ORIGINAL RESEARCH

Long-Term Antiplatelet Mono- and Dual Therapies After Ischemic Stroke or Transient Ischemic Attack: Network Meta-Analysis

Wuxiang Xie, MD, PhD*; Fanfan Zheng, MD, PhD*; Baoliang Zhong, MD, PhD; Xiaoyu Song, MD, MPH

***Background*—**The latest guidelines do not make clear recommendations on the selection of antiplatelet therapies for long-term secondary prevention of stroke. We aimed to integrate the available evidence to create hierarchies of the comparative efficacy and safety of long-term antiplatelet therapies after ischemic stroke or transient ischemic attack.

***Methods and Results*—**We performed a network meta-analysis of randomized controlled trials to compare 11 antiplatelet therapies in patients with ischemic stroke or transient ischemic attack. In December 2014, we searched Medline, Embase, and the Cochrane Library database for trials. The search identified 24 randomized controlled trials including a total of 85 667 patients with antiplatelet treatments for at least 1 year. Cilostazol significantly reduced stroke recurrence in comparison with aspirin (odds ratio 0.66, 95% credible interval 0.44 to 0.92) and dipyridamole (odds ratio 0.57, 95% credible interval 0.34 to 0.95), respectively. Cilostazol also significantly reduced intracranial hemorrhage compared with aspirin, clopidogrel, terutroban, ticlopidine, aspirin plus clopidogrel, and aspirin plus dipyridamole. Aspirin plus clopidogrel could not significantly reduce stroke recurrence compared with monotherapies but caused significantly more major bleeding than all monotherapies except terutroban. The pooled estimates did not change materially in the sensitivity analyses of the primary efficacy outcome.

***Conclusions*—**Long-term monotherapy was a better choice than long-term dual therapy, and cilostazol had the best risk–benefit profile for long-term secondary prevention after stroke or transient ischemic attack. More randomized controlled trials in non–East Asian patients are needed to determine whether long-term use of cilostazol is the best option for the prevention of recurrent stroke. **(*J Am Heart Assoc*. 2015;4:e002259 doi: 10.1161/JAHA.115.002259)**

Key Words: antiplatelet • network meta-analysis • stroke • transient ischemic attack

Stroke is the second most common cause of death and the third most common cause of disability worldwide.[1,2] As stroke mortality has decreased over the past 2 decades, the absolute number of stroke survivors has increased and is huge.[3] Given the high recurrence rate, secondary prevention of future stroke among these survivors plays a pivotal role in reducing disease burden.[4] The use of antiplatelet agents is the standard treatment for patients with noncardioembolic ischemic stroke or transient ischemic attack (TIA).[4] A number of randomized controlled trials (RCTs) have tested different antiplatelet mono- and dual therapies in secondary prevention after ischemic stroke or TIA[5–28]; however, comparisons of some antiplatelet therapies are currently lacking.

Several pairwise meta-analyses were performed previously to compare the efficacy of antiplatelet agents for the secondary prevention of stroke.[29–31] These studies, however, could not generate clear hierarchies for the efficacy and safety of all available antiplatelet therapies because many antiplatelet treatments have not been compared head to head and because such analyses could not integrate all of the evidence from several comparators. Using a statistical technique called *network meta-analysis*, we were able to take advantage of both direct (head-to-head) and indirect evidence and formally compare all existing therapies.[32,33]

Two previous network meta-analyses were conducted to compare the efficacy of antiplatelet therapies among stroke or TIA patients[34,35]; however, neither provided hierarchies for the efficacy and safety of antiplatelet therapies. The earlier study compared only a small number of antiplatelet therapies.[34] The

From the Department of Epidemiology, Beijing Anzhen Hospital, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Capital Medical University, Beijing, China (W.X.); Brainnetome Center, Institute of Automation, Chinese Academy of Sciences, Beijing, China (F.Z.); Department of Psychiatry, University of Rochester Medical Center, New York, NY (B.Z.); Department of Biostatistics, Columbia University, New York, NY (X.S.).

Accompanying Tables S1 through S5 and Figures S1 through S8 are available at http://jaha.ahajournals.org/content/4/8/e002259/suppl/DC1

*Dr Xie and Dr Zheng contributed equally to this work.

Correspondence to: Wuxiang Xie, MD, PhD, Department of Epidemiology, Beijing Anzhen Hospital, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Capital Medical University, No. 2 Anzhen Street, Chaoyang District, Beijing, China. E-mail: xiewuxiang@163.com

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later study identified 24 trials published before March 2012[35] but failed to incorporate a few major large-scale trials, such as the SPS3 trial,[24] the JASAP study,[17] and the study published by Fukuuchi et al.[14] In addition, the second network meta-analysis did not restrict the duration of antiplatelet therapy.[35] Because the American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend that patients with ischemic stroke or TIA continuously receive antiplatelet treatment,[4] we believe it is more important to evaluate overall recurrent stroke reduction and bleeding risk of long-term antiplatelet therapies in these patients. To achieve this goal, we performed the network meta-analysis of RCTs to compare the effectiveness and safety of long-term antiplatelet treatments among patients with ischemic stroke or TIA.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[36] Ethics approval was not necessary for this study because only deidentified pooled data from individual studies were analyzed.

Data Sources and Search Strategy

A systematic literature search was conducted December 26, 2014, by searching Medline via Web of Science, Embase and Journals@Ovid Full Text via OvidSP, and the Cochrane Library database for trials. We limited our search to RCTs conducted in humans. Details of our search strategy are provided in Table S1. The search strategy in the current study was similar to those used in previous studies.[37,38]

Study Selection

RCTs were eligible for inclusion if they met the following criteria: Antiplatelet monotherapy versus monotherapy or dual versus monotherapy was tested in adult patients (aged ≥18 years) with ischemic stroke or TIA and had a treatment duration of at least 1 year. Because network meta-analysis requires a reasonably homogeneous sample,[39,40] we did not include those RCTs assessing antiplatelet therapy (mostly aspirin) versus placebo because such studies had a wide range of daily doses (aspirin, from 75 to 1500 mg).[41,42] Another reason is that the evaluation of antiplatelet therapy versus placebo becomes less important.

Initially, titles alone were reviewed for suitability. The abstracts of suitable titles were obtained and reviewed for suitability for full-text retrieval. Data were then extracted from suitable full-text reports. Additional appropriate reports were added when discovered by citation tracking.

Data Extraction and Quality Assessment

Data were independently extracted and assessed by 2 authors (F.Z. and B.Z.) using a predetermined data collection template. To resolve discrepancies about inclusion of studies and interpretation of data, a third investigator (W.X.) was consulted, and consensus was reached by discussion.

The primary efficacy outcome was stroke recurrence, including ischemic, hemorrhagic, and unknown stroke, and fatal and nonfatal stroke. The secondary efficacy outcome was the composite outcome of vascular events and all-cause or vascular mortality. The safety outcomes were intracranial hemorrhage and major bleeding. The definitions of the 4 outcomes in included trials are summarized in Table S2.

Study quality was independently assessed by 3 reviewers (F.Z., B.Z., and X.S.) who used the Cochrane Collaboration's risk-of-bias method.[43] Figure S1 shows the risk of bias of the included trials.

