J Neurol (2016) 263:2247–2259
DOI 10.1007/s00415-016-8260-7

ORIGINAL COMMUNICATION

Efficacy and safety of short-term dual- versus mono-antiplatelet therapy in patients with ischemic stroke or TIA: a meta-analysis of 10 randomized controlled trials

Yang Liu[1] · Zhaoxia Fei[2] · Wei Wang[1] · Jingxue Fang[1] · Meijuan Zou[1] · Gang Cheng[1]

Received: 17 July 2016 / Revised: 5 August 2016 / Accepted: 5 August 2016 / Published online: 19 August 2016

Abstract Stroke is still a primary disease for death and disability all over the world. The optimal antiplatelet therapy for treatment of stroke is under controversy. We performed a meta-analysis to justify whether short-term (≤1 year) dual-antiplatelet therapy (DAPT) has advantages over mono-antiplatelet therapy. We systematically searched the databases of Cochrane library, Pubmed and Embase up to July 2016. Randomized controlled trials (RCTs) comparing DAPT with mono-antiplatelet therapy were included in our meta-analysis. Totally ten trials involving 8969 patients were satisfied with our inclusion criteria. At the end of follow-up, DAPT is associated with a significant reduction in recurrent stroke [risk ratio (RR) 0.65, 95 % confidence interval (CI) 0.56–0.76, $P < 0.00001$] and the net clinical outcome (ischemic stroke (IS) recurrence plus major bleeding) (RR 0.67, 95 % CI 0.58–0.79, $P < 0.00001$). In terms of safety outcomes of major bleeding (RR 1.44, 95 % CI 0.72–2.88, $P = 0.30$) and intracranial hemorrhage (RR 1.29, 95 % CI 0.56–2.93, $P = 0.55$), DAPT has a homologous safety profile compared with mono-antiplatelet therapy. The subgroup analysis according to different races, antiplatelet combinations or initiation time produced similar outcomes as comprehensive outcomes. Given short-term treatment regimen, DAPT can be superior to mono-antiplatelet therapy in treating IS or transient ischemic attack (TIA). No matter in acute or non-acute phase of IS, short-term DAPT has more efficacy than mono-antiplatelet therapy and has equivalent safety as mono-antiplatelet therapy.

Keywords Stroke · Transient ischemic attack · Antiplatelet agents · Short term · Meta-analysis

Introduction

Stroke is a major global health issue, and it is a leading cause for mortality and adult disability [1–4]. In China, up to 1.6 million people were dead for stroke every year [5], which is a huge burden for society and patients' family. IS accounts for about 70 % of total stroke patients [6]; recurrent stroke and stroke deterioration often come in the acute phase of IS occurrence. Without proper treatment, the probability of a recurrent stroke after the first stroke is about 3–10 % in the first month and about 5–14 % in the first year [7, 8]. Antithrombotic therapy can effectively prevent recurrence stroke or stroke deterioration, which significantly improves the prognosis of stroke patients.

Aspirin is a mainstay for antithrombotic therapy, two large RCTs of aspirin in acute IS reported that aspirin reduced the odds of early recurrent stroke by about 12 % [odds ratio (OR) 0.88, 95 % CI 0.79–0.97] and the odds of death or dependency at the end of follow-up by about 5 % (OR 0.95, 0.91–0.99) [9]. In the medication guideline of myocardial infraction (MI) published in June 2016 [10], dual-antiplatelet regimen is strongly recommended for MI patients or patients after percutaneous coronary intervention (PCI). Different types of antiplatelet drugs have distinct antithrombotic mechanisms; combination of these may strengthen antithrombotic effect and further improve the treatment of IS. Stroke has a similar formation

✉ Gang Cheng
chenggang63@hotmail.com

[1] Shenyang Pharmaceutical University, 103 Wenhua Road, Shenhe District, Shenyang 110016, Liaoning Province, China

[2] Department of Neurology, General Hospital of Shenyang Military Area, 83 Wenhua Road, Shenhe District, Shenyang 110016, Liaoning Province, China

mechanism to MI, it is reasonable and proper to hypothesize that DAPT would bring more benefits than mono-antiplatelet therapy in treating IS.

