

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

S troke 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

*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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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

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later study identified 24 trials published before March 2012³⁵ 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 \geq 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 allcause 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 metaanalyses 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 I² 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

Trial	Country	Centers	Patients	Sample Size	Treatment Onset, Month	Treatment Duration, Month	Male,	Mean Age, Y	Follow-Up, Mo	Lost to Follow-Up, %	Blinding
AASPS 2003 ⁵	SU	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	9>	42 (mean)	99	63	42 (mean)	3.8	Open
ESPS2 1996 ¹³	Europe	59	IS, TIA	4953	Ŷ	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	6	IS, TIA	329	NS	12 (mean)	71	64	12 (mean)	2.4	NS
MATCH 2004 ¹⁹	Worldwide	507	IS, TIA	7599	ŝ	18	63	66	18	4.3	Double-blind
Matias-Guiu 1987 ²⁰	Spain	1	TIA	186	<12	21 (mean)	17	55	21 (mean)	4.5	Open
PERFORM 2011 ²¹	Worldwide	802	IS, TIA	19 100	ŝ	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	9⊳	41 (mean)	63	63	41 (mean)	2.0	Double-blind
TACIP 2003 ²⁵	Portugal and Spain	43	IS, TIA	2107	€	12 to 36	99	65	30 (mean)	2.1	Double-blind
TAPIRSS 2004 ²⁶	Argentina	19	IS, TIA	429	9⊳	19 (mean)	68	65	19 (mean)	NS	Double-blind
Tohgi 1987 ²⁷	Japan	101	TIA	281	\$	36	NS	NS	36	NS	12-mo double-blind, ≥24-mo open
T0PALS 2003 ²⁸	Japan	25	IS, TIA	270	9⊳	19 (mean)	65	67	19 (mean)	NS	NS

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

Trials
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Table

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

Continued

	Arm 3				1
ding	Arm 2	42/1052	7/216	NS	SN
Major Bleed	Arm 1	20/1055	1/214	NS	SN
	Arm 3				
l Hemorrhage	Arm 2	11/1052	2/216	2/145	0/138
Intracrania	Arm 1	7/1055	1/214	2/136	2/132
	Arm 3				1
Dutcome	Arm 2	141/1052	34/216	46/145	14/138
Composite C	Arm 1	145/1055	27/213	29/136	13/132
urrence	Arm 3				
	Arm 2	112/ 1052	18/216	8/145	7/138
Stroke Rec	Arm 1	109/ 1055	18/213	4/136	9/132
	Arm 3				
osages	Arm 2	Asp (325 mg 0D)	Asp (325 mg 0D)	Asp (500 mg BID)	Tic (200 mg 0D)
Treatment Groups and D	Arm 1	Trif (600 mg 0D)	Trif (600 mg 0D)	Tic (200 mg 0D)	Asp (81 mg 0D)+Tic (100 mg 0D)
	Trial	TACIP 2003 ²⁵	TAPIRSS 2004 ²⁶	Tohgi 1987 ²⁷	TOPALS 2003 ²⁸

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 versus clopidogrel (1 trial with 7599 patients),¹⁹ aspirin plus dipyridamole versus 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.

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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

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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 Recurren	ce	Composite Outc	ome	Intracranial Hem	orrhage	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, $l^2=69.9$, P=0.019) (Figure 3), and the other compared ticlopidine with aspirin for composite outcome (including 4 trials, $l^2=73.1$, 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

ORIGINAL RESEARCH

Therapy-1 Therapy-2 Study OR (95% CI) Events/Total Events/Total Weight% 1. Cilo vs. Asp CASISP 2008 0.16 (0.02, 1.37) 6/359 1/360 4.95 0.39 (0.24, 0.64) 57/1335 92.70 CSPS2 2010 23/1337 Guo 2009 0.19 (0.01, 4.07) 0/34 2/34 2.36 0.37 (0.23, 0.59) Subtotal (I-squ uared = 0.0%, p = 0.668 24/1731 65/1728 100.00 2. Dip vs. Asp ESPS2 1996 0.44 (0.27, 0.72) 24/1654 53/1649 100.00 3. Teru vs. Asr PERFORM 2011 1.00 (0.83, 1.22) 211/9479 210/9466 100.00 4. Tic vs. Asp 0.50 (0.15, 1.67) AAASPS 2003 4/902 8/907 17.42 Hass 1989 0.50 (0.26, 0.95) 0.99 (0.34, 2.90) 14/1529 28/1540 60.57 7/165 7/164 Li 2000 Subtotal (I-squared = 0.0%, p = 0.539) 0.58 (0.35, 0.96) 25/2596 43/2611 100.00 5. Tic vs. Clop Fukuuchi 2007 0.20 (0.02, 1.69) 1/578 5/573 100.00 6. Trif vs. Asp 20/1055 42/1052 TACIP 2003 0.46 (0.27, 0.80) 87.48 TAPIRSS 2004 0.14 (0.02, 1.15) 1/214 7/216 12.52 Subtotal (I-squared = 14.5%, p = 0.279) 21/1269 49/1268 0.40 (0.18, 0.87) 100.00 7. Asp+Clop vs. Asp CHARISMA 2011 1.54 (1.10, 2.13) 92/2157 61/2163 50.49 1.92 (1.38, 2.68) 1.72 (1.36, 2.17) 105/1517 56/1503 49.51 SPS3 2012 117/3666 Subtotal (I-squared = 0.0%, p = 0.347) 197/3674 100.00 8. Asp+Clop vs. Clop MATCH 2004 3.38 (2.10, 5.46) 73/3759 22/3781 100.00 9. Asp+Dip vs. Asp ACCSG 1985 0.69 (0.35, 1.37) 15/448 21/442 13.50 2.56 29.17 AICLA 1983 0.98 (0.20, 4.91) 3/202 3/198 ESPRIT 2006 0.66 (0.43, 1.02) 35/1363 53/1376 ESPS2 1996 1.14 (0.78, 1.65) 60/1650 53/1649 36.54 JASAP 2011 1 11 (0.62, 1.96) 26/655 23/639 18.23 Subtotal (I-squared = 12.3%, p = 0.335) 1 0.90 (0.69, 1.17) 139/4318 153/4304 100.00 10. Asp+Dip vs. Clop PRoFESS 2008 1.15 (1.00, 1.33) 419/10181 365/10151 100.00 11. Asp+Dip vs. Dip 2.56 (1.59, 4.14) 60/1650 ESPS2 1996 24/1654 100.00 Favors Therapy-1 Favors Therapy-2 1 .05 2 10 20 5