Data Synthesis and Analysis

Network meta-analysis combines direct and indirect evidence for all relative treatment effects and provides estimates with maximum statistical power.[44–47] We fit the models within a Bayesian framework using WinBUGS software (version 1.4.3).[48] The models, the WinBUGS codes, and R routines used in this study were open and could be found online.[49] Convergence was assessed by running 3 Markov chains, and all results pertain to 100 000 Markov chain Monte Carlo cycles after a 10 000-simulation burn-in phase. Relative effect sizes were calculated as odds ratios (ORs) with corresponding 95% credible intervals. We assessed the fitness of our model using the deviance information criterion, a measure of model fitness that penalizes model complexity. If the tradeoff between model fitness and complexity favored the model with assumed consistency, this model was preferred (smaller deviance information criterion values correspond to more preferable values).[50] As shown in Table S3, the assumption of consistency was supported for each outcome by a better tradeoff between model fitness and complexity (a smaller deviance information criterion value) when consistency was assumed rather than when it was not. We used the surface under the cumulative ranking curve, or SUCRA, probabilities to rank the antiplatelet therapies:[47,51] SUCRA is a proportion expressed as the percentage of efficacy of an intervention on the outcome that would be ranked first without uncertainty, which equals 100% when the treatment is certain to be the best and 0% when it is certain to be the worst.[47] The network results were assessed for consistency by comparing them with the results of pairwise meta-analyses. Furthermore, we estimated inconsistency as

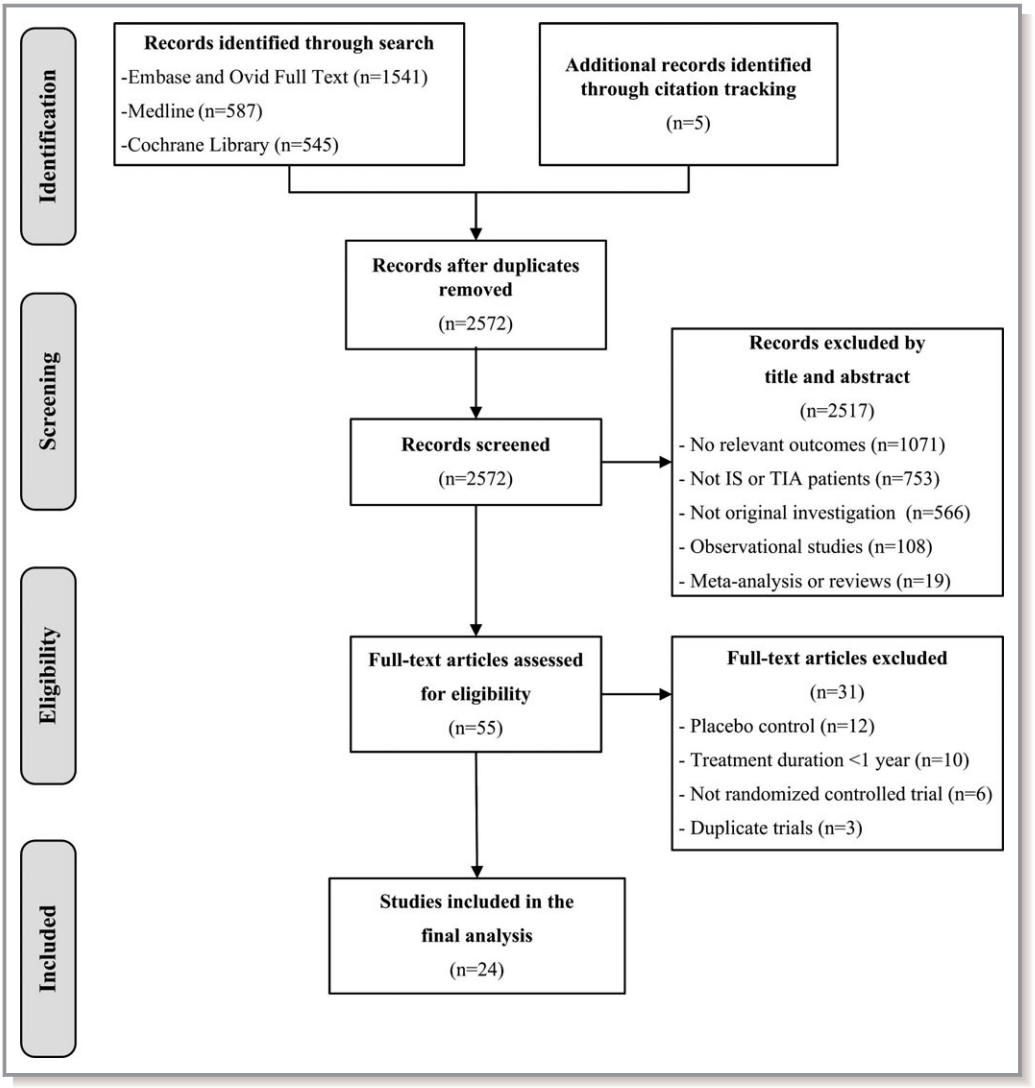

Figure 1. Study selection flow diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. IS indicates ischemic stroke; TIA, transient ischemic attack.

the difference between direct and indirect estimates (called the *inconsistency factor*) and the corresponding 95% confidence interval (CI) for inconsistency factor in each closed loop by using the R code *ifplot.fun*, which could be found online.[52] Inconsistent loops are those that present inconsistency factors with 95% CIs incompatible with zero. Pairwise meta-analyses were performed by using STATA (version 11; Stata Corp) within a random-effects framework that takes study heterogeneity into account to generate the pooled OR and 95% CI. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic.

We did sensitivity analyses on the primary efficacy outcome to explore whether the results of the present network meta-analysis were sensitive to certain restrictions on the data included. Those planned in advance were restricted to double-blind trials (n=18) and true randomization and allocation-concealed trials (n=16).

Results

Study Selection and Characteristics

Figure 1 shows the study selection process according to the PRISMA statement. The initial search and citation tracking identified 2678 publications. Fifty-five articles were reviewed by full text for details, and 31 of those were excluded. Finally, a total of 24 RCTs with 85 667 patients were included in the present network meta-analysis.[5–28] Tables 1 and 2 summarize the characteristics of the 24 included trials. The following antiplatelet therapies were tested in the trials: cilostazol versus aspirin (3 trials with 3459 patients),[9,11,15] clopidogrel versus

Table 1. Baseline Characteristics of Included Trials

Trial	Country	Centers	Patients	Sample Size	Treatment Onset, Month	Treatment Duration, Month	Male, %	Mean Age, Y	Follow-Up, Mo	Lost to Follow-Up, %	Blinding
AAASPS 2003[5]	US	62	IS	1809	0.25 to 3	19 (mean)	47	61	19 (mean)	3.8	Double-blind
ACCSG 1985[6]	US and Canada	15	TIA	890	<3	18 (median)	67	63	25 (median)	4.2	Double-blind
AICLA 1983[7]	France	4	IS, TIA	400	<12	36	69	63	36	3.8	Double-blind
CAPRIE 1996[8]	Worldwide	384	IS	6431	0.25 to 6	20 (mean)	64	65	23 (mean)	0.7	Double-blind
CASISP 2008[9]	China	13	IS	719	1 to 6	12 to 18	69	60	12 (mean)	1.3	Double-blind
CHARISMA 2011[10]	Worldwide	768	IS, TIA	4320	<60	25 (median)	63	65	25 (median)	0.5	Double-blind
CSPS2 2010[11]	Japan	278	IS	2672	<7	12 to 60	72	64	29 (mean)	0.2	Double-blind
ESPRIT 2006[12]	Worldwide	79	Minor IS, TIA	2739	<6	42 (mean)	66	63	42 (mean)	3.8	Open
ESPS2 1996[13]	Europe	59	IS, TIA	4953	<3	24	58	67	24	0.6	Double-blind
Fukuuchi 2007[14]	Japan	129	IS	1151	>0.25	52	73	65	52	NS	Double-blind
Guo 2009[15]	China	1	IS	68	1 to 6	12	35	61	12	NS	NS
Hass 1989[16]	US and Canada	56	IS, TIA, RI	3069	<3	27 (mean)	65	63	24 to 72	2.7	Double-blind
JASAP 2011[17]	Japan	157	IS	1294	0.25 to 6	15 (mean)	72	66	24	0.2	Double-blind
Li 2000[18]	China	9	IS, TIA	329	NS	12 (mean)	71	64	12 (mean)	2.4	NS
MATCH 2004[19]	Worldwide	507	IS, TIA	7599	<3	18	63	66	18	4.3	Double-blind
Matias-Guiu 1987[20]	Spain	1	TIA	186	<12	21 (mean)	77	55	21 (mean)	4.5	Open
PERFORM 2011[21]	Worldwide	802	IS, TIA	19 100	<3	28 (mean)	63	67	28 (mean)	0.3	Double-blind
PRoFESS 2008[22]	Worldwide	695	IS	20 332	<3	30 (mean)	64	66	30 (mean)	0.6	Double-blind
S-ACCESS 2008[23]	Japan	14	IS	1499	0.25 to 6	19 (mean)	72	65	19 (mean)	NS	Double-blind
SPS3 2012[24]	Worldwide	82	IS	3020	<6	41 (mean)	63	63	41 (mean)	2.0	Double-blind
TACIP 2003[25]	Portugal and Spain	43	IS, TIA	2107	<6	12 to 36	66	65	30 (mean)	2.1	Double-blind
TAPIRSS 2004[26]	Argentina	19	IS, TIA	429	<6	19 (mean)	68	65	19 (mean)	NS	Double-blind
Tohgi 1987[27]	Japan	101	TIA	281	<3	36	NS	NS	36	NS	12-mo double-blind, ≥24-mo open
TOPALS 2003[28]	Japan	25	IS, TIA	270	<6	19 (mean)	65	67	19 (mean)	NS	NS

