Efficacy and safety of clopidogrel and/or aspirin for ischemic stroke/transient ischemic attack

An overview of systematic reviews and meta-analysis

Youwen Yang, MD, Zongtao Huang, MD, Xueji Zhang, MD

Abstract

Objective: Patients experiencing acute ischemic stroke or transient ischemic attack are commonly treated with clopidogrel and/or aspirin (mono- and dual-antiplatelet therapy) to minimize the risk for recurrent stroke. Updated data from systematic studies can be used to guide practice. The present study aimed to compare findings from systematic reviews and meta-analyses addressing the efficacy and safety of clopidogrel or aspirin – alone or in combination – in patients experiencing acute ischemic stroke or transient ischemic attack.

Methods: The Cochrane Library, PubMed, Ovid, Scopus, EBSCO, and CINAHL databases were searched for relevant studies published from inception to 2020. Data from each study were extracted independently using a predefined data abstraction form. The Risk of Bias in Systematic Reviews tool and A Measurement Tool to Assess Systematic Reviews 2 were used to evaluate risk of bias and the quality of the included studies.

Results: Seven studies, published between 2010 and 2020, were eligible for analysis. The included studies evaluated a wide range of outcomes, including recurrent stroke, myocardial infarction, recurrent ischemic stroke, vascular mortality and vascular events, bleeding events, all-cause mortality, functional disability, and quality of life. The risk of bias and methodological validity of the included studies ranged from low to high according to ROBIS and AMSTAR 2 parameters. Results revealed that clopidogrel plus aspirin was more effective than aspirin alone in reducing the risk for recurrent stroke (ischemic or hemorrhagic), with high-quality evidence. However, compared with aspirin, dual treatment increased major bleeding events (intracranial bleeding and extracranial bleeding), supported by high-quality evidence.

Conclusions: High-quality evidence suggested that clopidogrel plus aspirin was more efficient than monotherapy, although the risk for hemorrhagic stroke was relatively higher in combined therapy regimens lasting >1 month.

Abbreviations: AIS = acute ischemic stroke, DAPT = dual-antiplatelet therapy, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, TIA = transient ischemic attack.

Keywords: aspirin, clopidogrel, effectiveness and safety, ischemic stroke/transient ischemic attack, overview of systematic reviews

1. Introduction

Acute ischemic stroke (AIS) is characterized by a lack of neurological control caused by a rapid loss of blood supply to part(s) of the brain.[1,2] Recurrent stroke often occurs a few days or weeks after initial AIS or transient ischemic attack (TIA), which emphasizes the importance of therapies aimed at preventing stroke recurrence.[1,3] Treatment strategies for AIS include thrombolytic, antiplatelet and anticoagulant, neuroprotective therapies, and endovascular treatment techniques. The most common therapy is dual antiplatelet therapy (DAPT; e.g., clopidogrel plus aspirin).[4–7] Numerous studies investigating the effectiveness and safety of DAPT and monotherapy have been conducted in the past 10 years.[8–12]

The highest standard of evidence used to support therapeutic efficacy and safety is from systematic analyses and meta-analysis of randomized controlled trials (RCTs). Due to the increasing number of systematic reviews and meta-analyses, it is necessary to combine various analyses into overviews to provide clinicians with readily accessible knowledge.

The present review summarizes findings from systematic studies and meta-analyses addressing the efficacy and safety of
clopidoogrel or aspirin alone (monotherapy) or combinations (i.e., DAPT) for patients experiencing AIS or TIA.

2. Method

The current overview of systematic reviews and meta-analyses was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (i.e., PRISMA) guidelines.

2.1. Inclusion criteria

Systematic reviews and meta-analyses that examined clopidoogrel and/or aspirin for individuals experiencing acute AIS or TIA, published between 2010 and 2021, were included. Reviews including patients with AIS from all causes (including >50% carotid stenosis and large artery disease) were also included. A combination of major ischemic events, such as ischemic stroke, myocardial infarction (MI), or death, was the primary efficacy endpoint. Safety outcomes, reported as intracranial bleeding and major bleeding, were also considered.

