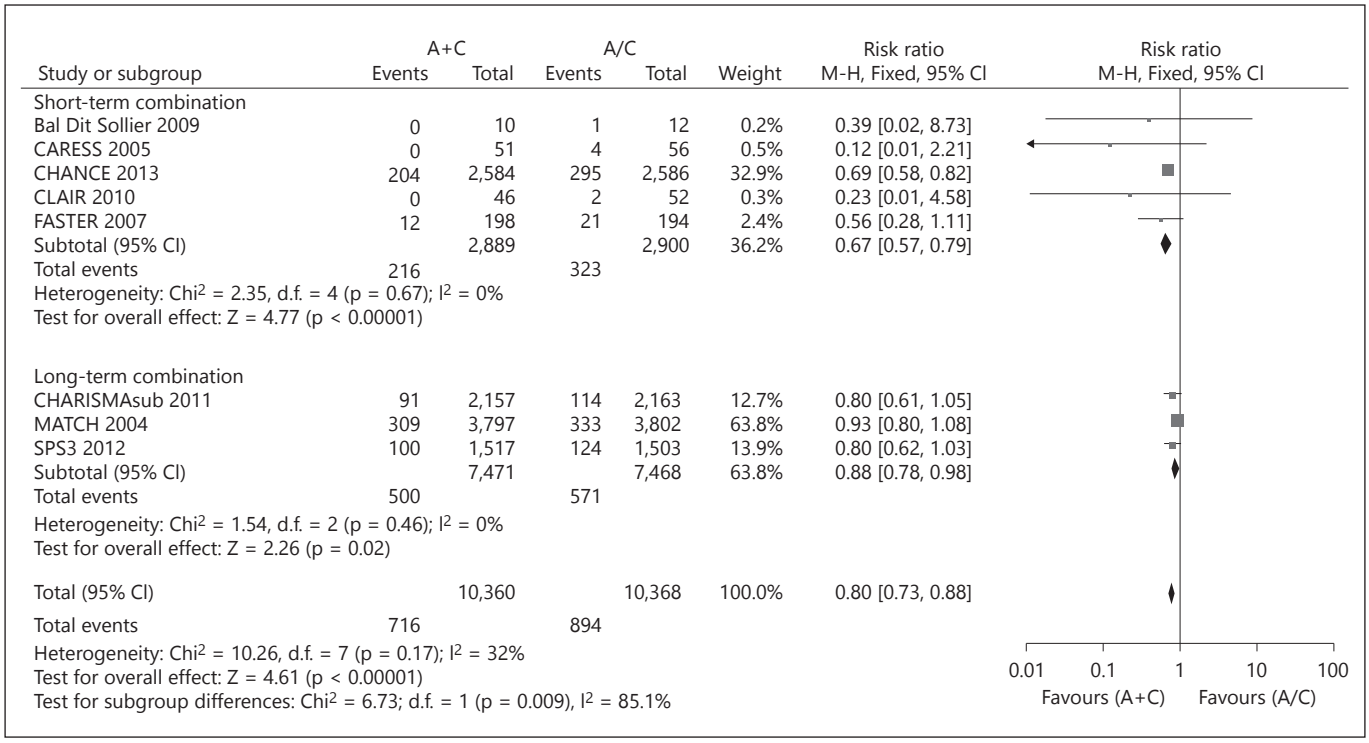


**Fig. 3.** Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on ischemic stroke.

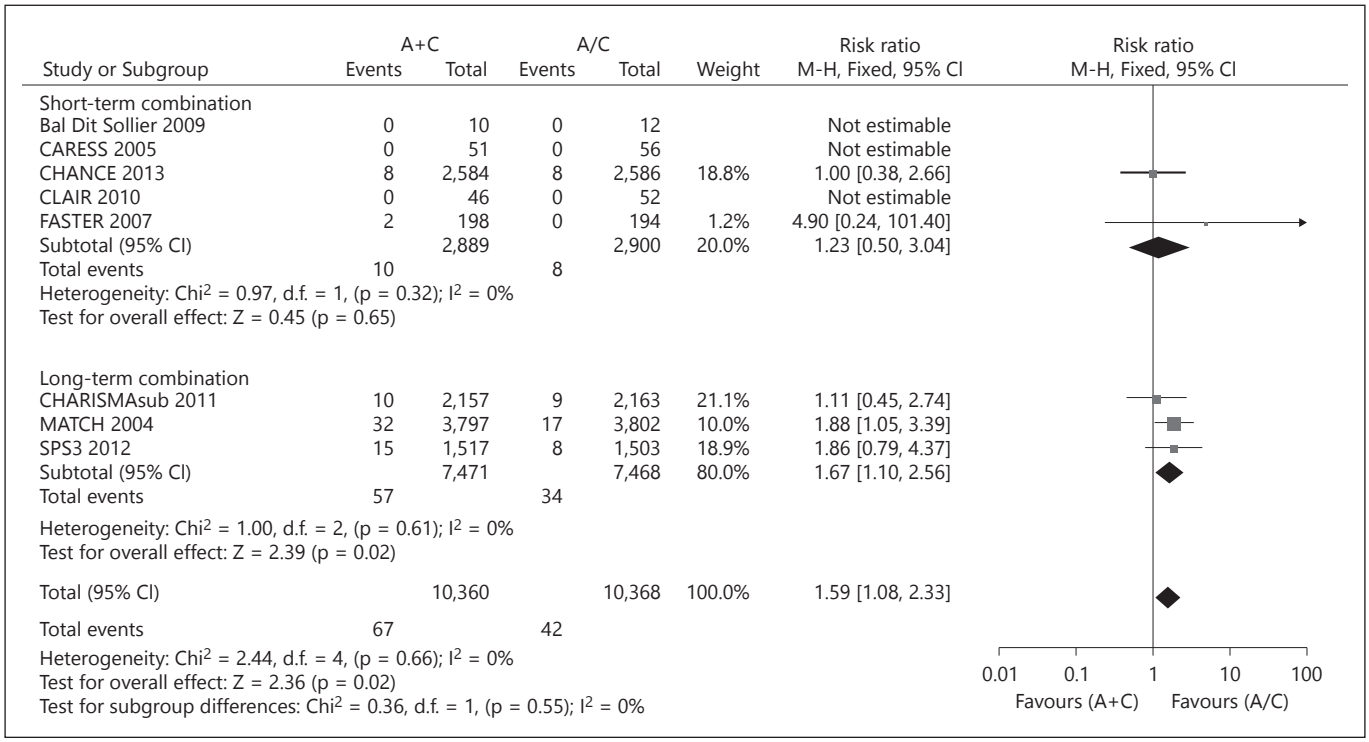