IS indicates ischemic stroke; NS, not specified; RI, retinal ischemia; TIA, transient ischemic attack.

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Table 2. Antiplatelet Treatments and Outcomes of Included Trials

	Treatment Groups and Dosages			Stroke Recurrence			Composite Outcome			Intracranial Hemorrhage			Major Bleeding		
Trial	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3
AAASPS 2003[5]	Tic (250 mg BID)	Asp (325 mg BID)	—	107/902	86/907	—	145/902	125/907	—	NS	NS	—	4/902	8/907	—
ACCSG 1985[6]	Asp (325 mg QID)+Dip (75 mg QID)	Asp (325 mg QID)	—	53/448	60/442	—	99/448	96/442	—	2/448	4/442	—	15/448	21/442	—
AICLA 1983[7]	Asp (330 mg TID)+Dip (75 mg TID)	Asp (330 mg TID)	—	18/202	17/198	—	28/202	30/198	—	1/202	2/198	—	3/202	3/198	—
CAPRIE 1996[8]	Clop (75 mg OD)	Asp (325 mg OD)	—	315/3233	338/3198	—	433/3233	461/3198	—	NS	NS	—	NS	NS	—
CASISP 2008[9]	Cilo (100 mg BID)	Asp (100 mg OD)	—	12/360	20/359	—	24/360	37/359	—	1/360	5/359	—	1/360	6/359	—
CHARISMA 2011[10]	Asp (75 to 162 mg OD)+Clop (75 mg OD)	Asp (75 to 162 mg OD)	—	105/2157	131/2163	—	174/2157	207/2163	—	13/2157	11/2163	—	92/2157	61/2163	—
CSPS2 2010[11]	Cilo (100 mg BID)	Asp (81 mg OD)	—	82/1337	119/1335	—	138/1337	186/1335	—	8/1337	27/1335	—	23/1337	57/1335	—
ESPRIT 2006[12]	Asp (30 to 325 mg OD)+Dip (200 mg BID)	Asp (30 to 325 mg OD)	—	108/1363	137/1376	—	198/1363	239/1376	—	12/1363	21/1376	—	35/1363	53/1376	—
ESPS2 1996[13]	Asp (25 mg BID)+Dip (200 mg BID)	Dip (200 mg BID)	Asp (25 mg bid)	157/1650	211/1654	206/1649	206/1650	271/1654	266/1649	NS	NS	NS	60/1650	24/1654	53/1649
Fukuuchi 2007[14]	Clop (75 mg OD)	Tic (200 mg OD)	—	17/573	15/578	—	25/573	24/578	—	4/573	1/578	—	5/573	1/578	—
Guo 2009[15]	Cilo (100 mg BID)	Asp (100 mg OD)	—	2/34	2/34	—	2/34	5/34	—	0/34	1/34	—	0/34	2/34	—
Hass 1989[16]	Tic (250 mg BID)	Asp (650 mg BID)	—	172/1529	212/1540	—	306/1529	349/1540	—	7/1529	7/1540	—	14/1529	28/1540	—
JASAP 2011[17]	Asp (25 mg BID)+Dip (200 mg BID)	Asp (81 mg OD)	—	57/655	39/639	—	69/655	58/639	—	13/655	13/639	—	26/655	23/639	—
Li 2000[18]	Tic (250 mg OD)	Asp (50 mg OD)	—	11/165	21/164	—	13/165	26/164	—	6/165	4/164	—	7/165	7/164	—
MATCH 2004[19]	Asp (75 mg OD)+Clop (75 mg OD)	Clop (75 mg OD)	—	339/3797	347/3802	—	552/3797	567/3802	—	40/3759	25/3781	—	73/3759	22/3781	—
Matias-Guiu 1987[20]	Asp (50 mg OD)+Dip (100 mg TID)	Dip (100 mg QID)	—	9/115	7/71	—	25/115	15/71	—	NS	NS	—	NS	NS	—
PERFORM 2011[21]	Teru (30 mg OD)	Asp (100 mg OD)	—	842/9556	828/9544	—	1530/9556	1485/9544	—	146/9479	121/9466	—	211/9479	210/9466	—
PRoFESS 2008[22]	Asp (25 mg BID)+Dip (200 mg BID)	Clop (75 mg OD)	—	916/10 181	898/10 151	—	1637/10 181	1630/10 151	—	147/10 181	103/10 151	—	419/10 181	365/10 151	—
S-ACCESS 2008[23]	Sarp (100 mg TID)	Asp (81 mg OD)	—	79/747	70/752	—	110/747	98/752	—	9/750	12/757	—	NS	NS	—
SPS3 2012[24]	Asp (325 mg OD)+Clop (75 mg OD)	Asp (325 mg OD)	—	125/1517	138/1503	—	239/1517	232/1503	—	22/1517	15/1503	—	105/1517	56/1503	—

Continued

Table 2. Continued

Trial	Treatment Groups and Dosages			Stroke Recurrence			Composite Outcome			Intracranial Hemorrhage			Major Bleeding		
	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3
TACIP 2003[25]	Trif (600 mg OD)	Asp (325 mg OD)	—	109/1055	112/1062	—	145/1055	141/1052	—	7/1055	11/1052	—	20/1055	42/1052	—
TAPIRSS 2004[26]	Trif (600 mg OD)	Asp (325 mg OD)	—	18/213	18/216	—	27/213	34/216	—	1/214	2/216	—	1/214	7/216	—
Tohgi 1987[27]	Tic (200 mg OD)	Asp (500 mg BID)	—	4/136	8/145	—	29/136	46/145	—	2/136	2/145	—	NS	NS	—
TOPALS 2003[28]	Asp (81 mg OD)+Tic (100 mg OD)	Tic (200 mg OD)	—	9/132	7/138	—	13/132	14/138	—	2/132	0/138	—	NS	NS	—

Asp indicates aspirin; Cilo, cilostazol; Clop, clopidogrel; Dip, dipyridamole; NS, not specified; Sarp, sarpogrelate; Teru, terutroban; Tic, ticlopidine; Trif, triflusal.