2.2. Search methods for the identification of reviews and assessment of methodological quality

Two authors searched for systematic studies and meta-analyses in the Cochrane Library, PubMed, Ovid, Scopus, EBSCO, and CINAHL databases published from inception to 2020 using the following keywords “Clopidoogrel,” “Aspirin,” “Acute ischemic stroke,” “TIA,” “Dual-therapy,” “Mono-therapy,” “Efficacy,” and “safety.” For inclusion, all studies and evaluations of the clinical effects of DAPT were included. Based on the inclusion criteria described above, two authors assessed eligibility. Furthermore, two authors performed an unbiased quality assessment of the systematic reviews using the Risk of Bias in Systematic reviews tool and A Measurement Tool to Assess Systematic Reviews 2.

2.3. Study selection

Search results were exported from Endnote X7 (Clarivate, London, United Kingdom), and duplicates were removed. Study selection was completed in two stages: titles and abstracts were screened and, subsequently, the full texts of selected studies were accessed and screened against the eligibility criteria. Title and abstract screening was performed by YWY and ZTH. Two reviewers independently selected and evaluated the included studies and any disagreements were resolved through a larger team discussion. The literature search retrieved 530 records, of which 127 were included after duplicates were removed. Among these, 77 records were excluded through title and abstract screening, and 12 full-text articles fulfilled the eligibility criteria (Fig. 1). However, three of these were excluded for not reporting the outcome of interest and two for not reporting the comparison of interest, ultimately resulting in a total of seven studies included for analysis in the present study.[15–19]

2.4. Data extraction and synthesis

Two independent reviewers extracted the following data from the included systematic reviews: number of included studies and participants; outcome measures; and meta-analysis results. The quality of the evidence was rated based on the principles of Grading of Recommendations Assessment, Development, and Evaluation (Table 1).

2.5. Ethics approval

Given the nature of the present study (i.e., overview of systematic reviews and meta-analyses) and the use of anonymized patient data, requirements for ethics approval were waived.

3. Results

3.1. Characteristics of the included systematic reviews/ meta-analyses

The literature search retrieved 530 potentially eligible studies. After removing duplicates and eliminating others through reviewing titles and abstracts, potentially relevant articles were screened in two rounds, resulting in the selection of seven studies published between 2010 and 2020 (Fig. 1); of these studies, 85.6% underwent meta-analysis. The details and methodological quality of the included studies are summarized in Table 2. In addition, most of the analyzed reference citations had National Institutes of Health Stroke Scale (NIHSS) scores <3. In most of the studies, the doses of clopidogrel and aspirin were 75 mg and 325 mg once daily, respectively.

3.2. Assessment of quality

The quality of the included studies was assessed using the AMSTAR 2 tool (Table 3). Overall, the quality of the included studies ranged from low to high.

3.3. Efficacy and safety

3.3.1. Recurrent stroke.

Recurrent stroke referred to the incidence of recurrent stroke, including ischemic or hemorrhagic stroke, after ischemic stroke or TIA. As shown in Table 4, there were 7 included reviews, 36 RCTs, and 4 retrospective cohort studies that addressed the risk for recurrent stroke. Among these, five meta-analyses compared clopidogrel plus aspirin with aspirin monotherapy. Three analyses reached the same conclusion: clopidogrel plus aspirin significantly lowered the risk for

| Table 1 |
| --- |
| Quality of evidence. |
| Level of quality of evidence | Included criteria |
| High-quality | One or more high-quality systematic analyses of clear conclusions based on at least two high-quality primary studies. |
| Moderate-quality | One or more systematic reviews of high or moderate quality based on at least 1 high-quality primary study or at least 2 primary studies of moderate quality with consistent results. |
| Low-quality | One or more systematic reviews of variable quality based on primary studies of moderate quality or inconsistent results in the reviews or inconsistent results in primary studies. |

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Another review found that clopidogrel plus aspirin only significantly reduced recurrent stroke incidence when used for <3 months. However, in a review that included seven RCTs, with 39,574 patients, Lee reported no significant difference between clopidogrel plus aspirin compared with aspirin monotherapy in reducing recurrent stroke. Three reviews compared clopidogrel plus aspirin with aspirin monotherapy, and two showed that clopidogrel plus aspirin reduced the incidence of recurrent strokes, and one reported no significant difference compared with monotherapy. Paciaroni compared clopidogrel monotherapy with aspirin alone and found that clopidogrel monotherapy significantly lowered the risk for recurrent stroke compared with aspirin monotherapy.

