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Comparative efficacy and safety of multiple antiplatelet therapies for secondary prevention of ischemic stroke or transient ischemic attack: A network meta-analysis

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ABSTRACT

Background: Antiplatelet therapies for secondary prevention of ischemic stroke or transient ischemic attack (TIA) is a highly active research topic with five critical drugs obtained by visual analysis. We aimed to compare and rank multiple antiplatelet therapies using a network meta-analysis.

Methods: Relevant medical databases were searched. Eligible randomized controlled trials (RCTs) which examined any comparisons involving mono- or dual antiplatelet therapies, based on aspirin, clopidogrel, dipyridamole, ticlopidine, cilostazol and placebo for patients with noncardioembolic ischemic stroke or TIA, were included. 14 outcomes were assessed. Primary outcomes were stroke recurrence, composite events (stroke recurrence, myocardial infarction and vascular death), and intracranial hemorrhage. PROSPERO registered number CRD42017069728.

Results: 45 RCTs with 173,131 patients were included in network meta-analysis, involving eight antiplatelet therapies. Cilostazol and clopidogrel were statistically more efficacious than aspirin (odds ratio (OR) = 0.64, 95% confidence interval (CI) = 0.47–0.88; OR = 0.77, 95%CI = 0.62–0.95) and dipyridamole (OR = 0.64, 95%CI = 0.44–0.93; OR = 0.76, 95%CI = 0.58–0.99) in reducing stroke recurrence, and showed significant benefits in reducing composite events compared with aspirin (OR = 0.63, 95%CI = 0.45–0.89; OR = 0.90, 95%CI = 0.83–0.97). No significant difference was found between cilostazol and clopidogrel in intracranial hemorrhage. Weighted regression suggested cilostazol was hierarchically the optimum treatment in consideration of both efficacy and safety, followed by clopidogrel.

Conclusion: Cilostazol and clopidogrel are probably promising options for secondary prevention of ischemic stroke or TIA. Both of them reduce stroke recurrence similarly compared with aspirin or dipyridamole, and reduce composite events compared with aspirin. Further studies are needed to confirm this finding.

1. Introduction

Stroke, including both ischemic and hemorrhagic stroke, is the second leading cause of death and the third leading cause of disability worldwide, characterized by local neurological deficits resulting from cerebral blood circulation disorders [1,2]. To investigate scientific progress on stroke, novel methods, namely, visual analysis, cluster analysis and co-occurrence analysis, were employed on relevant literatures in Web of Science™ database by using CiteSpace software. We obtained seven representative knowledge groups, and among them,

Abbreviations: TIA, transient ischemic attack; RCT, randomized controlled trials; OR, odds ratio; CI, confidence interval; AHA/ASA, American Heart Association/American Stroke Association; ACCP, American College of Chest Physicians; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SUCRA, Surface under the cumulative ranking curve; RoR, Ratio of direct to indirect estimate; PDE-3, phosphodiesterase-3; ADP, adenosine diphosphate; TXA2, thromboxane A2; ATC, Antiplatelet Trialists' Collaboration; NIHSS, National Institutes of Health Stroke Scale

