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RESEARCH

Antiplatelet therapy for secondary prevention of lacunar stroke: a systematic review and network meta-analysis

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Abstract

Purpose To comprehensively compare the efficacy of different antiplatelet therapies for secondary prevention of lacunar stroke (LS).

Methods The relevant studies were identified by searching PubMed, EMBASE, Web of Science, and Cochrane Collaboration Database up to May 2022. Cardiovascular and cerebrovascular events were chosen to evaluate the efficacy of antiplatelet therapy for secondary prevention. Loop-specific approach and node-splitting analysis were used to evaluate consistency and inconsistency, respectively. The value of the surface under the cumulative ranking (SUCRA) was calculated and ranked. Funnel-plot symmetry was used to evaluate publication bias. The meta-analysis was performed by using STATA 16.0.

Results Thirteen studies with a total of 33,011 subjects were included in this network meta-analysis. Compared with placebo, aspirin, clopidogrel, cilostazol, ticlopidine, aspirin plus dipyridamole, and aspirin plus clopidogrel were associated with reducing cardiovascular and cerebrovascular events. The SUCRA estimated relative ranking of treatments showed that cilostazol may be the most effective (*RR* 0.56, 95% *CI* 0.42–0.74, *SUCRA* 95.8). No significant inconsistency or publication bias was found in the study.

Conclusions This meta-analysis suggests that cilostazol may be a priority option for secondary prevention of patients with LS. These findings still need further study in the future.

Keywords Antiplatelet therapy · Lacunar stroke · Secondary prevention · Meta-analysis

Introduction

Lacunar stroke (LS) is characterized by the ability to occlude the lumen of deep penetrating arteries, forming small lumens of 2 to 15 mm in the deep gray, subcortical white matte, and brainstem. LS is considered the most common type of cerebral small vessel disease, accounting for 25% of acute ischaemic stroke [1, 2]. The recurrence rate of LS over 3 years is about 20% [3]. A recent cohort study has shown that recurrent stroke, myocardial infarction, and all-cause mortality in patients with LS are similar to other ischaemic stroke types [4]. Therefore, physicians and patients should be as alert to secondary prevention of LS as other stroke types.

Antiplatelet therapy is one of the most common options for secondary prevention of patients with ischaemic stroke, including LS [5]. Researchers in the Accidents Ischemiques Cerebraux Lies a l' Atherosclerose (AICLA) trial reported that in patients with LS, the risk of recurrent stroke was significantly reduced in aspirin monotherapy group and clopidogrel plus aspirin group compared with placebo group [6]. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial reported that clopidogrel plus aspirin did not significantly reduce the risk of recurrent stroke in patients with LS, but significantly increased the risk of bleeding and death compared with aspirin monotherapy [7]. Therefore, clopidogrel plus aspirin was not recommended for patients with LS unless there were specific indications. The European Stroke Prevention Study-2 (ESPS-2) showed that dipyridamole plus aspirin had a lower risk of stroke recurrence than either agent alone [8]. Furthermore, the second Cilostazol Stroke Prevention Study (CSPS 2) reported that cilostazol may be superior to aspirin for stroke prevention of patients with LS [9].

Although studies have investigated the efficacy of antiplatelet therapy for secondary prevention of patients with LS, it is difficult to compare the efficacy of different

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antiplatelet therapies in one study at the same time. More importantly, it is not clear which antiplatelet therapy is the most suitable for secondary prevention of patients with LS. Therefore, a network meta-analysis was conducted in this study to simultaneously synthesize direct or indirect evidence from individual pairwise studies.

Methods

The study was performed in accordance with the guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10].

Search strategy

Relevant studies were identified by searching databases up to May 2022, including PubMed, EMBASE, Web of Science, and Cochrane Collaboration Database. The following terms were used during the searching: (lacunar stroke OR LS OR lacunar infarct OR lacune OR cerebral small vessel disease OR SVD) AND (antiplatelet OR aspirin OR clopidogrel OR dipyridamole OR ticlopidine OR cilostazol). No language or other restrictions were used. Meanwhile, the references used in the eligible articles were carefully reviewed to identify potential studies.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) the study should be a clinical trial; (2) all patients or subpopulation of the study had been diagnosed with LS; (3) eligible patients had received antiplatelet therapy given at any dosage or placebo or blank control; (4) the study should provide the efficacy of secondary prevention for each group, respectively. Cardiovascular and cerebrovascular events were chosen to evaluate the efficacy of antiplatelet therapy for secondary prevention, including stroke recurrence, myocardial infarction, vascular death, and other vascular events. Studies were excluded when they were (1) reviews, letters, case reports, protocols, or animal studies; (2) duplicate publications of data from the same study; and (3) the study providing insufficient information to conduct the meta-analysis.