3.3.2. Myocardial infarction. MI is a sudden interruption of blood circulation in the myocardium and damage to the myocardium caused by the inability to obtain sufficient oxygen. As shown in Table 4, three reviews, including 19 RCTs, listed MI as a separate outcome measure. Among these, 16 RCTs compared clopidogrel plus aspirin with aspirin alone and found no significant difference in the probability of MI between clopidogrel dual therapy and aspirin monotherapy. Kheiri and Lee included three RTCs comparing clopidogrel plus aspirin with clopidogrel alone. Similarly, results revealed that, compared with clopidogrel monotherapy, clopidogrel plus aspirin did not affect the incidence of MI.

3.3.3. Recurrent ischemic stroke. Regarding the incidence of recurrent ischemic stroke after AIS/TIA, a total of four reviews with 27 RCTs and four retrospective cohort studies included measures of recurrent ischemic stroke (Table 4). Three reviews compared clopidogrel plus aspirin with aspirin alone. Kheiri found that clopidogrel plus aspirin significantly reduced
the incidence of ischemic stroke by 1.9% compared with aspirin alone,\textsuperscript{16} and Rahman found that clopidogrel plus aspirin reduced the ischemic stroke rate only if dual therapy lasted <3 months.\textsuperscript{14} Lee reported that clopidogrel plus aspirin and aspirin alone had no significant effect on the risk for ischemic stroke.\textsuperscript{18} Finally, Paciaroni compared clopidogrel monotherapy with aspirin monotherapy and found that clopidogrel significantly lowered the incidence of recurrent ischemic stroke.\textsuperscript{13}

### 3.3.4. Vascular mortality and vascular events.
A total of six reviews with 41 RCTs and four retrospective cohort studies included a measure of vascular mortality and major vascular events (Table 4). Four of the reviews compared clopidogrel plus aspirin with aspirin alone and reported an incidence for vascular mortality. Among them, three reviews reported that clopidogrel plus aspirin demonstrated no significant differences in vascular mortality rate compared with aspirin alone,\textsuperscript{13,16,18} while another review found that clopidogrel plus aspirin was superior to aspirin alone only if the treatment lasted <3 months.\textsuperscript{14} Three reviews reported the incidence of vascular events, two of which found that DAPT significantly reduced the incidence of vascular events compared with monotherapy.\textsuperscript{18,19} Similar results were found in a study comparing clopidogrel with aspirin alone, in which clopidogrel monotherapy significantly lowered the risk for major vascular events compared with aspirin monotherapy.\textsuperscript{13}

### 3.3.5. Bleeding events.
Measures of bleeding events included major bleeding, and intracranial and extracranial bleeding. As shown in Table 5, four reviews compared clopidogrel plus aspirin with aspirin for major bleeding. A review by Kheiri found that, compared with aspirin alone, clopidogrel plus aspirin increased the incidence of major bleeding by 1.1%\textsuperscript{16}; similar results were also reported by Geeganage but were nonsignificant.\textsuperscript{19} In addition, Rahman found that as the duration of treatment with clopidogrel plus aspirin increased, the incidence of major bleeding also increased.\textsuperscript{14} In contrast, Zhou reported that clopidogrel plus aspirin had no significant effect on major bleeding compared with aspirin alone.\textsuperscript{13} The other two reviews reported intracranial bleeding events. Lee found that DAPT had no significant effect on intracranial bleeding compared with aspirin monotherapy.\textsuperscript{18} However, when compared with clopidogrel monotherapy, DAPT demonstrated a higher risk for intracranial bleeding. An updated review by Kheiri found that clopidogrel plus aspirin increased the rate of intracranial bleeding by 0.4% compared with aspirin alone.\textsuperscript{16} In terms of extracranial hemorrhage, Hao included three RCTs that measured moderate or major extracranial hemorrhage and mild or minor extracranial hemorrhage and found that, compared with aspirin alone, clopidogrel plus aspirin increased both the incidence of moderate or major and mild or minor extracranial hemorrhage.\textsuperscript{17}

### 3.3.6. All-cause mortality.
A total of five reviews measured all-cause mortality, four of which compared clopidogrel plus aspirin with aspirin alone (Table 5). Three reviews obtained similar results: clopidogrel plus aspirin demonstrated no significant differences compared with aspirin alone in terms of mortality rate.\textsuperscript{16–18} However, an updated review found that the use of clopidogrel plus aspirin increased mortality, but only after ≥3 months of long-term use.\textsuperscript{14} Paciaroni compared clopidogrel monotherapy with aspirin monotherapy and found no significant differences in mortality between the two groups.\textsuperscript{13}