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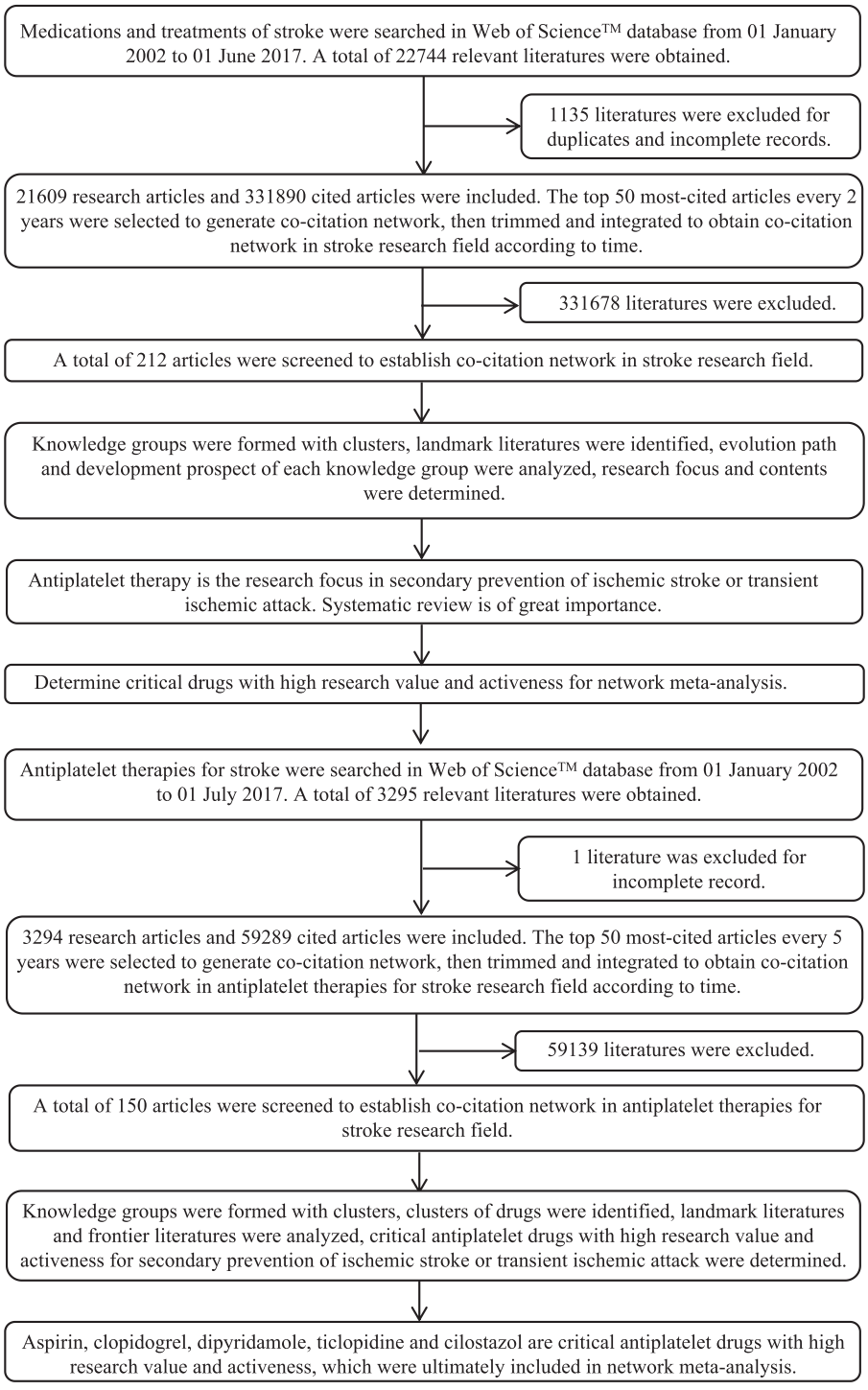

Fig. 1. Detailed process of visual analysis by CiteSpace software.

knowledge group on antiplatelet therapy is of the earliest concern, largest information quantity, and longest-lasting investigation. Cited history shows it is highly active concerned and widely applied in secondary prevention of ischemic stroke or transient ischemic attack (TIA), meanwhile, clinical trials are updated and new findings are published in succession. However, it is still difficult to draw coincident conclusions concerning the efficacy and safety of antiplatelet therapies, and controversial voices still exist. Therefore, a comprehensive evaluation on the large amount of critical literatures is of great importance (Fig. 1 and Appendix S1).

After further visual analysis on antiplatelet therapies for secondary prevention of ischemic stroke or TIA, we obtained five critical antiplatelet drugs with high research value and activeness, among which aspirin and clopidogrel are dominant drugs, dipyridamole, ticlopidine and cilostazol are frontier drugs (Fig. 1 and Appendix S1). In the American Heart Association/American Stroke Association (AHA/ASA) guidelines, aspirin, clopidogrel and aspirin plus dipyridamole were recommended for secondary prevention of noncardioembolic ischemic stroke or TIA [3]. Additionally, cilostazol was recommended in the American College of Chest Physicians (ACCP) guidelines [4]. Nevertheless, the latest 2018 AHA/ASA guidelines indicated that the benefit of alternative antiplatelet agents to aspirin had not been well

established in secondary stroke prevention [5].

Based on the analysis above, we performed a comprehensive systematic review with network meta-analysis, to evaluate the relative efficacy and safety of eight mono- or dual antiplatelet therapies for secondary prevention of ischemic stroke or TIA based on these five critical drugs.

2. Methods

This systematic review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplement S1–S2) [6]. We registered a protocol prospectively for this study in the PROSPERO, number CRD42017069728 [7].

2.1. Data sources and searches

For visual analysis, we searched Web of Science™ datebase to identify articles and reviews on stroke published from 2002 to 2017 without language restrictions. Search strategy and search terms are given in Appendix S1.