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

Study	OR (95% CI)	Therapy-1 Events/Total	Therapy-2 Events/Total	Weight%
1. Cilo vs. Asp CASISP 2008 CSPS2 2010 Guo 2009 Subtotal (I-squared = 0.0%, p = 0.872)	0.58 (0.28, 1.21) 0.67 (0.50, 0.89) 1.00 (0.13, 7.54) 0.66 (0.50, 0.86)	12/360 82/1337 2/34 96/1731	20/359 119/1335 2/34 141/1728	13.52 84.70 1.77 100.00
2. Clop vs. Asp CAPRIE 1996	0.91 (0.78, 1.07)	315/3233	338/3198	100.00
3. Dip vs. Asp ESP\$2 1996	1.02 (0.83, 1.26)	211/1654	206/1649	100.00
4. Sarp vs. Asp S-ACCESS 2008	1.15 (0.82, 1.62)	79/747	70/752	100.00
5. Teru vs. Asp PERFORM 2011	1.02 (0.92, 1.12)	842/9556	828/9544	100.00
6. Tic vs. Asp AASPS 2003 Hass 1989 Li 2000 Tohgi 1987 Subtotal (I-squared = 69.9%, p = 0.019)	1.28 (0.95, 1.73) 0.79 (0.64, 0.98) 0.49 (0.23, 1.04) 0.52 (0.15, 1.76) 0.83 (0.55, 1.25)	107/902 172/1529 11/165 4/136 294/2732	86/907 212/1540 21/164 8/145 327/2756	35.17 38.76 17.22 8.86 100.00
7. Tic vs. Clop Fukuuchi 2007	0.87 (0.43, 1.76)	15/578	17/573	100.00
8. Trif vs. Asp TACIP 2003 TAPIRSS 2004 Subtotal (I-squared = 0.0%, p = 0.897)	0.97 (0.73, 1.28) 1.02 (0.51, 2.01) 0.97 (0.75, 1.26)	109/1055 18/213 127/1268	112/1052 18/216 130/1268	85.71 14.29 100.00
9. Asp+Clop vs. Asp CHARISMA 2011 SPS3 2012 Subtotal (I-squared = 0.0%, p = 0.547)	0.79 (0.61, 1.03) 0.89 (0.69, 1.14) 0.84 (0.70, 1.01)	105/2157 125/1517 230/3674	131/2163 138/1503 269/3666	47.93 52.07 100.00
10. Asp+Clop vs. Clop MATCH 2004	0.98 (0.83, 1.14)	339/3797	347/3802	100.00
11. Asp+Dip vs. Asp ACCSG 1985 AICLA 1983 ESPRIT 2006 ESPS2 1996 JASAP 2011 Subtotal (I-squared = 54.2%, p = 0.068)	0.85 (0.58, 1.27) 1.04 (0.52, 2.08) 0.78 (0.60, 1.01) 0.74 (0.59, 0.92) 1.47 (0.96, 2.24) 0.89 (0.71, 1.13)	53/448 18/202 108/1363 157/1650 57/655 393/4318	60/442 17/198 137/1376 206/1649 39/639 459/4304	18.50 8.77 26.25 29.29 17.19 100.00
12. Asp+Dip vs. Clop PRoFESS 2008	1.02 (0.93, 1.12)	916/10181	898/10151	100.00
13. Asp+Dip vs. Dip ESPS2 1996 Matias-Guiu 1987 Subtotal (I-squared = 0.0%, p = 0.887)	0.72 (0.58, 0.90) 0.78 (0.28, 2.19) 0.72 (0.58, 0.89)	157/1650 9/115 166/1765	211/1654 7/71 218/1725	95.72 4.28 100.00
14. Asp+Tic vs. Tic TOPALS 2003	1.37 (0.49, 3.79)	9/132	7/138	100.00
Favors Therapy-1 Favors T	herapy-2			
I I I I I I .05 .1 .2 1 5 10	20			

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% Cls. Asp indicates aspirin; Cl, 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,