There are many trials [11–20] and meta-analyses [21–23] conducted to investigate the efficacy and safety of dual-antiplatelet therapy. FASTER [16] is a randomized controlled trial comparing the effect and safety of dual-antiplatelet therapy in treating stroke or TIA; their outcomes showed that DAPT is not superior to monotherapy in treating IS or TIA. A few meta-analyses [21, 22] were conducted in recent years, but they did not focus on short-term regimen and they only included the combination of aspirin and clopidogrel. Both analyses indicated that short-term dual therapy is better than monotherapy, but they also suspected that beneficial outcomes may be related to timely treatment initiation time. A meta-analysis [23] also showed that the acute phase is critical for treatment of stroke patients. Our meta-analysis aims to further justify the efficacy and safety of comprehensive DAPT in treating stroke patients and test if the beneficial outcomes associated with initiation treatment time.

This meta-analysis complied with preferred reporting items for systematic review and meta-analysis (PRISMA) [24] and was registered in PROSPERO website (CRD42016033680).

Methods

Data source and searching

We made a systematic search in databases of Pubmed, Embase and Cochrane library through July 2016, using the following medical subject heading (MeSH) and free-text terms: stroke, cerebral infraction, cerebrovascular disease, TIA, aspirin, clopidogrel, cilostazol, dipyridamole, tirofiban, ticlopidine, triflusal, terutrobran, aspirin and clopidogrel, aspirin and dipyridamole, aspirin and cilostazol, aspirin and ticagrelor, aspirin and ticlopidine, aspirin and triflusal, aspirin and terutobran, dual-antiplatelet, mono-antiplatelet. No other search restrictions were applied. To find out newly developed clinical trials, we searched the clinicaltrials.gov. Finally, we also searched references of former meta-analyses and trials for additional trials which were not identified in databases.

Study selection

Two researchers (Y. L. and Zx. F.) independently selected eligible studies which are included in our meta-analysis. If there exists a disagreement, they would resolve it by consulting another researcher (Jx. F.). Inclusion criteria were listed as following: (1) randomized controlled trials; (2) DAPT versus monotherapy in any doses were assessed; (3) treatment duration is no more than 1 year; (4) patients involved were with a clinical diagnosis of IS or TIA; (5) sufficient data for outcomes were provided. Papers were excluded if they are (1) non-RCTs; (2) papers only with abstract; (3) anticoagulant drugs, like warfarin, were also tested in the trial; (4) case report; (5) retrospective studies. If several papers have published about one trial, the paper which contains more detailed information needed was included in our meta-analysis.

Data extraction

We abstracted the information in included studies from three aspects: the baseline characteristics of included trials, the baseline characteristics of participants, and the basic outcomes. Two researchers (W. W. and Mj. Z.) independently abstracted the needed information, if there exists a disagreement, they will reach a consensus by discussing with other researchers (G. C., Y. L. and Jx. F.). We collected the following information in each trial: trial name, country, sample size, blinding, treatment group and dosage, intention to treatment (ITT) analysis, DAPT treatment duration, follow-up, mean age, gender percentage, hypertension and diabetes mellitus (DM) percentage, patients disease, treatment initiation time, and loss to follow-up. We also abstracted following trials' outcomes: recurrent stroke, the net clinical outcome, IS recurrence, TIA, composite outcome of major vascular events, bleeding episodes, major bleeding, and intracranial hemorrhage. The information on major bleeding and intracranial hemorrhage was collected according to the definition in each study. We counted Jadad score of trials to make a primary assessment of each trial. Composite outcome of major vascular events include myocardial infraction, stroke and vascular death. If included studies did not report the composite outcome of major vascular events while gave the separated information on myocardial infraction, stroke and vascular death, we will add these figures together to calculate this outcome.

Based on the Cochrane collaboration tool for assessing risk, we abstracted following information to further assess the quality of included studies: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other forms of bias. Authors of these included studies were not contacted for additional information.

Quality assessment

With Cochrane collaboration tools, we assessed bias of included studies in following seven aspects: random sequence generation, allocation concealment, blinding of

participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other forms of bias. For the limitation of sample size, we assessed the publication bias by visual funnel plot without conducting the Egger's or Begg's test. Finally, we made recommendation ranks of studied outcomes by Grading of Recommendations Assessment, Development, and Evaluation (GRADE) systems. Two authors (Y. L. and Zx. F.) independently carried out the risk of bias assessment and quality assessment of evidence, and any differences were resolved by discussion.