For network meta-analysis, we searched PubMed, Embase, Cochrane Library, Web of Science and ClinicalTrials.gov, to identify eligible randomized controlled trials (RCTs) from inception to 01 August 2017 without language restrictions. Any comparisons involving mono- or dual antiplatelet therapies, based on aspirin, clopidogrel, dipyridamole, ticlopidine and cilostazol, and placebo for secondary prevention of noncardioembolic ischemic stroke or TIA, were considered in this study. Moreover, we searched relevant studies and meta-analyses for citation tracking to avoid omission, and contacted authors to revise and supplement data when necessary. Search strategy and search terms are given in Appendix S2.

2.2. Study selection

Inclusion criteria: 1) Any comparisons involving mono- or dual antiplatelet therapies, based on aspirin, clopidogrel, dipyridamole, ticlopidine and cilostazol, and placebo; 2) Patients involved were adults diagnosed as noncardioembolic ischemic stroke or TIA; 3) Sample size was > 90.

Exclusion criteria: 1) Trials with a treatment duration of less than one week; 2) Trials with the use of anticoagulant drugs; 3) Ongoing or prematurely terminated trials.

2.3. Data extraction and quality assessment

Two researchers (RWX and RBH) searched and selected eligible studies independently. Two researchers (RBH and MYZ) extracted relevant outcomes and baseline characteristics with a predefined data extraction template, and meanwhile assessed the risk of bias with the Cochrane risk of bias assessment tool from seven aspects as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias [8]. When five or more aspects were rated as low bias risk and no more than one aspect rated as high bias risk, the study was classified as of high quality. Those with two or more aspects rated as high bias risk were classified as low-quality ones. The remaining studies were classified as of moderate quality. Consensus was reached from arbitration to resolve disagreement by a panel of other researchers (JYY, QCZ, and HSC) within our review team.

14 outcomes were assessed for network meta-analysis. In terms of efficacy, primary outcomes were stroke recurrence and composite events, and secondary outcomes included ischemic stroke, fatal stroke, nonfatal stroke, all-cause mortality, vascular death, myocardial infarction and transient ischemic attack. In terms of safety, primary outcome was intracranial hemorrhage, and secondary outcomes included any bleeding, major bleeding, severe bleeding and gastrointestinal bleeding. Detailed definitions are presented in Appendix S3.

2.4. Data synthesis and analysis

Visual analysis was performed with CiteSpace software [9]. First, representative datasets were created based on treatments, related medications and technical terms. Then, network and visualization map were gradually synthesized and established, to assist research on domain structure and dynamic trend. Finally, citation trajectories were formed by critical authors and articles presented the research progress and potential development (Appendix S1).

For traditional meta-analysis, we used R3.3.2 software. Heterogeneity was assessed by *P* value [8]. If statistical heterogeneity was found (P < .05), a random effects model would be used. Otherwise, a fixed effects model would be used. Odds ratios (ORs) with 95% confidence intervals (CIs) were applied to evaluate outcomes. To assess publication bias, funnel plot, Egger's test and weighted-adjusted Egger's test were used [8].

For network meta-analysis, we used R3.3.2 and Stata12.0 software with frequentist model [10]. Heterogeneity was assessed and model was selected in the same way as traditional meta-analysis. When heterogeneity was found among different comparisons, net heat plot was used to seek for the source. ORs with 95%CIs were applied to evaluate outcomes. To assess publication bias, a comparison-adjusted funnel plot (an extension of the common funnel plot in cases of multiple treatment comparisons) was used [11,12].

Surface under the cumulative ranking curve (SUCRA) was used to estimate the relative ranking probabilities of antiplatelet therapies in each outcome [11]. Due to lack of evidence for some treatments in some outcomes, we weighted SUCRAs by the number of involved treatments for each outcome and summed efficacy and safety of each treatment, respectively, and in turn generated a scatter plot by weighted regression. Finally, a clear hierarchy was obtained.

Inconsistency of network meta-analysis was assessed in two ways: global inconsistency and local inconsistency [12]. Global inconsistency was assessed by using design-by-treatment interaction model to calculate the inconsistency between direct and indirect evidence for each comparison. Local inconsistency was assessed by using loop-specific approach to calculate the difference between direct and indirect evidence in each closed loop [12]. Ratio of direct to indirect estimate (RoR) was applied.

Sensitivity analysis was performed based on the leave-one-out approach.

A two-sided p value of < 0.05, was considered as statistically significant.