### 3.3.7. Functional disability and quality of life.
Only two reviews measured functional disability and quality of life (Table 6). Geeganage found that DAPT had no significant difference in functional outcomes compared with monotherapy.\textsuperscript{19} Hao included two RCTs and found that, in terms of functional disability, clopidogrel plus aspirin conferred a small—but significant—benefit; a similar result was also found in quality of life criteria, but only in one RCT.\textsuperscript{17}
4. Discussion

In the present overview of systematic reviews addressing the efficacy and safety outcomes of clopidogrel or aspirin alone (monotherapy) or combination (i.e., DAPT) for patients with ischemic stroke/TIA, we assessed seven systematic reviews encompassing 54 RCTs and four retrospective cohort studies including 133,502 patients. Overall, we revealed a large body of scientific data supporting DAPT to be superior to monotherapy in preventing recurrent stroke (ischemic and hemorrhagic) in patients experiencing ischemic stroke/TIA. DAPT has been shown to have little effect on MI in a large number of studies with reasonably consistent outcomes. For other outcomes, such as vascular mortality and vascular events, contradictory results were found among the reviews. Some studies reported no differences between DAPT and monotherapy, while others found that DAPT was superior to aspirin monotherapy but only within 3 months of treatment. Compared with aspirin alone or clopidogrel alone, substantial evidence suggests that clopidogrel plus aspirin is associated with increased bleeding, intracranial bleeding, and extracranial bleeding, with bleeding

| AMSTAR 2 criteria                                                                 | Zhou et al, 2017 | Rahman et al, 2019 | Paciaroni et al, 2019 | Kheiri et al, 2018 | Hao et al, 2018 | Lee et al, 2013 | Geeganage et al, 2012 |
|----------------------------------------------------------------------------------|------------------|-------------------|----------------------|-------------------|----------------|------------------|----------------------|
| 1. Did the research questions and inclusion criteria for the review include the components of PICO? | Yes              | Yes               | Yes                  | Yes               | Yes            | Yes              | Yes                  |
| 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | Yes              | No                | Partial yes          | Partial yes       | Yes            | Yes              | Partial yes          |
| 3. Did the review authors explain their selection of the study designs for inclusion in the review? | Yes              | Yes               | Yes                  | Yes               | Yes            | Yes              | Yes                  |
| 4. Did the review authors use a comprehensive literature search strategy?         | Partial yes      | Partial yes       | Partial yes          | Yes               | Yes            | Partial yes     | Partial yes          |
| 5. Did the review authors perform study selection in duplicate?                   | Yes              | Yes               | Yes                  | Yes               | Yes            | Yes              | Yes                  |
| 6. Did the review authors perform data extraction in duplicate?                   | Yes              | Yes               | Yes                  | Yes               | Yes            | Yes              | Yes                  |
| 7. Did the review authors provide a list of excluded studies and justify the exclusions? | No               | No                | Yes                  | No                | Partial yes    | No               | No                   |
| 8. Did the review authors describe the included studies in adequate detail?       | Yes              | Yes               | Yes                  | Yes               | Yes            | Yes              | Yes                  |
| 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | Yes              | Yes               | Yes                  | Yes               | No             | Yes              | No                   |
| 10. Did the review authors report on the sources of funding for the studies included in the review? | No               | No                | No                   | No                | No             | Yes              | No                   |
| 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? | Yes              | Yes               | Yes                  | Yes               | Yes            | Yes              | Yes                  |
| 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | Yes              | No                | Yes                  | Yes               | Yes            | No               | No                   |
| 13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? | Yes              | No                | Yes                  | Yes               | Yes            | Yes              | Yes                  |
| 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | Yes              | Yes               | Yes                  | Yes               | Yes            | Yes              | Yes                  |
| 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | No               | No                | Yes                  | No                | Yes            | Yes              | Yes                  |
| 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | Yes              | Yes               | Yes                  | Yes               | Yes            | Yes              | Yes                  |
| AMSTAR 2 score                                                                  | 12               | 9                 | 13                   | 11                | Moderate       | 14               | 14                   |
| Quality                                                                         | Moderate         | Low               | High                 | Moderate          | High           | High             | Low                  |

Table 3

Quality assessment (AMSTAR 2) of included systematic reviews/meta-analysis.
rate related to the length of treatment. One review reported that restricting the duration of treatment to 1 month can avoid increases in bleeding rate.\textsuperscript{[14]} Most reviews reported that DAPT had no effect on mortality, and one showed that DAPT compared to monotherapy could reduce mortality; however, due to the relatively small sample size and low AMSTAR 2 score, the quality of the results was relatively low.\textsuperscript{[19]}