Data extraction

Information was extracted independently by two experienced investigators and discrepancy was resolved by the third investigator. The authors whose studies did not provide adequate information should be contacted. The following data were collected: first author's name, publication year, age, male ratio, follow-up time, antiplatelet drug type, and number of cardiovascular and cerebrovascular events in each group.

Quality assessment

Because most of the included studies were randomized controlled trials (RCTs), the Cochrane's quality evaluation assessment scale for RCTs was utilized to assess the quality of studies [11]. All studies were evaluated by two researchers and disagreement was resolved by consulting the third author. The assessment scale included sequence generation, allocation concealment, blinding, incomplete outcome data, non-selective outcome report, and other sources of bias. The study with best quality can be scored six points. A study was considered of high quality if it scored ≥ 4.

Statistical analysis

The pooled estimation of included studies was conducted based on the Frequentist theorem. Relative risk (RR) with 95% confidence interval (CI) were presented in the results for each possible network comparison. Consistency was evaluated by comparing direct and indirect treatment effects in all closed loops. Loop-specific approach was used for loop-specific heterogeneity examination [12, 13]. To evaluate inconsistency of antiplatelet therapy in the network, node-splitting analysis was used [14, 15]. The value of the surface under the cumulative ranking (SUCRA) was used to represent the ranking of the efficacy of each antiplatelet therapy [16]. Funnel-plot symmetry was used to evaluate publication bias. A value of $P < 0.05$ indicated that there was significant publication bias. The network meta-analysis for each result was performed using the network package in STATA software (version 16.0).

Results

Study and data included in the meta-analysis

The process of study selection is shown in Fig. 1. According to our searching strategy, thirteen trials involving a total of 33,011 participants were included. The efficacy between placebo, blank control, and 7 antiplatelet therapies, including aspirin, clopidogrel, cilostazol, ticlopidine, dipyridamole, aspirin plus dipyridamole, and aspirin plus clopidogrel, was compared. The characteristics of the included studies are shown in Table 1. No study was excluded on grounds of quality.