3. Results

3.1. Characteristics and quality of included studies

Literature screening process is summarized in Fig. 2. 45 eligible RCTs with 173,131 patients were included for network meta-analysis, involving eight mono- or dual therapies as follows: aspirin, cilostazol, clopidogrel, dipyridamole, ticlopidine, cilostazol plus aspirin, clopidogrel plus aspirin, and dipyridamole plus aspirin. Among them 42 were two-arm trials, 1 was three-arm trial and 2 were four-arm trials. According to the Cochrane risk of bias assessment tool, > 75% of the studies were assessed as of high quality, and the rest were moderate quality (Fig. 3). No low-quality studies were included. Characteristics of the included studies are provided in Appendix S3.

3.2. Traditional meta-analysis

Results of traditional meta-analysis are given in Appendix S4. For

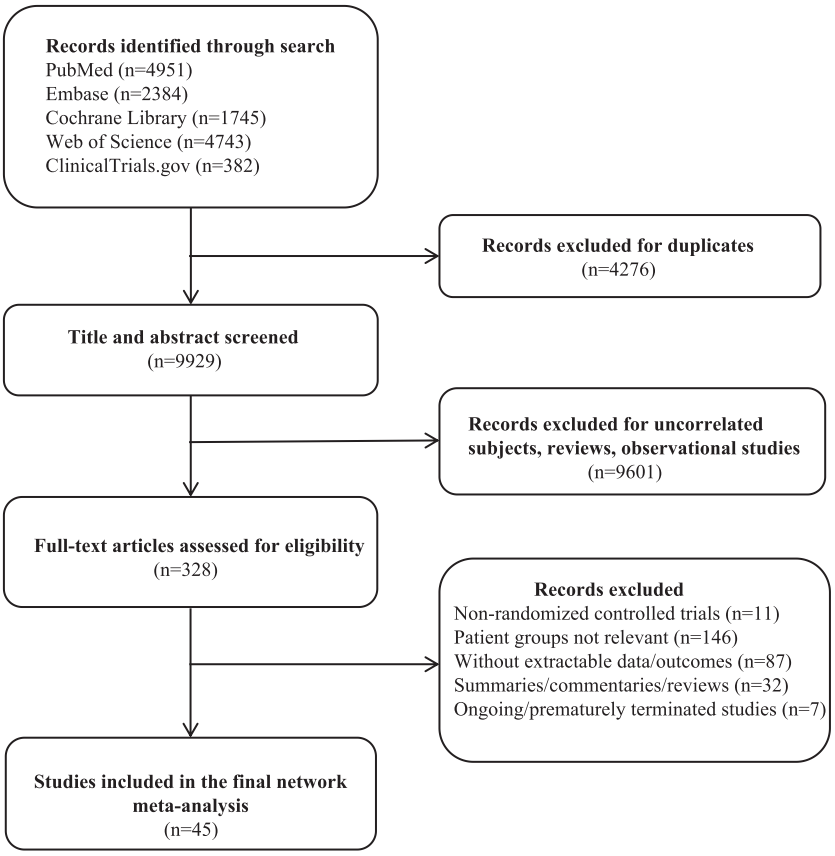

Fig. 2. Flow diagram of literature search and selection.

primary efficacy outcomes, cilostazol and clopidogrel plus aspirin were statistically more efficacious than aspirin in reducing risk of stroke recurrence (OR = 0.65, 95%CI = 0.50–0.84; OR = 0.74, 95%CI = 0.68–0.81). Dipyridamole plus aspirin was superior to dipyridamole (OR = 0.71, 95%CI = 0.59–0.86). Meanwhile, clopidogrel and clopidogrel plus aspirin showed significant benefits in reducing risk of composite events compared with aspirin (OR = 0.91, 95%CI = 0.83–0.99; OR = 0.80, 95%CI = 0.71–0.90). For the primary safety outcome, both clopidogrel plus aspirin and dipyridamole plus aspirin significantly increased risk of intracranial hemorrhage compared with clopidogrel (OR = 1.74, 95%CI = 1.19–2.55; OR = 1.43, 95%CI = 1.11–1.84). As for assessment of publication bias, both Egger's test and weighted-adjusted Egger's test indicated no publication bias in any outcome though some funnel plots did not show apparent symmetry (Appendix S5).