aspirin (1 trial with 6431 patients),[8] dipyridamole versus aspirin (1 trial with 3303 patients),[13] sarpogrelate versus aspirin (1 trial with 1499 patients),[23] terutroban versus aspirin (1 trial with 19 100 patients),[21] ticlopidine versus aspirin (4 trials with 5488 patients),[5,16,18,27] ticlopidine versus clopidogrel (1 trial with 1151 patients),[14] triflusal versus aspirin (2 trials with 2536 patients),[25,26] aspirin plus clopidogrel versus aspirin (2 trials with 7340 patients),[10,24] aspirin plus clopidogrel versus clopidogrel (1 trial with 7599 patients),[19] aspirin plus dipyridamole versus aspirin (5 trials with 8622 patients),[6,7,12,13,17] aspirin plus dipyridamole versus clopidogrel (1 trial with 20 332 patients),[22] aspirin plus dipyridamole versus dipyridamole (2 trials with 3490 patients),[13,20] and aspirin plus ticlopidine versus ticlopidine (1 trial with 270 patients).[28]

Network Meta-Analysis

The network of antiplatelet treatment comparisons for stroke recurrence is shown in Figure 2. The network meta-analysis results for stroke recurrence and intracranial hemorrhage are reported in Table 3. Cilostazol significantly reduced stroke recurrence compared with aspirin (OR 0.66, 95% credible interval 0.44 to 0.92) and dipyridamole (OR 0.57, 95% credible interval 0.34 to 0.95), respectively. Intracranial hemorrhage was also significantly reduced by cilostazol compared with aspirin, clopidogrel, terutroban, ticlopidine, aspirin plus clopidogrel, and aspirin plus dipyridamole.

Similarly, cilostazol significantly reduced the composite outcome compared with aspirin (OR 0.68, 95% credible interval 0.48 to 0.93) and dipyridamole (OR 0.59, 95%

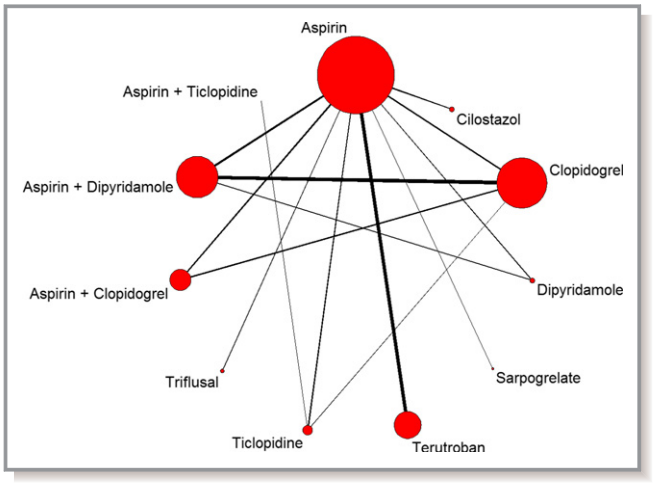

Figure 2. Network of treatment comparisons for the primary efficacy outcome. The size of the node corresponds to the total sample size of the treatment from all included trials. Directly comparable treatments are linked with a line, the thickness of which corresponds to the total sample size for assessing the comparison.

Table 3. Results for Stroke Recurrence (Upper Diagonal Part) and Intracranial Hemorrhage (Lower Diagonal Part) From Network Meta-Analyses

Treatment	Asp	Cilo	Clop	Dip	Sarp	Teru	Tic	Trif	Asp+Clop	Asp+Dip	Asp+Tic
Asp	1.00	0.66 (0.44 to 0.92)*	0.89 (0.72 to 1.14)	1.13 (0.80 to 1.54)	1.19 (0.69 to 1.87)	1.04 (0.72 to 1.44)	0.87 (0.65 to 1.10)	0.98 (0.68 to 1.37)	0.85 (0.68 to 1.09)	0.89 (0.74 to 1.06)	1.45 (0.40 to 3.78)
Cilo	0.27 (0.08 to 0.58)*	1.00	1.39 (0.91 to 2.16)	1.77 (1.06 to 2.94)*	1.85 (0.97 to 3.12)	1.62 (0.98 to 2.64)	1.36 (0.85 to 2.15)	1.53 (0.90 to 2.47)	1.33 (0.86 to 2.05)	1.38 (0.91 to 2.13)	2.27 (0.59 to 6.48)
Clop	0.74 (0.37 to 1.49)	3.62 (1.07 to 10.60)*	1.00	1.28 (0.85 to 1.79)	1.35 (0.75 to 2.15)	1.18 (0.75 to 1.73)	0.99 (0.70 to 1.32)	1.12 (0.70 to 1.65)	0.97 (0.74 to 1.23)	1.01 (0.77 to 1.27)	1.65 (0.43 to 4.39)
Dip	—	—	—	1.00	1.07 (0.59 to 1.80)	0.94 (0.58 to 1.50)	0.79 (0.50 to 1.16)	0.89 (0.52 to 1.41)	0.77 (0.52 to 1.12)	0.80 (0.58 to 1.12)	1.32 (0.33 to 3.56)
Sarp	0.88 (0.23 to 2.32)	4.44 (0.78 to 14.55)	1.32 (0.27 to 3.90)	—	1.00	0.93 (0.49 to 1.64)	0.78 (0.43 to 1.28)	0.88 (0.46 to 1.50)	0.76 (0.42 to 1.29)	0.79 (0.44 to 1.27)	1.30 (0.31 to 3.68)
Teru	1.27 (0.53 to 2.45)	6.15 (1.55 to 16.85)*	1.94 (0.56 to 4.37)	—	2.06 (0.41 to 6.21)	1.00	0.87 (0.53 to 1.28)	0.98 (0.57 to 1.57)	0.85 (0.56 to 1.24)	0.88 (0.59 to 1.31)	1.44 (0.35 to 3.83)
Tic	0.96 (0.39 to 2.02)	4.71 (1.09 to 14.72)*	1.43 (0.46 to 3.34)	—	1.60 (0.31 to 5.17)	0.87 (0.28 to 2.19)	1.00	1.14 (0.75 to 1.75)	0.99 (0.71 to 1.37)	1.03 (0.75 to 1.43)	1.67 (0.47 to 4.38)
Trif	0.68 (0.18 to 1.72)	3.23 (0.59 to 10.75)	1.02 (0.20 to 2.89)	—	1.09 (0.15 to 3.94)	0.65 (0.13 to 1.67)	0.83 (0.16 to 2.62)	1.00	0.90 (0.56 to 1.35)	0.93 (0.63 to 1.34)	1.53 (0.37 to 3.93)
Asp+Clop	1.31 (0.67 to 2.46)	6.45 (1.72 to 19.79)*	1.91 (0.94 to 3.50)	—	2.11 (0.48 to 6.08)	1.18 (0.42 to 2.87)	1.63 (0.52 to 3.90)	2.72 (0.66 to 7.90)	1.00	1.05 (0.78 to 1.40)	1.73 (0.45 to 4.73)
Asp+Dip	0.85 (0.46 to 1.37)	4.17 (1.20 to 11.06)*	1.25 (0.55 to 2.03)	—	1.38 (0.32 to 3.81)	0.77 (0.26 to 1.78)	1.05 (0.34 to 2.30)	1.74 (0.42 to 5.12)	0.70 (0.29 to 1.32)	1.00	1.65 (0.45 to 4.21)
Asp+Tic	—	—	—	—	—	—	—	—	—	—	1.00

Each cell gives an odds ratio (OR) and 95% credible interval. In the upper diagonal part, the OR compares the column condition with the row condition, and in the lower diagonal part, this OR compares the row condition with the column condition. Asp indicates aspirin; Cilo, cilostazol; Clop, clopidogrel; Dip, dipyridamole; NS, not specified; Sarp, sarpogrelate; Teru, terutroban; Tic, ticlopidine; Trif, triflusal.
*Significant results.