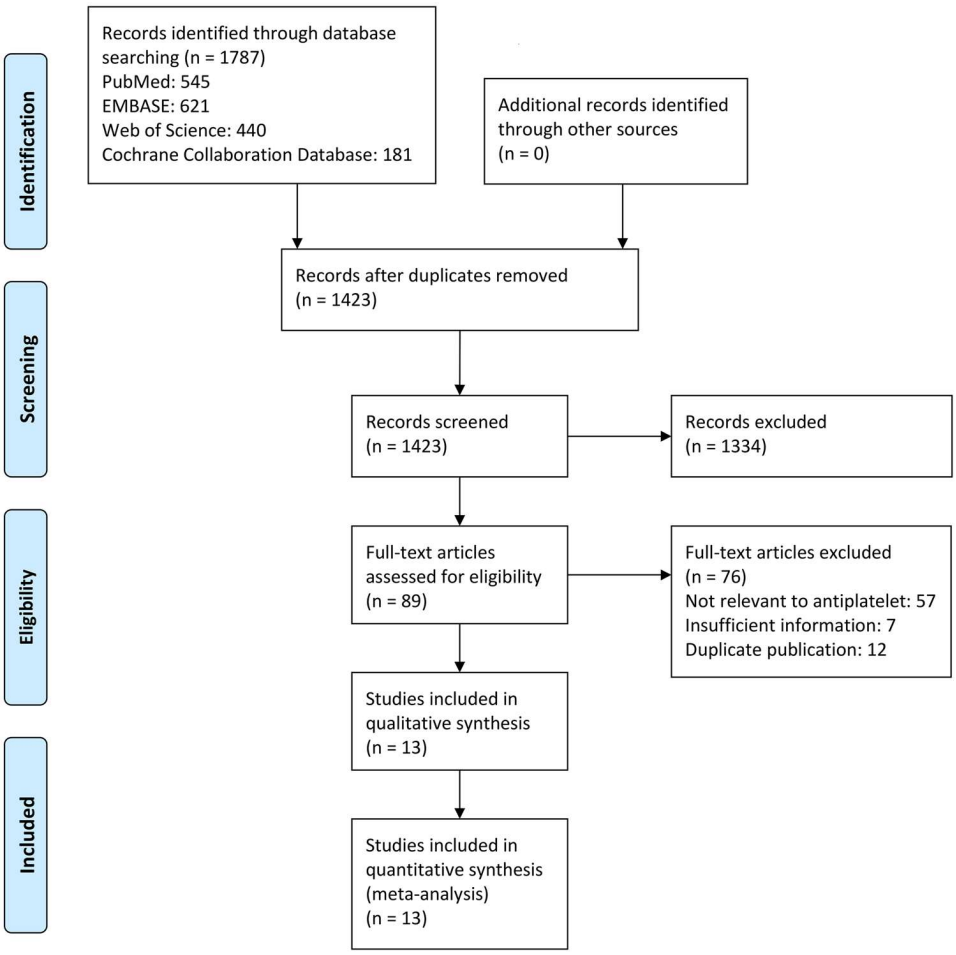

Fig. 1 Flow diagram of the process of selecting studies

Inconsistency evaluation

The loop-specific approach showed no significant heterogeneity existed between closed loops (Table 2). Furthermore, statistical inconsistency was not found by side-splitting analysis (Table 3).

Efficacy of antiplatelet therapy for secondary prevention

The network plots for comparing efficacy of antiplatelet therapy for secondary prevention are shown in Fig. 2. Compared with placebo, aspirin (*RR*: 0.83, 95% *CI*: 0.70–0.98), clopidogrel (*RR*: 0.72, 95% *CI*: 0.58–0.89), cilostazol (*RR*: 0.56, 95% *CI*: 0.42–0.74), ticlopidine (*RR*: 0.71, 95% *CI*: 0.51–0.98), aspirin plus dipyridamole (*RR*: 0.69, 95% *CI*: 0.57–0.84), aspirin plus clopidogrel (*RR*: 0.71, 95% *CI*: 0.57–0.89) were associated with reducing cardiovascular and cerebrovascular events (Fig. 3). Furthermore, cilostazol had the highest SUCRA value (95.8) and the highest probability of being ranked the best (81.0%) on the prevention of cardiovascular and cerebrovascular events (Table 4 and Fig. 4).

Publication bias

Funnel plots were performed to evaluate publication bias. The shape of funnel plots did not show any strong evidence of asymmetry (Fig. 5). Therefore, no significant publication bias was found in the network meta-analysis.

Discussion

Although the use of antiplatelet therapy for secondary prevention of patients with LS has been evaluated by review and meta-analysis [28, 29], the present study is the first network meta-analysis to evaluate the efficacy of different antiplatelet therapies at the same time in patients with LS. In this study, thirteen trials were included with a total of 33,011 subjects. The results indicated that cilostazol may be the most effective antiplatelet drug to reduce cardiovascular and cerebrovascular events.

The pathophysiology of LS may mainly involve two main methods of pathogenesis: endothelial dysfunction and blood–brain-barrier (BBB) disruption [30]. Endothelium is