**Fig. 4.** Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on hemorrhagic stroke.

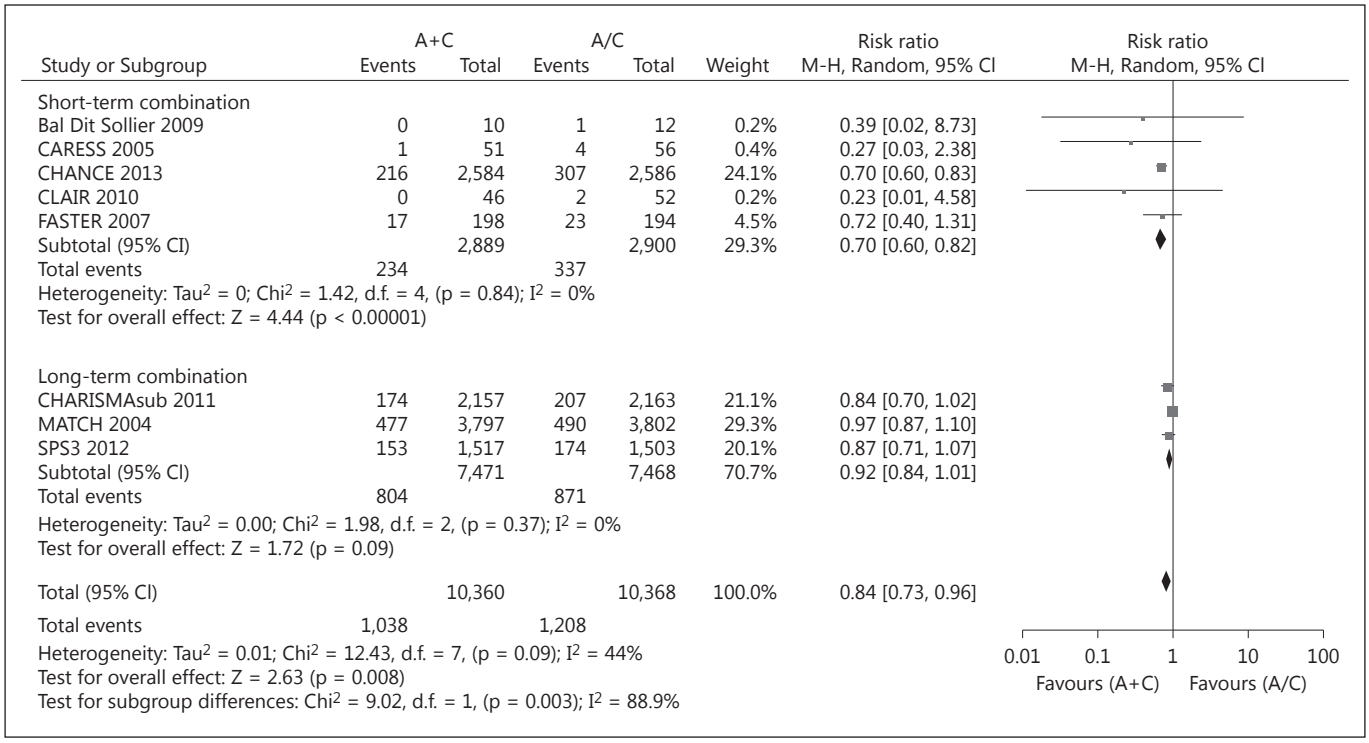


**Fig. 5.** Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on