Statistical analysis

The primary efficacy outcomes are recurrent stroke and the net clinical outcomes, and the main safety indexes are major bleeding and intracranial hemorrhage. We made subgroup analysis according to races, treatment initiation time and different combinations of DAPT.

RR of all outcomes was calculated with 95 % CI. Two-tailed $P < 0.05$ was considered statistically significant. Heterogeneity was assessed by Cochrane's Chi-square test, $P < 0.10$ and $I^2 > 50\ \%$ was considered significant heterogeneity. Pooled analyses were conducted using a fixed-effects model, whereas a random-effects model was applied if there was heterogeneity ($P < 0.10$ and $I^2 > 50\ \%$). All the analyses were conducted by Revman5.2 software (Nordic Cochrane Centre, Cochrane Collaboration, 2013) and sensitivity analysis was conducted by Stata 11.0 (Stata Corp, College Station, TX, USA). With STATA software, we tested the robustness of primary outcome by omitting the included studies once a time.

Results

Search results

We identified 3581 potentially eligible records and included 10 studies that met our inclusion criteria. The selected procedure is shown in Fig. 1. There are totally 8969 patients involved in our meta-analysis: 4481 patients were randomized to DAPT (experimental group) and 4488 patients were randomized to monotherapy (control group). The characteristics of the included trials are described in Tables 1 and 2. All trials were published between 2005 and 2014. Five [11–13, 16, 20] of ten trials are double-blind design, four trials [14, 17–19] were open-label design but they were blindly assessed. All trials but two [18, 19] are ITT analysis. DAPT treatment duration ranges from 7 days to 6 months, and the onset-to-treatment interval ranges from 24 h to 3 months. Among ten trials, seven trials

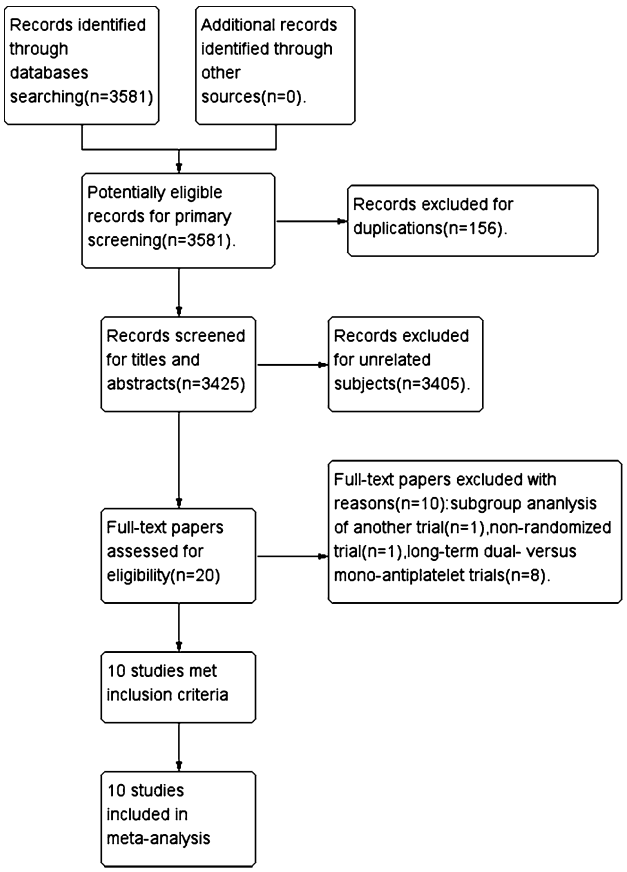

Fig. 1 Flowchart illustrating the process used to select the studies included in this meta-analysis

[11–17] were allocated to receive aspirin and clopidogrel; the other three trials [18–20] were allocated to aspirin and dipyridamole. The bias assessment of all ten trials is detailed in Fig. 2.