3.3. Network meta-analysis and weighted regression

Network plots of pairwise comparisons are presented in Appendix S6. Results of network meta-analysis are given in Table 1 and Appendix S7. For primary efficacy outcomes, cilostazol, clopidogrel, clopidogrel plus aspirin and dipyridamole plus aspirin were statistically more efficacious than aspirin (OR = 0.64, 95%CI = 0.47–0.88; OR = 0.77, 95%CI = 0.62–0.95; OR = 0.74, 95%CI = 0.66–0.84; OR = 0.75, 95%CI = 0.63–0.88) and dipyridamole (OR = 0.64, 95%CI = 0.44–0.93; OR = 0.76, 95%CI = 0.58–0.99; OR = 0.74, 95%CI = 0.58–0.94; OR = 0.74, 95%CI = 0.59–0.93) in reducing risk of stroke recurrence. Meanwhile, cilostazol, clopidogrel and clopidogrel plus aspirin showed significant benefits in reducing risk of composite events compared with aspirin (OR = 0.63, 95%CI = 0.45–0.89; OR = 0.90, 95%CI = 0.83–0.97; OR = 0.82, 95%CI = 0.77–0.88). For the primary safety outcome, aspirin, clopidogrel plus aspirin and dipyridamole plus aspirin significantly increased risk of intracranial

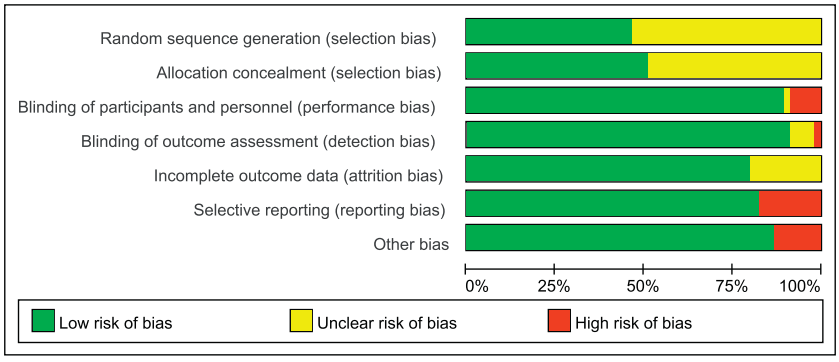

Fig. 3. Risk of bias assessment. Each risk of bias item was presented by the percentage of corresponding studies in all included studies.

Table 1
Results of network meta-analysis in primary outcomes.

Stroke recurrence (Upper diagonal part) and Ischemic stroke (Lower diagonal part)

Treatment	Plac	ASA	Cilo	Clop	Dip	Tic	Cilo + ASA	Clop + ASA	Dip + ASA
Plac	1	**0.82(0.73,0.93)**	**0.53(0.38,0.74)**	**0.63(0.51,0.79)**	0.83(0.67,1.02)	**0.73(0.58,0.91)**	0.85(0.05,13.91)	**0.61(0.52,0.72)**	**0.62(0.52,0.73)**
ASA	**0.74(0.62,0.87)**	1	**0.64(0.47,0.88)**	**0.77(0.62,0.95)**	1.01(0.82,1.24)	0.89(0.72,1.09)	1.03(0.06,16.84)	**0.74(0.66,0.84)**	**0.75(0.63,0.88)**
Cilo	**0.56(0.42,0.75)**	**0.76(0.58,0.99)**	1	1.20(0.82,1.75)	**1.57(1.08,2.29)**	1.38(0.95,2.01)	1.61(0.10,26.71)	1.16(0.83,1.63)	1.16(0.81,1.66)
Clop	**0.66(0.54,0.80)**	**0.89(0.81,0.98)**	1.17(0.88,1.56)	1	**1.31(1.01,1.72)**	1.15(0.86,1.54)	1.34(0.08,22.12)	0.97(0.79,1.19)	0.97(0.80,1.18)
Dip	1.07(0.21,5.51)	1.45(0.28,7.41)	1.90(0.36,9.95)	1.62(0.32,8.29)	1	0.88(0.66,1.17)	1.02(0.06,16.84)	**0.74(0.58,0.94)**	**0.74(0.59,0.93)**
Tic	**0.58(0.36,0.92)**	0.78(0.50,1.21)	1.03(0.61,1.72)	0.88(0.57,1.35)	0.54(0.10,2.92)	1	1.16(0.07,19.16)	0.84(0.66,1.07)	0.84(0.65,1.09)
Cilo + ASA	0.76(0.05,12.38)	1.03(0.06,16.70)	1.35(0.08,22.24)	1.15(0.07,18.75)	0.71(0.03,17.98)	1.32(0.08,22.14)	1	0.72(0.04,11.82)	0.72(0.04,11.9)
Clop + ASA	**0.56(0.46,0.67)**	**0.75(0.69,0.82)**	0.99(0.75,1.31)	**0.85(0.76,0.94)**	0.52(0.10,2.67)	0.97(0.62,1.50)	0.73(0.05,11.88)	1	1.00(0.83,1.22)
Dip + ASA	**0.65(0.53,0.80)**	**0.88(0.78,0.99)**	1.16(0.86,1.55)	0.98(0.90,1.08)	0.61(0.12,3.09)	1.13(0.72,1.75)	0.85(0.05,13.86)	**1.17(1.02,1.33)**	1