Therapy-2 Events/Total Therapy-1 Events/Total Weight% OR (95% CI) Study 1. Cilo vs. Asp CASISP 2008 CSPS2 2010 Guo 2009 Subtotal (I-squared = 0.0%, p = 0.688) 15.83 82.62 1.55 100.00 24/360 138/1337 2/34 164/1731 37/359 186/1335 5/34 228/1728 0.62 (0.36, 1.06) 0.71 (0.56, 0.90) 0.36 (0.07, 2.01) 0.69 (0.56, 0.85) 0 2. Clop vs. Asp CAPRIE 1996 0.92 (0.80, 1.06) 433/3233 461/3198 100.00 Dip vs. Asp ESPS2 1996 1.02 (0.85, 1.23) 271/1654 266/1649 100.00 4. Sarp vs. Asp S-ACCESS 2008 1.15 (0.86, 1.55) 110/747 98/752 100.00 5. Teru vs. Asp PERFORM 2011 1485/9544 1.03 (0.96, 1.12) 1530/9556 100.00 6. Tic vs. Asp AAASPS 2003 Hass 1989 Li 2000 1.20 (0.92, 1.55) 0.85 (0.72, 1.02) 0.45 (0.22, 0.92) 0.58 (0.34, 1.00) 0.81 (0.58, 1.13) 145/902 306/1529 13/165 29/136 493/2732 125/907 349/1540 26/164 46/145 31.44 35.16 14.17 19.23 100.00 Li 2000 Tohgi 1987 Subtotal (I-squared = 73.1%, p = 0.011) 546/2756 7. Tic vs. Clop Fukuuchi 2007 0.95 (0.54, 1.68) 24/578 25/573 100.00 8. Trif vs. Asp TACIP 2003 TAPIRSS 2004 Subtotal (I-squared = 0.0%, p = 0.358) 141/1052 34/216 175/1268 82.69 17.31 100.00 1.03 (0.80, 1.32) 0.78 (0.45, 1.34) 0.98 (0.78, 1.23) 27/213 172/1268 9. Asp+Clop vs. Asp CHARISMA 2011 0.83 (0.67, 1.02) 1.02 (0.84, 1.25) 0.93 (0.75, 1.14) 48.29 51.71 100.00 174/2157 207/2163 239/1517 413/3674 232/1503 439/3666 S3 2012 Subtotal (I-squared = 51.6%, p = 0.150) 10. Asp+Clop vs. Clop MATCH 2004 0.97 (0.85, 1.10) 552/3797 567/3802 100.00 11. Asp+Dip vs. Asp ACCSG 1985 1.02 (0.74, 1.40) 0.90 (0.52, 1.57) 0.81 (0.66, 0.99) 0.74 (0.61, 0.90) 1.18 (0.82, 1.70) 0.87 (0.74, 1.03) 96/442 30/198 239/1376 266/1649 58/639 689/4304 99/448 28/202 198/1363 206/1650 17.89 7.47 29.42 30.64 14.58 100.00 AICLA 1983 ESPRIT 2006 ESPS2 1996 JASAP 2011 69/655 600/4318 Subtotal (I-squared = 38.2%, p = 0.167) 12. Asp+Dip vs. Clop PRoFESS 2008 1.00 (0.93, 1.08) 1637/1018 1630/10151 100.00 13. Asp+Dip vs. Dip ESPS2 1996 0.73 (0.60, 0.89) 1.04 (0.50, 2.13) 0.75 (0.62, 0.90) 206/1650 271/1654 93.16 Matias-Guiu 1987 Subtotal (I-squared = 0.0%, p = 0.354) 25/115 231/1765 15/71 286/1725 6.84 100.00 0 14. Asp+Tic vs. Tic TOPALS 2003 0.97 (0.44, 2.14) 13/132 14/138 100.00 Favors Therapy-1 Favors Therapy-2 1 20 05 10