Table 1 Characteristics of all studies included in the meta-analysis

First author, published year	Mean/ median age (years)	Male ratio (%)	Follow-up time (years)	Study comparison	Cardiovascular and cerebrovascular events (n/total)	RCT	Quality scores
Kong, 2019 [17]	61	63	4.1	Aspirin alone (100 mg/d) vs. blank control	(68/342) vs. (57/202)	No	4
SPS3 investigators, 2012 [7]	63	63	3.4	Aspirin (325 mg/d) vs. aspirin (325 mg/d) plus clopidogrel (75 mg/d)	(174/1503) vs. (153/1517)	Yes	5
Shinohara, 2010 [9]	63	72	2.4	Aspirin alone (81 mg/d) vs. cilostazol alone (200 mg/d)	(85/874) vs. (59/869)	Yes	5
Uchiyama, 2009 [18]	65	71	1.0	Ticlopidine alone (200 mg/d) vs. clopidogrel alone (75 mg/d)	(22/664) vs. (19/677)	Yes	5
Sacco, 2008 [19]	66	64	2.5	Aspirin (50 mg/d) plus dipyridamole (400 mg/d) vs. clopidogrel (75 mg/d)	(418/5292) vs. (437/5286)	Yes	5
Ariesen, 2006 [20]	66	61	1.7	Aspirin alone (50 mg/d) vs. dipyridamole alone (400 mg/d) vs. aspirin (50 mg/d) plus dipyridamole (400 mg/d) vs. placebo	(101/609) vs. (108/651) vs. (82/659) vs. (128/681)	Yes	5
ESPRIT Study Group, 2006 [21]	63	65	3.5	Aspirin alone (30–325 mg/d) vs. aspirin (30–325 mg/d) plus dipyridamole (400 mg/d)	(106/690) vs. (96/687)	Yes	5
Matsumoto, 2005 [22]	65	66	2.0	Cilostazol alone (200 mg/d) vs. placebo	(24/400) vs. (46/394)	Yes	5
Diener, 2004 [23]	66	63	1.5	Aspirin (75 mg/d) plus clopidogrel (75 mg/g) vs. clopidogrel (75 mg/d)	(160/1590) vs. (161/1558)	Yes	5
Gorelick, 2003 [24]	61	47	2.0	Aspirin alone (650 mg/d) vs. ticlopidine alone (500 mg/d)	(40/621) vs. (38/600)	Yes	5
CAST Collaborative Group, 1997 [25]	63	63	0.1	Aspirin alone (160 mg/d) vs. placebo	(78/3117) vs. (88/3146)	Yes	5
Weisberg, 1995 [26]	59	69	1.0	Aspirin alone (80–1300 mg/d) vs. ticlopidine alone (500 mg/d) vs. blank control	(13/73) vs. (1/25) vs. (4/10)	No	4
Gent, 1989 [27]	65	62	2.0	Ticlopidine alone (500 mg/d) vs. placebo	(14/137) vs. (27/137)	Yes	5

RCT randomized controlled trial

essential for fibrinolysis/coagulation, inflammation, regulation of vessel tone, and angiogenesis. Endothelial dysfunction may lead to impaired autoregulation, procoagulant, proinflammation, and proliferation, which is related to thrombosis and vascular occlusion [31]. Disruption of BBB is also crucial in the vascular pathology of LS. A proposed cause of degradation of the BBB is high arterial pressure. This leads to local edema and plasma protein deposition in the vascular wall, deteriorating the structure of vascular wall and damaging smooth muscle cells, which is closely related to LS [32]. At present, the effect of platelet aggregation on LS formation is still unclear. Lavallée et al. found that there was no significant difference in the markers of platelet activation (activated glycoprotein IIb/IIIa, P-selectin, and platelet microparticles) between LS patients and healthy controls [33].

Based on the results of this study, we considered cilostazol as a priority choice of antiplatelet drugs for secondary prevention of patients with LS. This may be related to the multiple pharmacological effects of cilostazol. On one hand,

Table 2 Consistency tests based on loop-specific approach

Loop	IF	95% *CI*	*P*	Loop-specific heterogeneity (r^2)
B–E–G	1.89	(0.00, 4.02)	0.082	<0.001
A–C–E–H	0.46	(0.00, 1.35)	0.320	<0.001
A–B–E	0.45	(0.00, 1.22)	0.247	0.001
A–B–H	0.20	(0.00, 0.60)	0.604	<0.001
B–F–H	0.19	(0.00, 0.64)	0.395	<0.001
A–B–D	0.19	(0.00, 0.79)	0.543	<0.001
B–C–E–I	0.14	(0.00, 0.93)	0.733	<0.001
B–C–E–H	0.13	(0.00, 1.15)	0.804	0.019
B–C–H–I	0.03	(0.00, 0.40)	0.878	<0.001
A–B–F	0.01	(0.00, 0.47)	0.952	<0.001

A placebo, *B* aspirin, *C* clopidogrel, *D* cilostazol, *E* ticlopidine, *F* dipyridamole, *G* blank control, *H* aspirin + dipyridamole, *I* aspirin + clopidogel