Risk of bias in included studies, and quality of evidence

Eight studies [11, 13–18, 20] explicitly described the random sequence generation, mainly by a computer random number generator, a random number table, choosing marked ball, or an interactive voice response system. Eight studies [11, 13–18, 20] all used unpredicted methods to generate random sequence which stated a low risk of allocation concealment process, and two studies [12, 19] which lack random sequence generation method were regarded as having an unclear risk of bias in this domain. There are five trials [11–13, 16, 20] having double-blind and blind assessment design, the trials' risk of these two domains was low. Four open-label trials [14, 17–19] have adopted blind assessment design and the open-label design has little influence on final outcomes, so the risk of performance bias for these four trials were low. Only one

Table 1 Baseline characteristics of included studies

Trial	Country and centers	Sample size	Blinding	Treatment groups and dosages		ITT analysis	DAPT treatment duration	Follow-up	Jadad score
				Dual therapy	Mono therapy				
CARESS 2005	France, Germany, Switzerland, United Kingdom	107	Double blind	A (75 mg) + C (300 mg load then 75 mg)	A 75 mg	ITT	7 days	7 days	4
Bal dit Sollier 2009	France	44	Double blind	A 325 mg + C 75 mg ($n = 12$) or T 10 mg + A 300 mg ($n = 10$)	A 300 mg ($n = 10$) or T 10 mg ($n = 12$)	ITT	10 days	10 days	3
CHANCE 2013	China	5170	Double blind	C (300 mg load then 75 mg od) + A (75-300 mg load then 75 mg od) for 21 days; then C alone (75 mg od) afterward	A 75 mg	ITT	30 days	3 m	5
CLAIR 2010	Hong Kong, Singapore, China, Thailand, Malaysia	98	Open label, blinded end point	A (75–160 mg od) + C (300 mg load on then 75 mg od)	A 75–160 mg	ITT	7 days	7 days	5
Fan He 2014	China	647	Open label	A (100 mg) + C (300 mg load on then 75 mg od)	A 300 mg	ITT	14 days	14 days	3
FASTER 2007	Canada	392	Double blind	A (162 mg load then 81 mg) + C (300 mg load then 75 mg)	A 162 mg load then 81 mg	ITT	3 m	3 m	5
Yi2014	China	570	UNK	A (200 mg) + C (75 mg)	A 100 mg	ITT	30 days	30 days	2
EARLY 2010	Germany	543	Open, blinded outcomes	A (25 mg bd) + D (200 mg bd)	A (100 mg od) for 7 days, then A (25 mg bd) + D (200 mg bd) thereafter	Analyzed as treated	3 m	3 m	3
Chairangsarit 2005	Thailand	38	Open label	A (300 mg od) + D (225 mg od)	A 300 mg	UNK	6 m	6 m	2
PRoFESS 2009	Worldwide, 695 centers	1360	Double blind	A (25 mg bd) + D (200 mg bd)	C 75 mg	ITT	3 m	3 m	5

A aspirin, *C* clopidogrel, *T* tirofiban, *D* dipyridamole, *od* once daily, *bd* twice daily, *UNK* unknown, *DAPT* dual-antiplatelet therapy, *ITT* intention to treatment

study [19] described neither the number of withdrawal nor loss to follow-up and the reason for these aspects; therefore, this study [19] was regarded as having a high risk of bias in the domain of incomplete outcome data. All except one [20] study was considered to have a high risk of bias in selective reporting because it is a subgroup of PRoFESS trial. Because of premature termination, FASTER [16] was regarded as having a high risk in the part of other bias, and other trials were regarded as having an unclear risk in this domain.

The evidence classification results, summarized from the GRADE evidence profile assessed by the GRADEpro software, are shown in Table 3. The quality of evidence was high for the composite outcome of major vascular events, moderate for the net clinical outcome, low for the outcome of recurrent stroke, IS recurrence, bleeding episodes, and very low for TIA, major bleeding and intracranial hemorrhage.

Clinical results

All outcomes were reported in total analysis and subgroup analysis. We made subgroup analysis of both efficacy and safety outcomes in accordance with predefined groups.