stroke, MI, or vascular death.

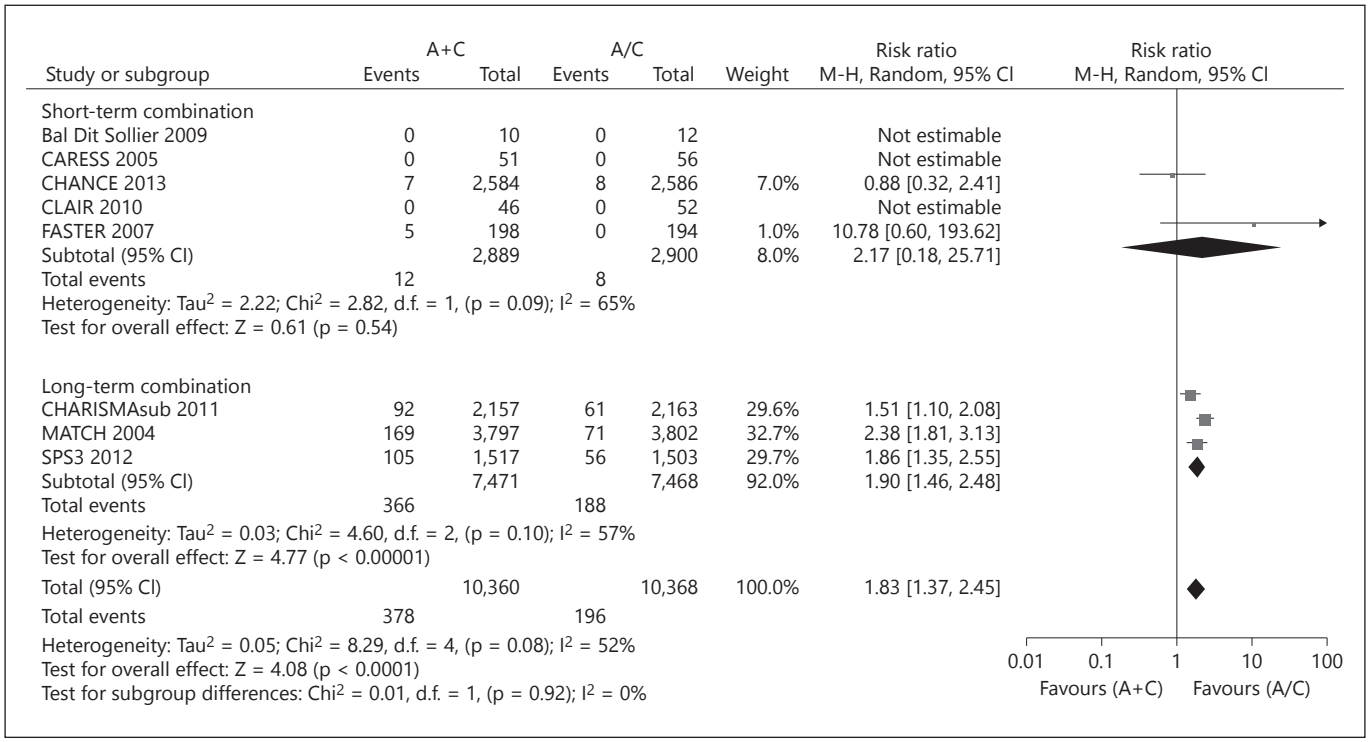


**Fig. 6.** Comparison of aspirin and clopidogrel versus aspirin or clopidogrel alone on major bleeding.