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Table 4. Results for Composite Outcome (Upper Diagonal Part) and Major Bleeding (Lower Diagonal Part), From Network Meta-Analyses

Treatment	Asp	Cilo	Clop	Dip	Sarp	Teru	Tic	Trif	Asp+Clop	Asp+Dip	Asp+Tic
Asp	1.00	0.68 (0.48 to 0.93)*	0.93 (0.77 to 1.16)	1.11 (0.78 to 1.51)	1.17 (0.72 to 1.77)	1.04 (0.73 to 1.43)	0.86 (0.67 to 1.06)	0.96 (0.64 to 1.33)	0.92 (0.73 to 1.18)	0.88 (0.74 to 1.10)	0.93 (0.33 to 2.15)
Cilo	0.35 (0.15 to 0.62)*	1.00	1.42 (0.95 to 2.10)	1.68 (1.06 to 2.54)*	1.79 (0.98 to 2.95)	1.59 (0.95 to 2.48)	1.32 (0.85 to 1.92)	1.47 (0.86 to 2.33)	1.40 (0.91 to 2.06)	1.41 (0.97 to 2.04)	1.43 (0.48 to 3.49)
Clop	0.74 (0.43 to 1.15)	2.50 (1.02 to 5.85)*	1.00	1.20 (0.79 to 1.72)	1.27 (0.75 to 2.05)	1.13 (0.75 to 1.56)	0.93 (0.67 to 1.20)	1.04 (0.65 to 1.57)	0.99 (0.75 to 1.30)	1.00 (0.78 to 1.28)	1.01 (0.35 to 2.34)
Dip	0.40 (0.19 to 0.74)*	1.30 (0.46 to 3.10)	0.57 (0.24 to 1.12)	1.00	1.09 (0.56 to 1.79)	0.97 (0.57 to 1.56)	0.80 (0.52 to 1.17)	0.89 (0.53 to 1.37)	0.86 (0.57 to 1.29)	0.86 (0.62 to 1.17)	0.87 (0.28 to 2.02)
Sarp	—	—	—	—	1.00	0.94 (0.50 to 1.57)	0.78 (0.44 to 1.22)	0.87 (0.46 to 1.54)	0.83 (0.49 to 1.34)	0.83 (0.51 to 1.34)	0.84 (0.26 to 2.06)
Teru	1.04 (0.56 to 1.76)	3.35 (1.35 to 7.55)*	1.48 (0.66 to 2.90)	2.89 (1.12 to 6.04)*	—	1.00	0.85 (0.56 to 1.27)	0.95 (0.56 to 1.49)	0.91 (0.61 to 1.37)	0.91 (0.63 to 1.36)	0.92 (0.31 to 2.30)
Tic	0.53 (0.29 to 0.89)*	1.75 (0.61 to 3.69)	0.76 (0.33 to 1.37)	1.49 (0.56 to 2.92)	—	0.56 (0.24 to 1.00)	1.00	1.13 (0.72 to 1.67)	1.08 (0.80 to 1.51)	1.09 (0.83 to 1.49)	1.08 (0.41 to 2.46)
Trif	0.41 (0.18 to 0.74)*	1.31 (0.45 to 2.92)	0.59 (0.20 to 1.22)	1.13 (0.37 to 2.53)	—	0.42 (0.15 to 0.87)*	0.83 (0.30 to 1.85)	1.00	0.99 (0.63 to 1.56)	0.99 (0.64 to 1.49)	1.00 (0.35 to 2.39)
Asp+Clop	1.93 (1.30 to 3.05)*	6.32 (2.86 to 14.22)*	2.71 (1.58 to 4.43)*	5.37 (2.39 to 11.10)*	—	2.02 (0.94 to 3.91)	3.94 (1.83 to 7.81)*	5.41 (2.33 to 11.28)*	1.00	1.02 (0.75 to 1.37)	1.03 (0.35 to 2.36)
Asp+Dip	0.87 (0.62 to 1.19)	2.86 (1.26 to 6.18)*	1.23 (0.79 to 1.87)	2.39 (1.21 to 4.44)*	—	0.91 (0.47 to 1.65)	1.78 (0.87 to 3.22)	2.46 (1.09 to 5.34)*	0.47 (0.27 to 0.76)*	1.00	1.01 (0.37 to 2.35)
Asp+Tic	—	—	—	—	—	—	—	—	—	—	1.00

Each cell gives an odds ratio (OR) and 95% credible interval. In the upper diagonal part, the OR compares the column condition with the row condition, and in the lower diagonal part, this OR compares the row condition with the column condition. Asp indicates aspirin; Cilo, cilostazol; Clop, clopidogrel; Dip, dipyridamole; NS, not specified; Sarp, sarpogrelate; Teru, terutroban; Tic, ticlopidine; Trif, triflusal.
*Significant results.

Table 5. The SUCRA Probabilities of Antiplatelet Therapies on Efficacy and Safety Outcomes

	Stroke Recurrence		Composite Outcome		Intracranial Hemorrhage		Major Bleeding	
Treatment	SUCRA	Rank*	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank
Aspirin	0.3551	7	0.3465	8	0.3361	7	0.2136	8
Cilostazol	0.9343	1	0.9252	1	0.9718	1	0.8850	1
Clopidogrel	0.6252	5	0.5380	6	0.6487	3	0.4950	5
Dipyridamole	0.2250	11	0.2446	10	—	—	0.8221	2
Sarpogrelate	0.2433	10	0.2223	11	0.5538	4	—	—
Terutroban	0.3547	8	0.3234	9	0.2025	8	0.2451	7
Ticlopidine	0.6510	3	0.6854	2	0.4496	6	0.6740	4
Triflusal	0.4551	6	0.4811	7	0.6794	2	0.8096	3
Aspirin plus clopidogrel	0.7033	2	0.5741	4	0.1650	9	0.0064	9
Aspirin plus dipyridamole	0.6321	4	0.5657	5	0.4931	5	0.3492	6
Aspirin plus ticlopidine	0.3208	9	0.5937	3	—	—	—	—

SUCRA indicates surface under the cumulative ranking curve.
*Ranking SUCRA probabilities in order as the best treatment, the second best, the third best, and so on, among the antiplatelet therapies.

credible interval 0.39 to 0.95) and reduced major bleeding compared with aspirin, clopidogrel, terutroban, aspirin plus clopidogrel, and aspirin plus dipyridamole (Table 4). In addition, dipyridamole, ticlopidine, and triflusal caused significantly less major bleeding than aspirin; terutroban caused significantly more major bleeding than dipyridamole and triflusal; aspirin plus clopidogrel caused significantly more major bleeding than aspirin, clopidogrel, dipyridamole, ticlopidine, triflusal, and aspirin plus dipyridamole; and aspirin plus dipyridamole caused significantly more major bleeding than dipyridamole and triflusal.

Table 5 shows the mean values of SUCRA probabilities that provided the hierarchies for the efficacy and safety of the 11 antiplatelet therapies. In particular, cilostazol displayed the best risk–benefit profile, with SUCRA probabilities of 0.9343, 0.9252, 0.9718, and 0.8850 for reducing stroke recurrence, composite outcome, intracranial hemorrhage, and major bleeding, respectively. Figures S2 through S5 show the ranking probability of each treatment for outcomes.

No inconsistent loop was identified in the analyses of inconsistency factor (Figure S6).