Only two reviews assessed functional disability and quality of life and found that DAPT did not affect these outcomes; as such, more RCTs are needed to confirm these findings.\textsuperscript{[17,19]}

The time to initiation of DAPT after an ischemic stroke or TIA and the duration of therapy are the most important factors determining the efficacy of treatment. Rahman et al reported that to achieve maximum efficacy, DAPT should be initiated within 12 to 24 hours after minor ischemic stroke (NIHSS < 3) or TIA, and the duration of therapy should be less than 1 month.\textsuperscript{[14]} Hao et al suggested that DAPT administered within 24 hours following a high-risk TIA or minor ischemic stroke decreased the risk for a future stroke by approximately 2%, with minimal significant side effects.\textsuperscript{[17]} Furthermore, discontinuation of DAPT as soon as 10 days but no later than 21 days after commencement is likely to optimize its net effect. Kheiri et al found that regardless of the duration of DAPT, both short- and long-term use will reduce the risk for stroke; however, the risk for intracranial bleeding increased as the duration of DAPT increased (>3 months).\textsuperscript{[16]}

Moreover, DAPT was more effective in reducing the incidence of

| Table 4 | Efficacy and safety. |
|---------|---------------------|
| **Comparison** | **Results (RR; 95% CI)** | **Quality of evidence** |
| Recurrent stroke | | |
| Zhou et al, 2017 | Clopidogrel + Aspirin | Aspirin | Reduce risk | (0.76; 0.67–0.87) |
| Kheiri et al, 2018 | Clopidogrel + Aspirin | Aspirin | Reduce risk | (0.80; 0.72–0.89) |
| Hao et al, 2018 | Clopidogrel + Aspirin | Aspirin | Reduce risk | (0.70; 0.61–0.80) |
| Rahman et al, 2019 | Clopidogrel + Aspirin | Aspirin | Reduce risk only <3 mo | (0.53; 0.37–0.78) |
| Lee et al, 2013 | Clopidogrel + Aspirin | Aspirin | No difference | (0.89; 0.78–1.01) |
| Kheiri et al, 2018 | Clopidogrel + Aspirin | Clopidogrel | Reduce risk | (0.67; 0.49–0.93) |
| Geeganage et al, 2011 | Clopidogrel + Aspirin | Clopidogrel | Reduce risk | (N/A) |
| Lee et al, 2013 | Clopidogrel + Aspirin | Clopidogrel | No difference | (N/A) |
| Paclaroni et al, 2019 | Clopidogrel | Aspirin | Reduce risk | (0.76; 0.58–0.99) |
| Myocardial infarction | | |
| Kheiri et al, 2018 | Clopidogrel + Aspirin | Aspirin | No difference | (1.04; 0.84–1.29) |
| Lee et al, 2013 | Clopidogrel + Aspirin | Aspirin | No difference | (1.08; 0.83–1.41) |
| Zhou et al, 2017 | Clopidogrel + Aspirin | Clopidogrel | No difference | (N/A) |
| Kheiri et al, 2018 | Clopidogrel + Aspirin | Clopidogrel | No difference | (N/A) |
| Lee et al, 2013 | Clopidogrel + Aspirin | Clopidogrel | No difference | (N/A) |
| Recurrent ischemic stroke | | |
| Rahman et al, 2019 | Clopidogrel + Aspirin | Aspirin | Reduce risk | (0.75; 0.66–0.85) |
| Lee et al, 2013 | Clopidogrel + Aspirin | Aspirin | Reduce risk only <3 mo | (0.72; 0.58–0.90) |
| Paclaroni et al, 2019 | Clopidogrel | Aspirin | No difference | (0.72; 0.55–0.94) |
| Vascular mortality | | |
| Zhou et al, 2017 | Clopidogrel + Aspirin | Aspirin | No difference | (1.08; 0.83–1.41) |
| Kheiri et al, 2018 | Clopidogrel + Aspirin | Aspirin | No difference | (1.12; 0.88–1.42) |
| Lee et al, 2013 | Clopidogrel + Aspirin | Aspirin | No difference | (N/A) |
| Rahman et al, 2019 | Clopidogrel + Aspirin | Aspirin | Reduce risk only <3 mo | (0.68; 0.60–0.78) |
| Vascular events | | |
| Paclaroni et al, 2019 | Clopidogrel | Aspirin | Reduce risk | (0.77; 0.63–0.95) |
| Lee et al, 2013 | Clopidogrel + Aspirin | Aspirin | Reduce risk | (N/A) |
| Geeganage et al, 2011 | Clopidogrel + Aspirin | Aspirin | Reduce risk | (0.75; 0.56–0.99) |

CI=confidence interval, N/A=non available.
stroke without increasing risk if initiated within 7 days after the minor IS or TIA.