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

12

1. Clo vs. Ang CASISP 2006 CASISP 2006 Subtotal (1-squared = 0.0%, p = 0.942) 2. Sarp vs. Agp S-ACCESS 2009 3. Teru vs. Agp PERFORM 2011 4. Tc vs. Agp PERFORM 2011 5. Tc vs. Clop Fukuadi 2007 5. Tc vs. Clop Fukuadi 2007 5. Tc vs. Clop 5. Tc vs. Clop Fukuadi 2007 7. Agp-Clop vs. Glop ALT vs. Agp CASISP 2008 5. Tc vs. Clop TAPIRS 2004 5. Tc vs. Clop TAPIRS 2005 5. Tc vs. Clop TAPIRS 2004 5. Tc vs. Clop TAPIRS 2004 5. Tc vs. Clop TAPIRS 2005 5. Tc vs. Clop TAPIRS 2004 5. Tc vs. Clop TAPIRS 2005 5. To vs. Clop TAPIRS 2005 5. Tr vs. Clop TAPIRS 2005 5. Tr vs. Clop TAPIRS 2005 5. Tr vs. Clop TAPIRS 2005 5. Tr vs. Tc Tc Tr vs. Tc Tc TCPALS 2005 5. Tr vs. Tc Tc Tc Tc Tc Tc Tc Tc TCPA	Study						OR (95% CI)	Therapy-1 Events/Total	Therapy-2 Events/Total	Weight%
CASISP 22010 CASISP 22010 Gar 22009 Subtol (1-squared = 0.0%, p = 0.942) 2. Sarp vs. Asp S-ACCESS 2008 3. Teru vs. Asp PERFORM 2011 4. Tic vs. Asp PERFORM 2011 4. Tic vs. Asp PERFORM 2017 4. Tic vs. Asp PERFORM 2017 4. Tic vs. Asp PERFORM 2017 4. Tic vs. Asp PERFORM 2017 5. Tic vs. Cop Fukuchi 2007 5. Tic vs. Cop Fukuchi 2007 5. Tic vs. Cop Fukuchi 2007 5. Tic vs. Cop Charles Asp Subtol (1-squared = 0.0%, p = 0.886) 5. Tic vs. Cop Fukuchi 2007 5. Tic vs. Cop Charles Asp Charles Asp Face State Asp Fukuchi 2007 5. Tic vs. Cop Fukuchi 2007 6. Tif vs. Asp TACIP 2003 TACIP 2003	1. Cilo vs. Asp									
CSP82 2010 0.29 (0.1, 0.29) 0.29 (0.1, 0.29) 0.24 (0.1, 0.28) 0.24 (0.1, 0.28) 0.24 (0.1, 0.28) 0.24 (0.1, 0.28) 0.24 (0.1, 0.28) 0.24 (0.1, 0.28) 0.24 (0.1, 0.28) 0.28 (0.28, 1.18) 1.10 (0.28, 2.48) 1.10 (0.28, 2.48) 1.10 (0.28, 2.48) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.11 (0.28) 1.21 (0	CASISP 2008			<u> </u>			0.20 (0.02, 1.70)	1/360	5/359	11.35
Subbola 0.32 (201) 8.23 (034) 104 5.02 (201) 8.23 (034) 104 5.02 (201) 8.23 (034) 104 5.02 (201) 8.23 (034) 104 5.02 (201) 8.23 (034) 104 5.02 (201) 8.23 (034) 104 5.02 (201) 8.23 (034) 104 5.02 (201) 8.23 (034) 104 5.02 (201) 8.23	CSPS2 2010						0.29 (0.13, 0.64)	8/1337	27/1335	83.64
Subtratil (-squared = 0.0%, p = 0.942) 0.28 (0.14, 0.58) 9/750 12/757 100.00 2. Sary vs. Asp 0.75 (0.32, 1.80) 9/750 12/757 100.00 3. Teru vs. Asp 1.21 (0.95, 1.54) 146/9479 12/18465 100.00 4. Tic vs. Asp 1.851 (0.42, 5.45) 6/165 4/164 34.26 1.00 (0.35, 2.80) 7/1529 7/1540 51.24 1.21 (0.95, 1.54) 146/9479 12/18465 100.00 4. Tic vs. Asp 1.51 (0.42, 5.45) 6/165 4/164 34.26 1.00 (0.35, 2.80) 7/1529 7/1540 51.24 1.450 Subtoal (I-squared = 0.0%, p = 0.880) 1.17 (0.55, 2.47) 19/1830 13/1849 100.00 6. Tit vs. Asp 1.450 1.241 1.26 1.35 10/1052 86.49 CHARISMA 2011 1.17 (0.55, 2.67) 10/1052 86.49 1.416 34.26 1.000 8. Asp-Clop vs. Clop 1.19 (0.53, 2.85) 1.12/183 40.20 1.36 (0.18, 2.24) 59.90 1.34 (0.18, 2.24) 59.90 1.34 (0.18, 2.24) 59.90 1.34 (0.18, 2.24) 59.93 1.34 (0.1	Guo 2009						0.32 (0.01 8.23)	0/34	1/34	5.02