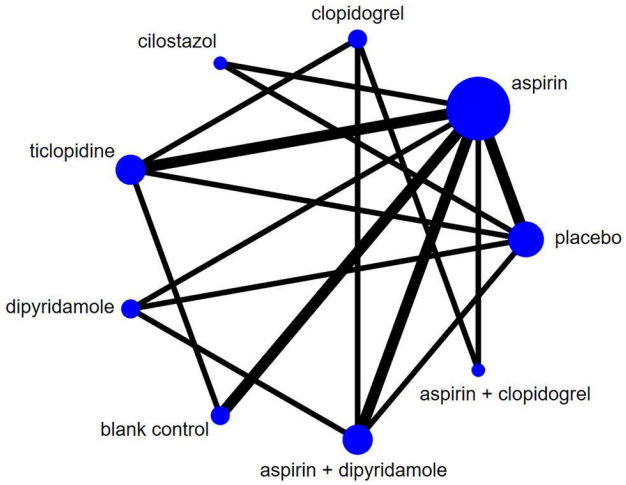

Fig. 2 Network plots of antiplatelet therapy for secondary prevention of lacunar stroke (network diagrams showing how antiplatelet drugs were compared in trials with respect to number of studies and sample sizes. The width of the lines is proportional to the number of trials directly comparing every pair of treatments, and the size of every node is proportional to the sample size)

cilostazol is a phosphodiesterase inhibitor, which can protect cyclic adenosine from degradation and thus inhibit thrombosis. In addition, cilostazol can also inhibit the proliferation of vascular smooth muscle, protect vascular wall and endothelium, scavenge free radicals, inhibit the release of inflammatory factors, and reduce cell apoptosis [34]. Since the effect of cilostazol is closely related to the mechanism of LS, it is plausible that cilostazol shows better effect than other antiplatelet drugs for the secondary prevention of LS. Other antiplatelet drugs act through a series of mechanisms, including platelet inhibition of thromboxane A2 production, inhibition of cyclic adenosine 3′, 5′-monophosphate production, and inhibition of P2Y12 receptors, thereby irreversibly inhibiting platelet aggregation [35, 36]. Although other antiplatelet drugs may also help prevent stroke recurrence, there is insufficient evidence that they can directly affect the mechanism of LS. This may be the reason why they are not as effective as cilostazol.

In this study, there was no significant difference in the efficacy between mono and dual antiplatelet therapy, which was consistent with the results of some large sample studies. The SPS3 trial reported that the efficacy of aspirin plus clopidogrel in the treatment of LS patients was similar to that of aspirin monotherapy, while dual antiplatelet therapy was associated with increased bleeding and mortality [7]. The CSPS 2 trial also showed that dual antiplatelet therapy was associated with higher hemorrhage and mortality rates than mono antiplatelet therapy [9]. The recent Acute Aspirin Plus Cilostazol Dual Therapy for Non-Cardiogenic Stroke Patients Within 48 Hours of Symptom Onset (ADS) trial reported that although the dual antiplatelet therapy using cilostazol plus aspirin was safe, it did not reduce the incidence of short-term neurological deterioration [37]. Therefore, dual antiplatelet therapy may be not superior to mono antiplatelet therapy for secondary prevention of patients with LS.

Table 3 Inconsistency tests based on side-splitting approach

Side	Coefficient			*P*
	Direct	Indirect	Difference	
A-B*	−0.12	−0.43	0.31	0.135
A-D	−0.67	−0.54	−0.13	0.669
A-E	−0.66	−0.22	−0.44	0.224
A-F*	−0.12	−0.21	0.09	0.796
A-H*	−0.40	−0.33	−0.07	0.742
B-D	−0.36	−0.49	0.13	0.669
B-E	−0.05	−0.28	0.23	0.436
B-F*	0.00	0.24	−0.24	0.384
B-G*	0.40	3.39	−2.99	0.141
B-H*	−0.19	−0.18	−0.01	0.970
B-I	−0.14	−0.18	0.05	0.803
C-E	0.17	−0.09	0.25	0.487
C-H	−0.05	−0.03	−0.02	0.923
C-I	−0.03	0.02	−0.05	0.803
E–G	1.78	0.47	1.31	0.116
F–H*	−0.29	−0.04	−0.25	0.441

A placebo, *B* aspirin, *C* clopidogrel, *D* cilostazol, *E* ticlopidine, *F* dipyridamole, *G* blank control, *H* aspirin + dipyridamole, *I* aspirin + clopidogel

*All the evidence about these contrasts comes from the trials which directly compare them