Due to inadequate documentation, it was challenging to collect data regarding methodological accuracy and findings from some reviews. The authors of systematic reviews should, therefore, collect, analyze, interpret, summarize, and report findings using clear and systematic approaches. Moreover, some reviews are too biased toward extracting data from one included study, which can lead to inaccurate results or bias.

A recent study from China showed that the antiplatelet drugs cilostazol and aspirin have the same effect in preventing recurrent strokes, and that cilostazol caused fewer bleeding events \(^4\). However, because cilostazol is used only in East Asia, there are few related systematic reviews available to evaluate; therefore, the present review only included reviews of clopidogrel plus aspirin dual therapy.

There are significant limitations to summarizing facts based purely on systematic reviews. First, important data from original research may be overlooked. Although review articles can be revised regularly, new reports are constantly being published. The present summary explicitly demonstrates that several articles must be updated. Second, because reviews offer little detail about RCTs, findings could be too broad for physicians to use in practice. Therefore, a simple overview of how the intervention should be implemented and how long it should last may be of limited value.

5. Conclusion

All included reviews concluded that DAPT appeared to be more effective and safer than monotherapy, and that using DAPT for as short as possible maximizes benefit without increasing the risk for bleeding. In addition, the benefits of DAPT were independent of ethnicity.

Author contributions

YWY, ZTH, and XJZ designed, performed, and analyzed the research. YWY, ZTH, and XJZ advised on article inclusion and exclusion. YWY and XJZ wrote the manuscript. YWY, ZTH, and XJZ read and revised the manuscript. All authors read and approved the final manuscript.

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Table 5

| Comparison | Results (RR; 95% CI) | Quality of evidence |
|------------|----------------------|---------------------|
| Major bleeding |
| Kheiri et al, 2018 | Clopidogrel + Aspirin | Increase the risk | High |
| Geeganage et al, 2011 | Aspirin | (1.90;1.33–2.72) | |
| Rahman et al, 2019 | Clopidogrel + Aspirin | Increase risk only > 3 mo | Low |
| Zhou et al, 2017 | Aspirin | No difference | Low |
| Intracranial bleeding |
| Kheiri et al, 2018 | Clopidogrel + Aspirin | Increase the risk | High |
| Lee et al, 2013 | Aspirin | No difference | Moderate |
| Lee et al, 2013 | Clopidogrel + Aspirin | Increase the risk | Moderate |
| Extracranial bleeding |
| Hao et al, 2018 | Clopidogrel + Aspirin | Increase risk | Moderate |
| All-cause mortality |
| Kheiri et al, 2018 | Clopidogrel + Aspirin | No difference | High |
| Lee et al, 2013 | Aspirin | (1.22;0.88–1.42) | Moderate |
| Hao et al, 2018 | (N/A) | |
| Rahman et al, 2019 | Clopidogrel + Aspirin | Increase risk only >3 mo | Low |
| Paciaroni et al, 2019 | Aspirin | No difference | High |

CI = confidence interval, N/A = non available.

Table 6

| Comparison | Results (RR; 95% CI) | Quality of evidence |
|------------|----------------------|---------------------|
| Hao et al, 2018 | Clopidogrel + Aspirin | Small but important benefit | Low |
| Geeganage et al, 2011 | Aspirin | (0.90; 0.81–1.01) | |
| | | No difference | N/A |

CI = confidence interval, N/A = non available.
Conceptualization: Youwen Yang, Zongtao Huang, Xueji Zhang.

Data curation: Youwen Yang, Zongtao Huang, Xueji Zhang.

Formal analysis: Youwen Yang, Zongtao Huang, Xueji Zhang.

Investigation: Youwen Yang, Xueji Zhang.

Methodology: Zongtao Huang.

Supervision: Youwen Yang.

Writing – original draft: Youwen Yang, Zongtao Huang, Xueji Zhang.

Writing – review & editing: Youwen Yang, Xueji Zhang.

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