2. Sarp vs. Asp S-ACCESS 2008 0.75 (0.32, 1.80) 9/750 12/757 100.00 3. Teru vs. Asp PERFORM 2011 4. Tic vs. Asp Hass 1898 1. 21 (0.95, 1.54) 146/9479 121/9465 100.00 4. Tic vs. Asp Hass 1898 1. 2000 5. Tic vs. Clop FukuedN 2007 6. Trl vs. Asp TACIP 2003 5. Tic vs. Clop FukuedN 2007 0. 25 (0.03, 2.21) 1578 0. 11/052 0. 41 (0.25, 148) 01209 1. 11/052 0. 41 (0.25, 248) 121/158 1. 11/052 0. 41 (0.25, 148) 01209 1. 46 (0.75, 248) 121/158 1. 2006 1. 46 (0.75, 248) 121/158 1. 2006 1. 46 (0.75, 248) 121/158 1. 2007 1. 46 (0.75, 248) 121/158 1. 2008 0. 40 (0.09, 2.69) 2/448 0. 40 (0.08, 1.17) 121/032 1. 40 (0.25, 111/58) 2/132 0. 138 100.00 1. Asp-Clo vs. Clop PROFESS 2008 1. 4. 1 1. 4. 1 1. 4. 147/10181 1. 00.00 1. Asp-Clo vs. Clop PROFESS 2008 1. 4. 1 1. 2 1 1 2 1 1 2 1 1 2 1 1 2 1 1 2 1 1 1 2 1 1 1 2 1 1 1 2 1 1 1 1 2 1 1 1 2 1 1 1 1 2 1	Subtotal (I-squared = 0.0%, p = 0.942)	<	>				0.28 (0.14, 0.58)	9/1731	33/1728	100.00
2. Sarp vs. Asp S-ACCES 2008 0.75 (0.32, 1.80) 9750 12757 100.00 3. Teru vs. Asp PERFORM 2011 4. Tic vs. Asp Has 1880 1.21 (0.95, 1.54) 1469479 121/9466 100.00 4. Tic vs. Asp Has 1880 1.01 (0.52, 2.89) 71529 71/540 51.24 1.51 (0.42, 548) 6165 41/164 54.25 1.07 (0.52, 647) 121/9406 100.00 5. Tic vs. Clop Fukuuchi 2007 0.25 (0.03, 2.21) 1/578 4573 100.00 6. Tif vs. Asp TACIP 2003 7. Asp-Clop vs. Clop MATCH 2004 9. Asp-Clop vs. Clop MATCH 2004 9. Asp-Clop vs. Clop MATCH 2004 1. Asp+Tic vs. Tic TOPALS 2003 1. Asp+Tic vs. Tic TOPALS										
S. ACCESS 2008 0.75 (0.32, 1.80) 9750 12757 100.00 3. Teru vs. Asp PERFORM 2011 1.21 (0.95, 1.54) 146/9479 121/9468 100.00 4. Tic vs. Asp PERFORM 2011 1.21 (0.95, 1.54) 146/9479 121/9468 100.00 4. Tic vs. Asp 1.01 (0.35, 2.88) 7/1529 7/1540 51.24 1.12 (0.95, 1.54) 146/9479 121/9468 100.00 5. Tic vs. Clop Pukusufi 2007 0.25 (0.03, 2.21) 1/578 4/573 100.00 5. Tic vs. Clop Pukusufi 2007 0.25 (0.03, 2.21) 1/578 4/573 100.00 6. Tid vs. Asp TAPIR5S 2004 0.55, p = 0.886) 5. Tic vs. Clop Pukusufi 2007 0.25 (0.03, 2.21) 1/578 4/573 100.00 6. Tid vs. Asp CHARJSMA 2011 SPS3 2012 0.55, p = 0.696) 8. Asp-Clop vs. Asp ACCS3 (1965 A.260) 12/157 11/1052 86.49 1.19 (0.53, 2.65) 132/157 11/12/163 40.20 1.46 (0.75, 2.69) 22/157 11/2168 100.00 8. Asp-Clop vs. Clop MATCH 2004 1.62 (0.98, 2.67) 403759 25/3781 100.00 1. Asp-Dip vs. Asp ACCS3 (1965 A.260) 2/448 4/442 8.33 ACCS3 (1965 A.210) 2/136 100.00 1. Asp-Dip vs. Asp ACCS3 (1965 A.210) 2/136 10.00 1. Asp-Dip vs. Clop PROFESS 2008 1.43 (1.11, 1.84) 147/10181 103/10151 100.00 1. Asp-Tic vs. Tic TOPALS 2003 5.31 (0.25, 111.59) 2/132 0/138 100.00 1. Asp-Tic vs. Tic TOPALS 2003 5.31 (0.25, 111.59) 2/132 0/138 100.00	2. Sarp vs. Asp									
3. Teru vs. Asp PERFORM 2011 1.21 (0.95, 1.54) 146/9479 121/9466 100.00 4. Tic vs. Asp Hass 1989 1.01 (0.35, 2.89) 7/1520 7/1540 51.24 12 2000 1.51 (0.42, 5.45) 6/165 14/64 34.28 10 (0.35, 2.89) 7/1520 7/1540 51.24 11 (0.55, 2.47) 15/1802 13/1849 100.00 5. Tic vs. Clop 0.25 (0.03, 2.21) 15/78 4/573 100.00 6. Tif vs. Asp 0.63 (0.24, 164) 7/1055 11/1052 86.49 7ACIP 2003 7ADIP 2003 11/1055 11/1052 86.49 7ADIP 2003 1.12 (0.55, 2.47) 15/1830 13/1849 100.00 8. Apr-Clop vs. Asp 0.63 (0.24, 164) 7/1055 11/1052 86.49 CHARISMA 2011 1.19 (0.53, 2.65) 13/2167 11/2168 40.20 Stabtoal (I-squared = 0.0%, p = 0.696) 8.49 20.20 1.46 (0.75, 2.82) 22/157 11/2163 40.20 Stabtoal (I-squared = 0.0%, p = 0.696) 8.49 20.20 1.46 (0.75, 2.82) 22/157 11/2163 40.20 Stabtoal (I-squar	S-ACCESS 2008		-				0.75 (0.32, 1.80)	9/750	12/757	100.00