Table 2 Baseline characteristics of participants

Trial	Mean age, Y	Male (%)	Hypertension		DM		Patients	Age, Y	Onset-to-treatment interval	Lost to follow-up
			Dual Therapy	Mono Therapy	Dual Therapy	Mono Therapy				
CARESS 2005	64	69	38 (75 %)	31 (55 %)	16 (31 %)	18 (32 %)	Stroke	>18	3 M	0
Bal dit Sollier 2009	71	73	UNK	UNK	UNK	UNK	Stroke, TIA	50–90	>8 days	0
CHANCE 2013	62	66	1716 (66 %)	1683 (65 %)	550 (21 %)	543 (21 %)	Minor stroke or TIA	≥40	<24 h	36
CLAIR 2010	58	78	27 (60 %)	35 (69 %)	21 (46 %)	16 (31 %)	Stroke, TIA	≥18	7 days	1
Fan He 2014	62	57	213 (66 %)	224 (69 %)	138 (43 %)	128 (39 %)	Stroke, TIA	≥40	<72 h	0
FASTER 2007	69	66	92 (46 %)	106 (55 %)	24 (12 %)	18 (9 %)	Minor stroke or TIA	≥40	<24 h	7
Yi2014	69	55	204 (72 %)	210 (73 %)	105 (37 %)	110 (38 %)	Stroke	≥18	<48 h	0
EARLY 2010	69	62	205 (72 %)	197 (76 %)	62 (22 %)	67 (26 %)	Stroke, TIA	≥18	<24 h	16
Chairangsarit 2005	64	53	14 (70 %)	5 (28 %)	6 (30 %)	6 (33 %)	Stroke	>45	<48 h	9
PRoFESS 2009	66	64	472 (70 %)	484 (70 %)	188 (28 %)	186 (27 %)	Stroke	≥50	<72 h	12

DM diabetes mellitus, *UNK* unknown, *TIA* transient ischemic attack

Recurrent stroke is the primary outcome of our meta-analysis. Totally 10 trials [11–20] reported the outcome of recurrent stroke (Fig. 3). Pooled evidence indicated that comparing with monotherapy, DAPT reduced the risk of recurrent stroke by 35 % (RR 0.65, 95 % CI 0.56–0.76).There was no statistical heterogeneity between included studies ($P = 0.67$, $I^2 = 0$ %). To detect the influence of initiation treatment time, we conducted a subgroup analysis according to acute phase and non-acute phase. The stratified analysis of acute phase combination therapy included 7 RCTs [13, 15–20] and revealed that compared with monotherapy, DAPT significantly decreased the risk of stroke recurrence (RR 0.66, 95 % CI 0.57–0.77) (Table 3). Three RCTs [11, 12, 14] were included in the stratified analysis of non-acute phase combination therapy; Table 3 shows significant reduction in stroke recurrence with DAPT group (RR 0.19; 95 % CI 0.03–1.07, $P = 0.06$).

Information regarding the net clinical outcome is reported in 6 trials [11, 13, 14, 16, 17, 20]. The pooled evidence showed that compared with monotherapy, DAPT decreased the risk of the net clinical outcome by 33 % (RR 0.67, 95 % CI 0.58–0.79) (Fig. 4). There did not exist a significant statistical heterogeneity between included studies ($P = 0.36$, $I^2 = 8$ %). Data of IS recurrence were available in eight trials [11–14, 16, 17, 19, 20]. As shown in Fig. 5, pooled evidence showed DAPT reduced the risk of IS recurrence by 35 %. No statistical heterogeneity was found between the eight trials.

The analysis of composite outcome of major vascular events included five trials [11, 13, 16, 18, 20]. Pooled evidence indicated that DAPT decreased the risk of composite outcome of major vascular events by 30 % (RR 0.70, 95 % CI 0.60–0.81) (Fig. 6). There is no statistical heterogeneity between the five trials (P= 0.94, $I^2 = 0$ %).

Five trials [11, 13, 14, 18, 19] reported data on TIA (Fig. 7). Based on the overall pooled evidence, compared with monotherapy, DAPT has a nonsignificant reduction in TIA (RR 0.81, 95 % CI 0.56–1.17) and heterogeneity ($P = 0.80$, $I^2 = 0$ %).