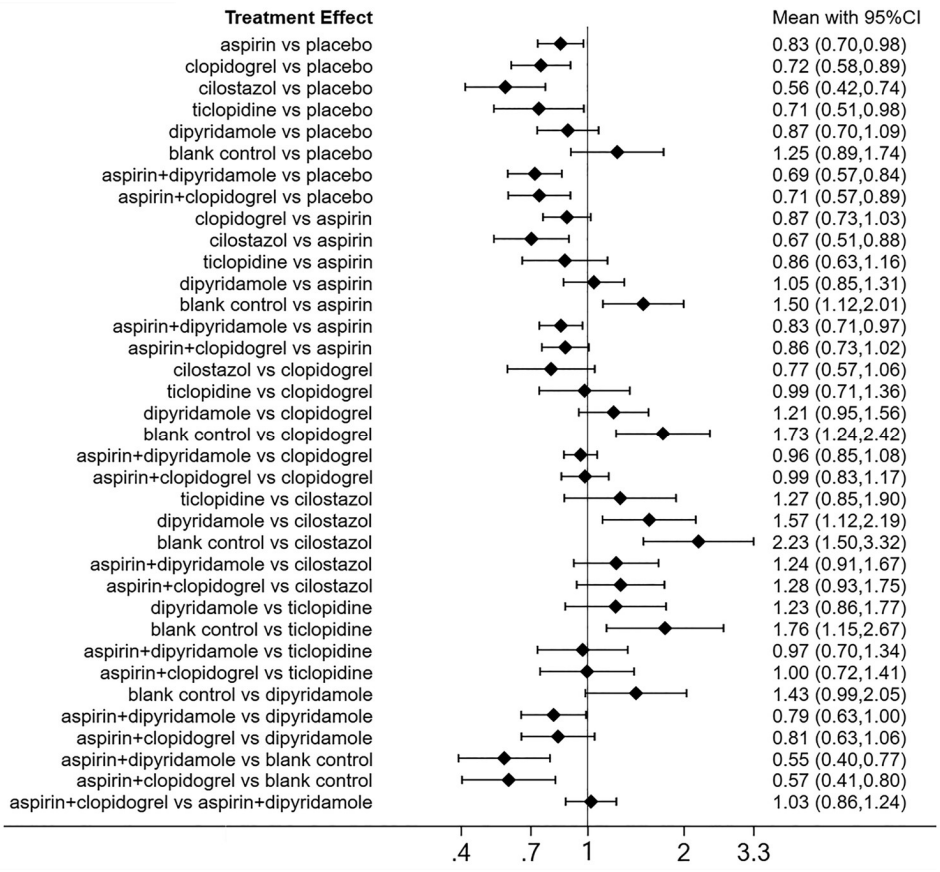

Fig. 3 Forest plot of antiplatelet therapy for secondary prevention of lacunar stroke (each horizontal line represents the 95% *CI* for estimating the result of two antiplatelet therapies (therapy A vs. therapy B) on secondary prevention. When the horizontal line crosses the vertical line through 1, it indicates that no statistically significant difference between the two therapies. When the upper and lower limits of 95% *CI* are < 1, it indicates that patients receiving therapy A have a lower incidence of cardiovascular and cerebrovascular events than receiving therapy B. When the upper and lower limits of 95% *CI* are > 1, it indicates that patients receiving therapy A have a higher incidence of cardiovascular and cerebrovascular events than therapy B)

Table 4 SUCRA of the antiplatelet therapies

Rank	Treatments	SUCRA	PrBest (%)
1	Cilostazol	95.8	81.0
2	Aspirin + dipyridamole	75.2	4.3
3	Aspirin + clopidogrel	67.3	3.0
4	Ticlopidine	66.2	10.6
5	Clopidogrel	63.4	1.0
6	Aspirin	36.6	0.0
7	Dipyridamole	30.6	0.0
8	Placebo	13.1	0.0
9	Blank control	1.7	0.0

SUCRA surface under the cumulative ranking, *PrBest* probability of being ranked the best

Some limitations of the study should be pointed out. First, insufficient data from the eligible studies hinders the efficacy evaluation of specific events, such as stroke recurrence and myocardial infarction. Second, all studies on cilostazol were conducted in Asian countries, so it is not clear whether the findings apply to other populations. Third, the sample size of the meta-analysis is still relatively small, so more large sample studies are needed in the future. Despite the limitations, the study is robust because most of the studies included in the network meta-analysis are RCTs, which are the most ideal type of evidence. In addition, the publication bias outcomes reflect that our results are statistically stable and reliable.