Pairwise Meta-Analysis

We examined pairwise comparisons of all interventions with available head-to-head data. The results are presented in Figures 3 through 6. In general, the results obtained from pairwise meta-analysis closely matched those of the network meta-analysis. Stroke recurrence, composite efficacy outcome, intracranial hemorrhage, and major bleeding were all significantly reduced by cilostazol versus aspirin. Among the 22 pairwise meta-analyses, each of which included at least 2 trials (Figures 3 through 6), significant heterogeneity was identified in 2 pairwise meta-analyses. One of the 2 pairwise meta-analyses compared ticlopidine with aspirin for preventing stroke recurrence (including 4 trials, I^2=69.9, P=0.019) (Figure 3), and the other compared ticlopidine with aspirin for composite outcome (including 4 trials, I^2=73.1, P=0.011) (Figure 4). There was no evidence of heterogeneity across trials in the remaining 20 pairwise meta-analyses.

Sensitivity Analysis

The pooled risk estimates did not change substantially in the sensitivity analyses on the primary efficacy outcome from both network meta-analyses and pairwise meta-analyses. Tables S4 and S5 and Figures S7 and S8 show the full results of the sensitivity analysis.

Discussion

Our network meta-analysis provided evidence-based hierarchies for the efficacy and safety of long-term antiplatelet mono- and dual therapies among patients with ischemic stroke or TIA. It overcame the major limitation of conventional pairwise meta-analyses by combining direct and indirect evidence of relative treatments in the analysis. Results from this study indicated that when compared with antiplatelet monotherapy, dual therapy was not associated with a reduction in stroke recurrence and composite outcome but rather with a significant increase in the risk of major bleeding, especially aspirin plus clopidogrel. In addition, our results showed that cilostazol displayed the

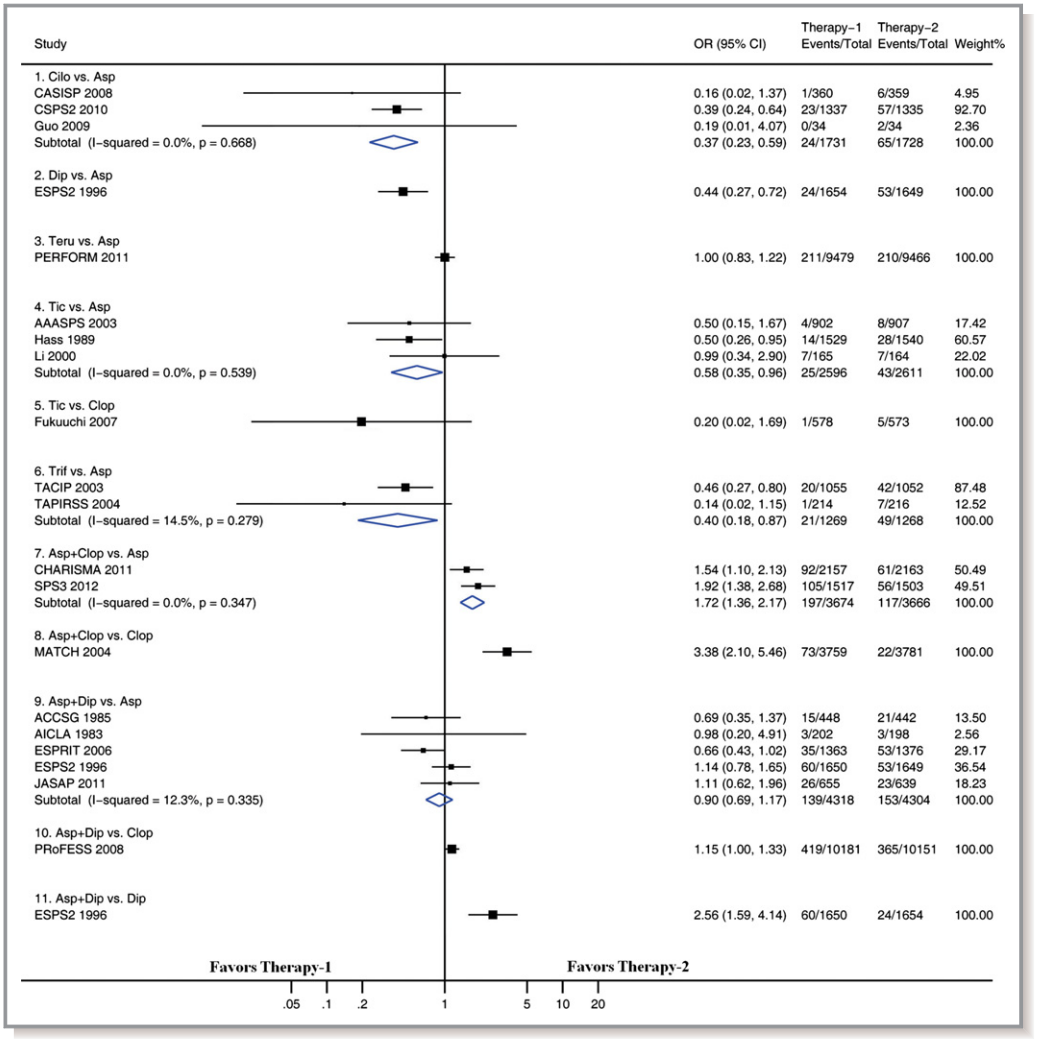

Figure 3. Pairwise meta-analyses comparing antiplatelet therapies on stroke recurrence. Squares represent point estimates for effect size expressed as an odds ratio, with the size proportional to the inverse variance of the estimate. Diamonds represent pooled estimates. Lines represent 95% CIs. Asp indicates aspirin; CI, confidence interval; Cilo, cilostazol; Clop, clopidogrel; Dip, dipyridamole; OR, odds ratio; Sarp, sarpogrelate; Teru, terutroban; Tic, ticlopidine; Trif, triflusal.

best risk–benefit profile among the 11 antiplatelet treatments.

The effects of dual therapy in short- and long-term prevention of recurrent stroke might be different. A recent meta-analysis that combined the results from 14 RCTs reported that dual therapy was more effective than monotherapy in reducing the risk of early recurrent stroke in patients with an index stroke in the previous 3 days.[37] The latest AHA/ASA guidelines also recommend that the combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA.[4] For long-term secondary prevention, however, the combination of aspirin and clopidogrel is not recommended by the AHA/ASA guidelines for routine long-term secondary prevention of stroke due to high risk of bleeding,[4] which is consistent with our results. Moreover, a recent pairwise meta-analysis based on 7 RCTs that involved 39 574 patients with ischemic stroke or TIA reported that antiplatelet dual therapy lasting >1 year is not associated with a greater reduction in overall recurrent stroke risk than monotherapy, and that finding also supported our results.[29] As far as we know, this network meta-analysis is the first to evaluate the efficacy and safety of long-term antiplatelet therapies after ischemic stroke or TIA and provides the most robust evidence in support of long-term monotherapy as a better choice than long-term dual therapy.

The present study indicated that cilostazol had the best risk–benefit profile among 11 antiplatelet therapies and supported cilostazol as a possible therapeutic option to recommend for secondary prevention of stroke. In the CASISP trial, which included 720 Chinese patients with ischemic