Composite events (Upper diagonal part) and Intracranial hemorrhage (Lower diagonal part)

Treatment	Plac	ASA	Cilo	Clop	Tic	Clop + ASA	Dip + ASA
Plac	1	**0.81(0.71,0.92)**	**0.51(0.37,0.72)**	**0.72(0.62,0.84)**	**0.62(0.47,0.81)**	**0.66(0.57,0.77)**	**0.72(0.61,0.86)**
ASA	1.29(0.99,1.68)	1	**0.63(0.45,0.89)**	**0.90(0.83,0.97)**	0.76(0.57,1.01)	**0.82(0.77,0.88)**	0.89(0.80,1.01)
Cilo	0.47(0.16,1.36)	0.36(0.12,1.07)	1	1.41(0.99,2.00)	1.20(0.79,1.84)	1.30(0.92,1.83)	1.41(0.98,2.02)
Clop	0.81(0.55,1.19)	**0.63(0.47,0.83)**	1.74(0.56,5.35)	1	0.85(0.64,1.13)	0.92(0.84,1.01)	1.00(0.92,1.08)
Tic	1.12(0.40,3.14)	0.86(0.32,2.34)	2.40(0.55,10.50)	1.38(0.49,3.86)	1	1.08(0.81,1.44)	1.17(0.87,1.58)
Clop + ASA	1.37(0.96,1.97)	1.06(0.83,1.36)	2.95(0.97,9.02)	**1.70(1.27,2.27)**	1.23(0.44,3.43)	1	1.09(0.96,1.23)
Dip + ASA	1.11(0.73,1.67)	0.86(0.62,1.18)	2.37(0.76,7.38)	**1.37(1.08,1.73)**	0.99(0.35,2.81)	0.80(0.57,1.14)	1

Each cell gives an odds ratio (OR) and 95% confidence interval. In the upper diagonal part, ORs are calculated by comparing column-defining treatments with row-defining treatments, and in the lower diagonal part, ORs are calculated by comparing row-defining treatments with column-defining treatments. Boldfaced indicates statistically significant. To obtain ORs(95%CIs) for comparisons in the opposite direction, reciprocals should be taken. Plac, placebo; ASA, aspirin; Cilo, cilostazol; Clop, clopidogrel; Dip, dipyridamole; Tic, ticlopidine.

hemorrhage compared with clopidogrel (OR = 1.60, 95%CI = 1.21–2.11; OR = 1.70, 95%CI = 1.27–2.27; OR = 1.37, 95%CI = 1.08–1.73). Forest plots showed that most results of network meta-analysis, with a set of more convergent intervals, were consistent with traditional meta-analysis (Appendix S7). As for assessment of publication bias, the comparison-adjusted funnel plots showed symmetry, indicating that there was no publication bias in any outcome (Appendix S8).

We ranked involved treatments according to the SUCRAs in concern of each outcome. For the outcomes of fatal stroke and vascular death, all comparisons between the involved treatments showed no statistical significance. Therefore, each treatment was treated as of the same rank and these two outcomes were excluded from weighting. Since cilostazol plus aspirin was only estimated in efficacy outcomes, this treatment was not considered in the synthetic evaluation. Scatter plot showed that cilostazol was hierarchically the best, clopidogrel the second. Dipyridamole performed well in safety but poorly in efficacy, whereas two dual therapies, clopidogrel plus aspirin and dipyridamole plus aspirin, performed well in efficacy but poorly in safety. Rankings of probabilities, the cumulative probability plots, and the scatter plot are presented in Appendix S9.