PERFORM 2011 1.21 (0.95, 1.54) 148/9479 121/9465 100.00 4. Tic vs. Asp Hass 1989 1.01 (0.35, 2.88) 7/1529 7/1540 51.24 1.2000 1.01 (0.35, 2.88) 7/1529 7/1540 51.24 5. To vs. Clop 0.25 (0.03, 2.21) 1/578 4/573 100.00 6. Trif vs. Asp TACIP 2003 0.53 (0.24, 1.54) 7/1529 11/1052 86.49 7. Asp-Clop vs. Clop 0.25 (0.03, 2.21) 1/578 4/573 100.00 6. Trif vs. Asp TACIP 2003 0.63 (0.24, 1.54) 7/1052 11/1052 86.49 1.021 (0.25, 2.47) 15/180 1/1052 86.49 1/100.00 1/1002 86.49 1.021 (0.25, 1.48) 8/1299 1/1052 86.49 1/1000 1/1002 86.49 7. Asp-Clop vs. Asp CHARISMA 2011 1.19 (0.52, 2.55) 1/12/151 1/1052 85.80 1/12/151 1/1002 86.49 8. Asp-Clop vs. Clop 1.48 (0.75, 2.82) 2/2/157 1/15/53 5/3.80 1/12/151 1/10.000 9. Asp-Dlop vs. Asp ACCA 1983 0.49 (0.09, 2.69) 2/448 4/442 8.33 1/2/	3. Teru vs. Asp									
4. Tic vs. Asp Hass 1989 1.01 (0.35, 2.88) 7/1529 7/1540 51.24 12 2000 1.51 (0.42, 5.45) 6/164 34.26 Subtolal (I-squared = 0.0%, p = 0.888) 1.07 (0.15, 7.88) 2/135 1.41 45.0 S. Tić vs. Cóp Fukuuchi 2007 0.25 (0.03, 2.21) 1/578 4/573 100.00 6. Trif vs. Asp TACIP 2003 0.63 (0.24, 1.64) 7/1055 11/1052 86.49 7. Asp + Clop vs. Asp CHARISMA 2011 0.59 (0.05, 5.58) 12/14 2/216 13.51 Subtolal (I-squared = 0.0%, p = 0.862) 0.61 (0.25, 1.48) 8/1269 13/1268 100.00 8. Asp-Clop vs. Asp CHARISMA 2011 SPS3 2012 0.63 (0.24, 1.64) 7/1055 11/1052 86.49 9. Subtolal (I-squared = 0.0%, p = 0.696) 1.49 (0.57, 2.68) 13/2157 11/2163 40.20 SPS3 2012 0.49 (0.09, 2.69) 244.8 4/442 8.33 ACICA 1983 0.49 (0.09, 2.69) 24/48 4/442 8.33 ACICA 1983 0.49 (0.045, 1.42) 10.00 1.43 (1.11, 1.84) 147/10181 103/10151 100.00 9. Asp+Dip vs. Clop PRoFESS 2008 1.42 (1.12 1.4	PERFORM 2011			•			1.21 (0.95, 1.54)	146/9479	121/9466	100.00
Has 1989 Li 2000 Tobji 1987 Subtolal (I-squared = 0.0%, p = 0.888) 5. To v. Clop Fukuuchi 2007 0.25 (0.03, 2.21) 1/578 4/573 100.00 6. Tif vs. Asp TACIP 2003 T.Asp+Clop vs. Asp CHARISMA 2011 System 4 = 0.0%, p = 0.665) Subtolal (I-squared = 0.0%, p = 0.666) 8. Asp+Clop vs. Clop MATCH 2004 9. Asp+Dip vs. Clop PRoFESS 2016 Subtolal (I-squared = 0.0%, p = 0.740) 1. Asp+Dip vs. Clop PROFESS 2008 1. Asp+Clop vs. Clop MATCH 2004 1. Start 2. Asp Clop S. 2479 1. Start 2. Asp Clop S. 2470 1. Start 2. Asp Clop S. 2480 1. Start 2. Asp Clop S. 2470 1. Start 2. Asp Clop S. 2480 1. Start 2. Asp Clop S. 2480 1. Start 2. Asp Clop S. 2470 1. Start 2. Asp Clop S. 2470 1. Start 2. Asp Clop S. 2470 1. Start 2. Asp Clop S. 2480 1. Start 2. Asp Clop S. 2470 1. Start 2. Asp Clop S. 2480 1. Start 2. Asp Clop S. 2448 1. Start 2. As	4. Tic vs. Asp									
Li 2000 Tohgi 1987 Subtolal (I-squared = 0.0%, p = 0.888) 5. Tic vs. Clop Fukuuchi 2007 6. Trif vs. Asp TACIP 2003 TACIP 2003 7. Asp-Clop vs. Asp CHARISMA 2011 Systemat = 0.0%, p = 0.862) 7. Asp-Clop vs. Asp CHARISMA 2011 9. Asp-Clop vs. Clop MATCH 2004 9. Asp-Clop vs. Clop MATCH 2004 9. Asp-Clop vs. Clop MATCH 2004 9. Asp-Clop vs. Asp ACCSG 1985 ACCSG 1985 ACCCSG 1985 ACCSG 1	Hass 1989			•			1.01 (0.35, 2.88)	7/1529	7/1540	51.24