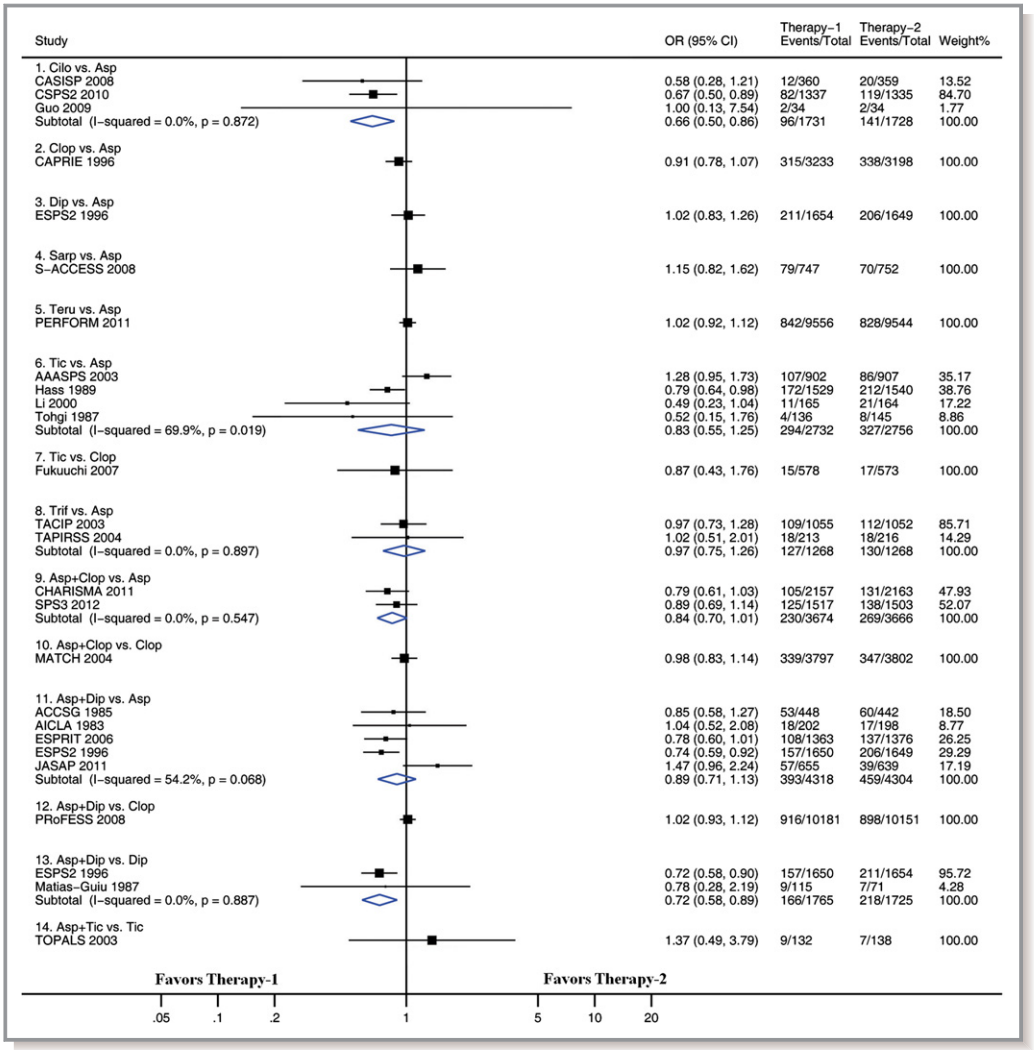

Figure 4. Pairwise meta-analyses comparing antiplatelet therapies on the composite outcome. Squares represent point estimates for effect size expressed as an odds ratio, with the size proportional to the inverse variance of the estimate. Diamonds represent pooled estimates. Lines represent 95% CIs. Asp indicates aspirin; CI, confidence interval; Cilo, cilostazol; Clop, clopidogrel; Dip, dipyridamole; OR, odds ratio; Sarp, sarpogrelate; Teru, terutroban; Tic, ticlopidine; Trif, triflusal.

stroke within the previous 1 to 6 months, cilostazol reduced the rate of recurrent stroke compared with aspirin (hazard ratio 0.62, 95% CI 0.30 to 1.26), although the benefit was not significant.[9] The rate of any hemorrhagic event was also lower in the cilostazol group than in the aspirin group.[9] The CSPS 2 study in 2757 Japanese patients is another trial conducted in an East Asian population to compare the efficacy and safety of cilostazol and aspirin in patients with ischemic stroke.[11] This trial found that cilostazol significantly reduced the recurrence rate of stroke compared with aspirin (hazard ratio 0.74, 95% CI 0.56 to 0.98) and that major bleeding events occurred in fewer patients on cilostazol than on aspirin (hazard ratio 0.46, 95% CI 0.30 to 0.71).[11] On the basis of this evidence, cilostazol has been approved by the China Food and Drug Administration for treatment of noncardioembolic ischemic stroke (license number H10960014), and the latest Chinese guidelines for secondary prevention of stroke recommends cilostazol (100 mg BID) as an alternative to aspirin.[53] Similarly, cilostazol is used in Japan for secondary prevention of stroke and is included in the Japanese guidelines for the treatment of ischemic stroke.[54] Cilostazol is not licensed in the United States for ischemic stroke or TIA treatment because the efficacy and safety of cilostazol have not been tested in non–East Asian patients. Generalizing the effect of cilostazol to other groups can be challenging because the risk of both ischemic and hemorrhagic stroke is higher in the East Asian population compared with other populations. Further trials in non–East Asian patients are needed to confirm whether cilostazol is effective and safe as a monotherapy for long-term secondary prevention after ischemic stroke or TIA. In addition,

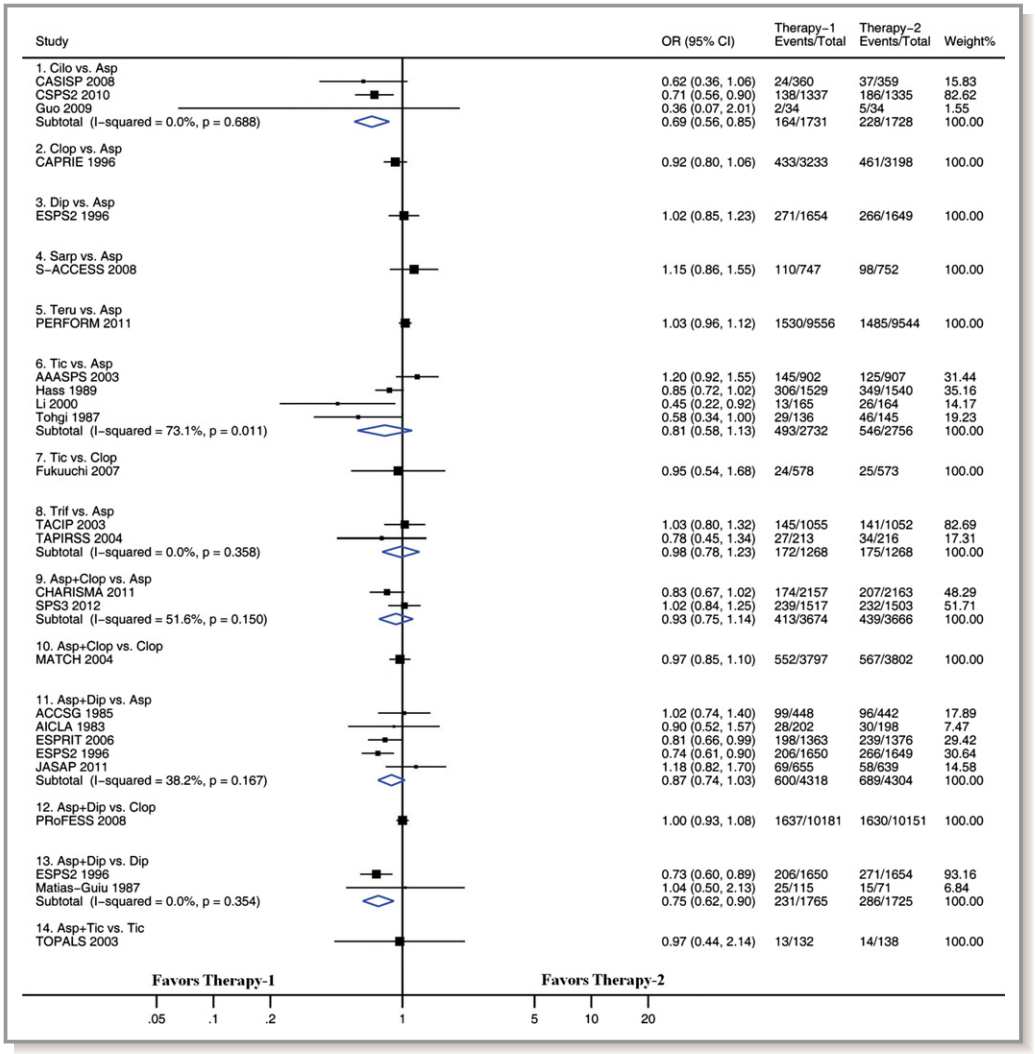

Figure 5. Pairwise meta-analyses comparing antiplatelet therapies on intracranial hemorrhage. Squares represent point estimates for effect size expressed as an odds ratio, with the size proportional to the inverse variance of the estimate. Diamonds represent pooled estimates. Lines represent 95% CIs. Asp indicates aspirin; CI, confidence interval; Cilo, cilostazol; Clop, clopidogrel; Dip, dipyridamole; OR, odds ratio; Sarp, sarpogrelate; Teru, terutroban; Tic, ticlopidine; Trif, triflusal.

cost-effectiveness studies are also required to explore whether long-term use of cilostazol is cost-effective compared with other monotherapies.