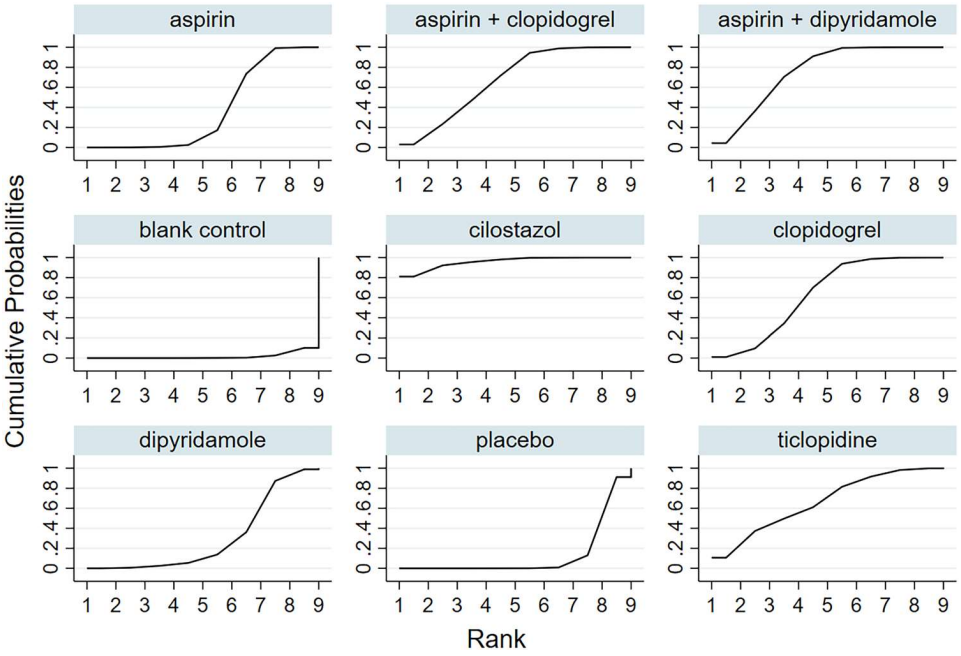

Fig. 4 Values of the surface under the cumulative ranking (SUCRA) of the efficacy of antiplatelet therapy on secondary prevention in lacunar stroke

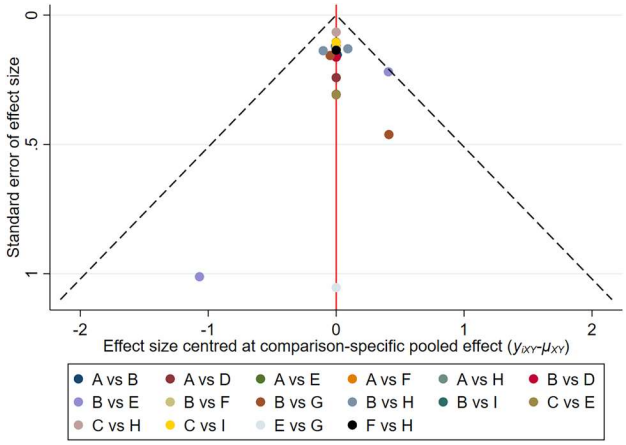

Fig. 5 Funnel plots of publication bias (A, placebo; B, aspirin; C, clopidogrel; D, cilostazol; E, ticlopidine; F, dipyridamole; G, blank control; H, aspirin + dipyridamole; and I, aspirin + clopidogrel)

Conclusions

The network meta-analysis shows that cilostazol may be a priority choice for secondary prevention of patients with LS, which deserves further research in the future. The findings provide important evidence for antiplatelet therapy for secondary prevention of patients with LS.

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Author contribution XW Hou designed the study and wrote the paper. KW Cen, Y Cui, and YH Zhang screened the literatures and extracted the data. X Feng analyzed the data.

Availability of data and materials The data that support the findings of the study are available from the corresponding author on reasonable request.

Declarations

Ethical approval Our study is a systematic review and network meta-analysis, which does not involve ethical approval.

Consent to participate Our study is a systematic review and network meta-analysis, which does not require informed consent.

Consent for publication There are no individual's data or image in our study.

Competing interests The authors declare no competing interests.

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