Tobji 1987 1.07 (0.15, 7.68) 2/136 2/145 14.50 Subtotal (I-squared = 0.0%, p = 0.888) 1.17 (0.55, 2.47) 15/1830 13/1849 100.00 5. Tic vs. Clop 0.25 (0.03, 2.21) 15/78 4/573 100.00 6. Tif vs. Asp 0.53 (0.24, 1.64) 7/1055 11/1052 86.49 7APIRSS 2004 0.63 (0.24, 1.64) 7/1055 11/1052 86.49 0.50 (0.05, 5.58) 1/214 2/216 13.51 Subtotal (I-squared = 0.0%, p = 0.862) 0.61 (0.25, 1.48) 8/1269 13/1268 100.00 7. Asp+Clop vs. Asp 1.19 (0.53, 2.65) 13/2157 11/2163 40.20 Subtotal (I-squared = 0.0%, p = 0.696) 1.34 (0.81, 2.24) 35/3674 26/3666 100.00 8. Asp-Clop vs. Asp 1.34 (0.81, 2.24) 35/3674 26/3666 100.00 9. Asp+Dip vs. Asp 0.49 (0.09, 2.69) 2/448 4/442 8.33 AICLS 1985 0.49 (0.09, 2.69) 2/448 4/442 8.33 AICLA 1983 ESPRIT 2006 0.57 (0.28, 1.17) 12/1363 4/0.42 8.33 Subtotal (I-squared = 0.0%, p	Li 2000			•	_		1.51 (0.42, 5.45)	6/165	4/164	34.26
Subtotal (I-squared = 0.0%, p = 0.888) 5. Tic vs. Clop Fukuuchi 2007 6. Tif vs. Asp TACIP 2003 7. Asp+Clop vs. Asp OLARISMA 2011 9. Asp+Clop vs. Clop MATCH 2004 9. Asp+Clop vs. Clop MATCH 2004 9. Asp+Clop vs. Clop MATCH 2004 9. Asp+Dip vs. Asp ACCCSG 1985 ACCCSG	Tohgi 1987						1.07 (0.15, 7.68)	2/136	2/145	14.50
5. Tic vs. Clop Fukuuchi 2007 0.25 (0.03, 2.21) 1/578 4/573 100.00 6. Tifl vs. Asp TAPIRSS 2004 0.63 (0.24, 1.64) 7/1055 11/1052 86.49 0.50 (0.05, 5.58) 11/214 2216 13.51 0.61 (0.25, 1.48) 8/1289 13/1268 100.00 7. Asp+Clop vs. Asp CHARISMA 2011 SpS3 2012 Subtotal (I-squared = 0.0%, p = 0.896) 8. Asp+Clop vs. Clop MATCH 2004 9. Asp+Dip vs. Asp ACCSG 1985 AICLA 1983 ESPRIT 2006 J. Asp 2011 Subtotal (I-squared = 0.0%, p = 0.740) 10. Asp+Dip vs. Asp ACCSG 1985 AICLA 1983 ESPRIT 2006 J. Asp+Clop vs. Clop MATCH 2004 1.62 (0.98, 2.67) 40/3759 25/3781 100.00 1.62 (0.98, 2.67) 40/3759 25/3781 100.00 1.63 (0.45, 2.12) 13/655 13/839 40.04 0.76 (0.43, 1.14) 28/2688 40/2655 100.00 11. Asp+Tic vs. Tic TOPALS 2003 TAPIREAD. TOPALS 2003 TAPICAL TO 20	Subtotal (I-squared = 0.0%, p = 0.888)		<	>			1.17 (0.55, 2.47)	15/1830	13/1849	100.00
Fukuuchi 2007 0.25 (0.03, 2.21) 1/578 4/573 100.00 6. Tifi vs. Asp TACIP 2003 0.63 (0.24, 1.64) 7/1055 11/1052 86.49 TAPIRSS 2004 0.63 (0.24, 1.64) 7/1055 11/1052 86.49 Subtotal (I-squared = 0.0%, p = 0.862) 0.61 (0.25, 1.48) 8/1269 13/1268 100.00 7. Asp+Clop vs. Asp CHARISMA 2011 1.19 (0.53, 2.65) 13/2157 11/2163 40.20 SPS3 2012 3.34 (0.61, 2.24) 3/3/3674 26/3666 100.00 8. Asp+Clop vs. Clop MATCH 2004 1.62 (0.98, 2.67) 40/3759 25/3781 100.00 9. Asp+Dip vs. Asp ACCSG 1985 0.49 (0.09, 2.69) 2/448 4/442 8.33 AICLA 1983 0.49 (0.09, 2.69) 2/448 4/042 8.33 Subtotal (I-squared = 0.0%, p = 0.740) 0.57 (0.28, 1.17) 12/1363 2/11/376 47.47 JASAP 2011 0.49 (0.09, 2.69) 2/448 4/02655 100.00 10. Asp-Dip vs. Clop PRoFESS 2008 1.43 (1.11, 1.84) 147/10181 103/10151 100.00 11. Asp+Tic vs. Tic TOPALS 2003 5.31 (0.25, 111.58) 2/132 0/138 100.00	5. Tic vs. Clop									
6. Trif vs. Asp TACIP 2003 TAPIRSS 2004 Subtotal (1-squared = 0.0%, p = 0.862) 7. Asp+Clop vs. Asp CHARISMA 2011 SPS3 2012 Subtotal (1-squared = 0.0%, p = 0.696) 8. Asp+Clop vs. Clop MATCH 2004 9. Asp+Dip vs. Asp ACCSG 1985 AICLA 1983 AICLA 1983 AICLA 1983 AICLA 1983 D. Asp 2011 Subtotal (1-squared = 0.0%, p = 0.740) 10. Asp+Dip vs. Clop MATCH 2004 1. Asp+Tic vs. Tic TOPALS 2003 TOPALS 2003 TOPALS 2003 TAPIRSS 2004 0. 53 (0.24, 1.64) 7/1055 13/1248 12/157 11/2163 0.63 (0.24, 1.64) 7/1055 13/2157 11/2163 0.63 (0.24, 1.64) 7/1055 13/2157 11/2163 0.63 (0.25, 1.48) 8/1299 13/1288 100.00 1.34 (0.81, 2.24) 3/53674 2/6366 100.00 1.34 (0.81, 2.24) 3/53674 2/138 4.16 0.57 (0.28, 1.17) 2/138 4.16 0.57 (0.28, 1.17) 12/1365 13/369 4.004 0.70 (0.43, 1.14) 2/132 1.1 1.1 1.1 1.1 1.2 1.1 1.1 1.	Fukuuchi 2007 —	•					0.25 (0.03, 2.21)	1/578	4/573	100.00