Two previous network meta-analyses have been conducted to compare the effect of antiplatelet therapies after ischemic stroke or TIA[34,35]; however, neither provided hierarchies for the efficacy and safety of antiplatelet therapies. In one of the studies,[34] Thijs et al found that the combination of aspirin and dipyridamole was more effective than aspirin, ticlopidine, and clopidogrel in the prevention of serious vascular events; this finding was not consistent with our analysis. We consider the main reason to be that 13 of the 24 trials identified by Thijs et al did not meet the inclusion criteria for our study because of placebo control or treatment duration <1 year. In addition, the network meta-analysis by Thijs et al excluded trials assessing triflusal, cilostazol, and sarpogrelate and did not report safety data.[34] In the other study,[35] Malloy et al reported that more overall hemorrhagic events seemed to occur with the combination of aspirin and clopidogrel than with other treatments, and that finding supported our results. Nevertheless, they found that aspirin plus dipyridamole was more protective than aspirin alone, which was not consistent with our results. Similarly, we consider the main reason to be that 9 of the 24 trials identified by Malloy et al did not meet the inclusion criteria for our study.

The main strength of our study is the inclusion of 24 RCTs with 85 667 patients, thus it is the largest evaluation of long-term antiplatelet therapies for stroke recurrence to date. Furthermore, the network meta-analysis based on a Bayesian model makes indirect comparison among multiple

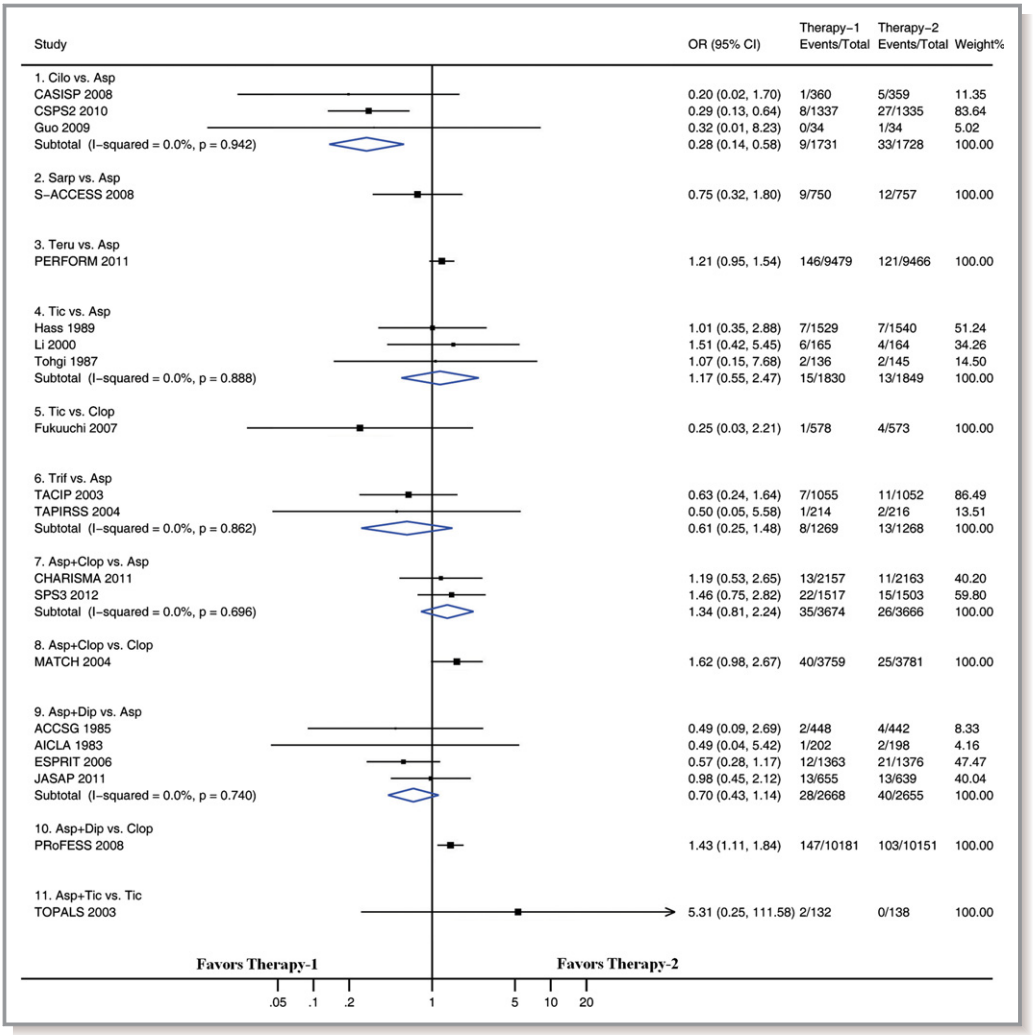

Figure 6. Pairwise meta-analyses comparing antiplatelet therapies on major bleeding. Squares represent point estimates for effect size expressed as an odds ratio, with the size proportional to the inverse variance of the estimate. Diamonds represent pooled estimates. Lines represent 95% CIs. Asp indicates aspirin; CI, confidence interval; Cilo, cilostazol; Clop, clopidogrel; Dip, dipyridamole; OR, odds ratio; Sarp, sarpogrelate; Teru, terutroban; Tic, ticlopidine; Trif, triflusal.

treatments available, especially when there are few trials for direct comparison between different antiplatelet therapies. Consequently, this study can provide evidence-based hierarchies for the long-term efficacy and safety of all available antiplatelet therapies among patients with ischemic stroke or TIA.

This study also has some limitations. First, the full-text articles reviewed were limited to English- and Chinese-language studies, and that can introduce selection bias. A relevant article in French identified from the literature was not included in this study.[55] Nonetheless, we believe that the possibility of selection bias is reduced by the relatively large number of studies available in English and Chinese. In addition, previous studies demonstrated that excluding studies published in languages other than English generally has little effect on summary effect estimates.[56,57] Second, not all included trials reported the results of intracranial hemorrhage or major bleeding, thus some comparisons between antiplatelet therapies for safety outcomes were not available. Third, all comparisons involving aspirin plus ticlopidine are tenuous, given that only 1 small trial was included in this study, and that may affect the stability of relevant results. Finally, most pairs for comparison included only 1 trial, and cilostazol versus aspirin has not been tested in non–East Asian patients, which might undermine the strength of our results to affect clinical practice.

In conclusion, based on this network meta-analysis, we suggested that long-term monotherapy was a better choice than long-term dual therapy and that cilostazol had the best risk–benefit profile for long-term secondary prevention after stroke or TIA. More high-quality trials in non–East Asian patients are needed to determine whether long-term use of

cilostazol is the best option for the prevention of recurrent stroke.

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Disclosures

None.

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