3.4. Heterogeneity and inconsistency assessment

As for heterogeneity, most comparisons showed generally low heterogeneity in traditional meta-analysis with $P > .05$ (Appendix S10). Whole network heterogeneity existed in stroke recurrence ($P = .04 < 0.05$). Therefore, within designs heterogeneity (heterogeneity among included studies under a comparison) and between designs heterogeneity (heterogeneity among different comparisons) were assessed respectively. Only between designs heterogeneity was found ($P = .006 < 0.05$). We then divided between designs heterogeneity by each comparison and removed one comparison each time, *P* value changed substantially from 0.006 to 0.22 only when dipyridamole plus aspirin vs aspirin comparison was removed, indicating that the heterogeneity in stroke recurrence might come from dipyridamole plus aspirin vs aspirin. Meanwhile, Q value showed that the heterogeneity in dipyridamole plus aspirin vs aspirin was much higher than any other comparisons. Net heat plot further confirmed the above results as well. Besides, within designs heterogeneity was found in any bleeding ($P = .027 < 0.05$), although whole network heterogeneity didn't exist ($P = .12 > 0.05$). We thus divided within designs heterogeneity by each comparison, only to find that the heterogeneity in any bleeding might come from clopidogrel plus aspirin vs aspirin ($P = .014 < 0.05$). No heterogeneity of whole network, within designs, and between designs was found in the remaining outcomes (Appendix S11).

Global inconsistency was only found in a few comparisons ($P < .05$) in stroke recurrence, while all comparisons with consistency were found in the remaining outcomes. As for local inconsistency, only one closed loop with inconsistency was found in stroke recurrence, while all closed loops with consistency were found in the remaining outcomes (Appendix S12).

3.5. Sensitivity analysis

Sensitivity analysis was performed in the following ways: 1) Excluded trials on immediate-release dipyridamole; 2) Excluded trials on patients with lacunar stroke or transient ischemic attack; 3) Excluded trials on treatment duration less than three months; 4) Excluded trials on follow-up duration less than three months. There were no substantial difference between sensitivity analysis and network meta-analysis, suggesting that the results of network meta-analysis were robust. The differences between immediate-release/extended-release dipyridamole, treatment duration, follow-up duration, and the severity of stroke had no significant effect on the results of network meta-analysis (Appendix S13). In addition, heterogeneity of dipyridamole plus aspirin vs aspirin still existed after the removal of immediate-release dipyridamole, indicating that the different dosage forms of dipyridamole were not the source of heterogeneity (Appendix S13).

4. Discussion

This research is the first one whose topic was obtained by the visual analysis, which guaranteed the research value and activeness. To the best of our knowledge, this study is currently the most comprehensive evaluation on antiplatelet therapies for secondary prevention of ischemic stroke or TIA, where eight mono- or dual antiplatelet therapies, including 14 outcomes, were evaluated upon their relative efficacy and safety by network meta-analysis, and a recommended hierarchy was generated by the weighted regression. Above all, all the aspects, from the selection of this research topic by visual analysis, to the data analysis on therapies by network meta-analysis, were quantified to ensure the preciseness of this study. Findings of this work can be summarized as follows: cilostazol was the optimum treatment for secondary prevention of ischemic stroke or TIA, and clopidogrel ranked second. Both of them reduced stroke recurrence similarly compared with aspirin or dipyridamole, and reduced composite events compared with aspirin. Clopidogrel reduced intracranial hemorrhage compared with aspirin. By contrast, dipyridamole, which performed poorly in efficacy, and two dual therapies clopidogrel plus aspirin and dipyridamole plus aspirin, which performed poorly in safety, were excluded from recommendation.

Cilostazol ranked first in reducing risk of stroke recurrence, composite events, vascular death, intracranial hemorrhage and major bleeding, and ranked relatively high in the remaining outcomes, suggesting its good performance in both efficacy and safety. Platelet adhesion, aggregation and activation have been proved as the core of stroke incidence [13]. As a high-selectivity phosphodiesterase-3 (PDE-3) inhibitor, cilostazol achieves a crucial balance between antithrombotic effect and bleeding risk, which making it unique among all antiplatelet drugs. We believe its superior efficacy is not only attributed to the antiplatelet aggregation effect, but also associates with its multitarget mechanisms [14], including increasing the endogenous vasodilatation factor nitric oxide [15], decreasing intracellular calcium concentration [15], inhibiting the release of inflammatory factors and the proliferation of smooth muscle cells [15,16]. Moreover, the effect of protecting the vessel endothelium, as well as the mechanism of reversibly inhibiting platelets, possibly makes a relatively short platelet function recovery time and a low bleeding risk [16]. Therefore, cilostazol is probably a promising option for secondary prevention of ischemic stroke or TIA.

We didn't assess other safety outcomes except for bleeding owing to the lack of descriptions though we did our best to include high-quality studies. A related high-level trial reported that though some adverse events, such as headache and palpitations which may be induced by vasodilatation, exhibited higher incidence in patients treated with cilostazol than aspirin, no serious adverse events occurred. Furthermore, the adverse symptoms could be resolved when cilostazol dose was reduced to 50 mg (clinical recommended dose 50-100 mg bid). A low beginning dose was suggested to patients who could not tolerate these adverse events [17].