TACIP 2003 0.63 (0.24, 1.64) 7/1055 11/1052 86.49 Subtotal (I-squared = 0.0%, p = 0.862) 0.50 (0.05, 5.58) 1/214 2/216 13.51 7. Asp+Clop vs. Asp CHARISMA 2011 1.19 (0.53, 2.65) 13/2157 11/163 40.20 SPS3 2012 1.46 (0.75, 2.82) 22/1517 15/1503 59.80 Subtotal (I-squared = 0.0%, p = 0.696) 1.34 (0.81, 2.24) 35/3674 28/3666 100.00 8. Asp+Clop vs. Asp ACCSG 1985 0.49 (0.09, 2.69) 2/448 4/442 8.33 ACCSG 1985 0.49 (0.09, 2.69) 2/148 4/442 8.33 ACCSG 1985 0.49 (0.04, 5.42) 1/2/1363 21/1376 47.47 JASAP 2011 0.57 (0.28, 1.17) 12/1363 21/1376 47.47 Subtotal (I-squared = 0.0%, p = 0.740) 0.70 (0.43, 1.14) 28/2688 40/2655 100.00 10. Asp+Dip vs. Clop 1.43 (1.11, 1.84) 147/10181 103/10151 100.00 11. Asp+Tic vs. Tic 70PALS 2003 5.31 (0.25, 111.58) 2/132 0/138 100.00 11. Asp+Tic vs. Tic 1 1 1 1 1	6. Trif vs. Asp									
TAPIRSS 2004 0.50 (0.05, 5.58) 1/214 2/216 13.51 Subtotal (I-squared = 0.0%, p = 0.862) 0.61 (0.25, 1.48) 8/1269 13/1268 100.00 7. Asp+Clop vs. Asp 1.19 (0.53, 2.65) 13/2157 11/2163 40.20 SPS3 2012 1.46 (0.75, 2.82) 22/1517 15/1503 59.80 Subtotal (I-squared = 0.0%, p = 0.696) 1.34 (0.81, 2.24) 35/3674 26/3666 100.00 8. Asp+Clop vs. Clop 1.62 (0.98, 2.67) 40/3759 25/3781 100.00 9. Asp+Dip vs. Asp 0.49 (0.09, 2.69) 2/448 4/442 8.33 ACCSG 1985 0.49 (0.09, 2.69) 2/448 4/442 8.33 ACCSG 1985 0.49 (0.04, 5.42) 1/2/365 13/639 40.04 Subtotal (I-squared = 0.0%, p = 0.740) 0.57 (0.28, 1.17) 1/2/383 21/1376 47.47 JASAP 2011 0.50 (0.25, 111.58) 2/132 0/138 100.00 10. Asp+Dip vs. Clop 1.43 (1.11, 1.84) 147/10181 103/10151 100.00 11. Asp+Tic vs. Tic Tic Tic Tic Tic Tic Tic Tic	TACIP 2003	-		<u> </u>			0.63 (0.24, 1.64)	7/1055	11/1052	86.49
Subtotal (I-squared = 0.0%, p = 0.862) 7. Asp+Clop vs. Asp CHARISMA 2011 SPS3 2012 Subtotal (I-squared = 0.0%, p = 0.696) 8. Asp+Clop vs. Clop MATCH 2004 9. Asp +Clop vs. Clop MATCH 2004 9. Asp +Dip vs. Asp ACCSG 1985 ACCSG 198	TAPIRSS 2004		•		_		0.50 (0.05, 5.58)	1/214	2/216	13.51
7. Asp+Clop vs. Asp CHARISMA 2011 1.19 (0.53, 2.65) 13/2157 11/2163 40.20 SPS3 2012 1.46 (0.75, 2.82) 22/1517 11/2163 40.20 Subtotal (I-squared = 0.0%, p = 0.696) 1.34 (0.81, 2.24) 35/3674 26/3666 100.00 8. Asp+Clop vs. Clop MATCH 2004 1.62 (0.98, 2.67) 40/3759 25/3781 100.00 9. Asp+Dip vs. Asp ACCSG 1985 0.49 (0.09, 2.69) 2/448 4/442 8.33 AICLA 1983 0.49 (0.04, 5.42) 1/2105 1/3639 40/04 Subtotal (I-squared = 0.0%, p = 0.740) 0.57 (0.28, 1.17) 1/1365 1/13639 40/04 Subtotal (I-squared = 0.0%, p = 0.740) 0.70 (0.43, 1.14) 28/2668 40/2655 100.00 10. Asp+Dip vs. Clop PRoFESS 2008 1.43 (1.11, 1.84) 147/10181 103/10151 100.00 11. Asp+Tic vs. Tic TOPALS 2003 5.31 (0.25, 111.58) 2/132 0/138 100.00	Subtotal (I-squared = 0.0%, p = 0.862)		$\langle \rangle$	>			0.61 (0.25, 1.48)	8/1269	13/1268	100.00
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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% Cls. Asp indicates aspirin; Cl, 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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