Clopidogrel was the second recommended treatment and recommended with a superior effect than ticlopidine in our findings. It can solve the problem of hematologic toxicity and thus gradually replace ticlopidine as a more effective adenosine diphosphate (ADP) receptor inhibitor [18]. Clopidogrel was superior to aspirin as well. A possible interpretation is that aspirin prevents platelet activation by blocking the only pathway of thromboxane A2 (TXA2) which has little effect on activated platelets [19], while clopidogrel blocks two pathways as the ADP and the one independent of TXA2 and ADP [18]. Therefore, clopidogrel is more effective in preventing vascular events

and suitable for high-risk patients [20].

It should be noted that though aspirin and clopidogrel are of major clinical application, relevant literatures pointed out that the resistance to these two drugs ranged from 5% to 45% and 4% to 30%, respectively [21]. Meanwhile, gastrointestinal reactions and bleeding events were reported in some patients. Moreover, Antiplatelet Trialists' Collaboration (ATC) provided that aspirin could only prevent 20% of ischemic events and was not sufficient for high-risk patients [22]. Owing to these patient-specific factors, searching for other antiplatelet agents or combination therapies is of great clinical value [23]. Findings of this work showed that cilostazol was superior to aspirin in both efficacy and safety, and significantly reduced risk of any bleeding compared with clopidogrel. Moreover, resistance to cilostazol has not been reported. Therefore, cilostazol might be a quite potential treatment. Our study also suggested that the two dual antiplatelet therapies, clopidogrel plus aspirin and dipyridamole plus aspirin, exhibited high risk of bleeding. Considering that cilostazol is an antiplatelet drug with low bleeding risk, its combination therapy might also be potential and deserve further exploration.

Since some of the included studies involved just Asian population, we did a further analysis by removing these studies, and found the recommended hierarchy was consistent with network analysis except that cilostazol was excluded (Appendix S14). Further research on cilostazol in other populations is required to reach a robust estimate in the future. In addition, the minimal differences between cilostazol and clopidogrel compared with aspirin should be taken with cautions on one hands factoring also the affordability and availability of the medication after stroke on the other hands.

Potential limitations deserve to be considered when the results of this work are interpreted. First, treatment duration and aspirin dosages varied among included studies, which may weaken the robustness of the results to some extent though sensitivity analysis suggested the results were robust and related research reported no substantial difference among different aspirin dosages [24]. Second, severity of stroke varied among included studies, which may weaken the robustness of the results to some extent though sensitivity analysis suggested the results were robust. Third, evidence of some comparisons was still limited though we did our best to include high-quality studies. Evidence of cilostazol plus aspirin was only based on one trial, which led to a wide confidence interval and an imprecise result. A large number of clinical trial data are required to reach a robust estimate in the future. Besides, owing to the lack of descriptions on some adverse events, such as headache, palpitations and hematologic toxicity, we didn't assess these outcomes and the safety was somewhat overestimated. Finally, the deficiency of the probability rankings could not be ignored. Though the SUCRA rating method has been widely accepted, it could not substitute for the presentation of results by the effect sizes and confidence intervals. The interpretation of the SUCRA rankings could not be separated from the results of network meta-analysis.

5. Conclusion

This systematic review provided that cilostazol and clopidogrel are probably promising options for secondary prevention of ischemic stroke or TIA in clinical practice. Both of them reduced stroke recurrence similarly compared with aspirin or dipyridamole, and reduced composite events compared with aspirin. Dipyridamole performed well in safety but poorly in efficacy, whereas two dual therapies, clopidogrel plus aspirin and dipyridamole plus aspirin, performed well in efficacy but poorly in safety. Though statistical methods used in this study have been widely accepted, they could not substitute for large-scale clinical trials. Future work is suggested to focus on prospective trials with large sample, multi-center and wide coverage to provide more sufficient evidence for secondary prevention of ischemic stroke or TIA. In general, our findings, when clinically important benefits of different antiplatelet therapies are balanced, are expected to help clinicians and patients to make evidence-based decisions that correlate with their values, preferences and the tolerance of risks of harm and benefits. However, further studies are needed to confirm this finding.

Declarations of interest

None.

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Data statement

Study protocol: PROSPERO registration number CRD42017069728.

Statistical code and data set: available from Prof Xiang (e-mail: xrwlove@163.com).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.02.037.

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