The safety endpoints were major bleeding, intracranial hemorrhage and bleeding episodes (Figs. 8, 9, 10). Major bleeding is a primary index for safety; totally eight trials [11, 13–18, 20] reported values on major bleeding. As shown in Fig. 8, there is no significant difference in the risk of major bleeding between DAPT and monotherapy (RR 1.44, 95 % CI 0.72–2.88). Eight trials [11, 13–17, 19, 20] have reported information regarding intracranial hemorrhage. The pooled evidence indicated that compared with monotherapy, DAPT has led to a nonsignificant increase in this domain (RR 1.29, 95 % CI 0.56–2.93). The bleeding episodes were available on seven trials [11, 13–17, 20];

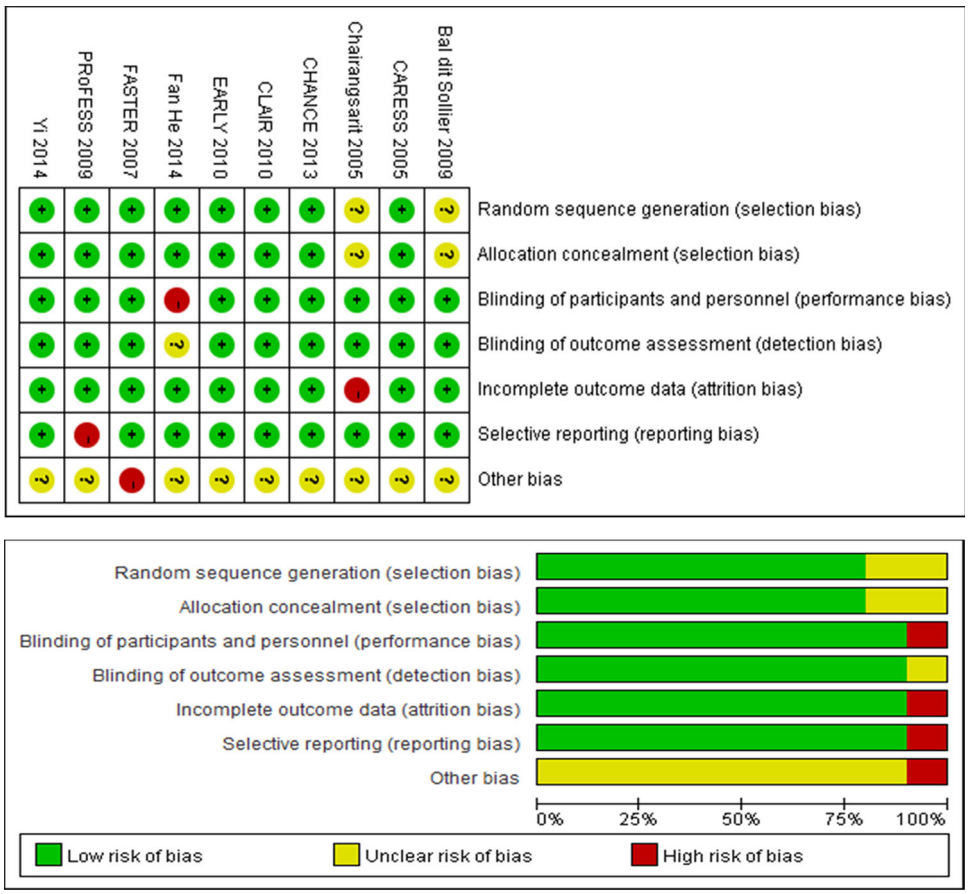

Fig. 2 Risk of bias graph and summary for included studies

Table 3 Summary of GRADE evidence profile

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Recurrent stroke	RCT	Serious[a]	No	No	No	Strongly suspected[c]	Low
The net clinical outcome	RCT	Serious[a]	No	No	No	Undetected	Moderate
Ischemic stroke recurrence	RCT	Serious[a]	No	No	No	Strongly suspected[c]	Low
TIA	RCT	Serious[a]	No	No	Very serious[b]	Undetected	Very low
Composite outcome of major vascular events	RCT	No	No	No	No	Undetected	High
Bleeding episodes	RCT	Serious[a]	No	No	No	Undetected	Low
Major bleeding	RCT	Serious[a]	No	No	Very serious[b]	Undetected	Very low
Intracranial hemorrhage	RCT	Serious[a]	No	No	Very serious[b]	Undetected	Very low

[a] Allocation concealment and blinding method of some included trials were not offered

[b] The total sample size is much less than OIS and the overall number of events was less than 300

[c] Publication bias may exist proved by asymmetrical funnel plot

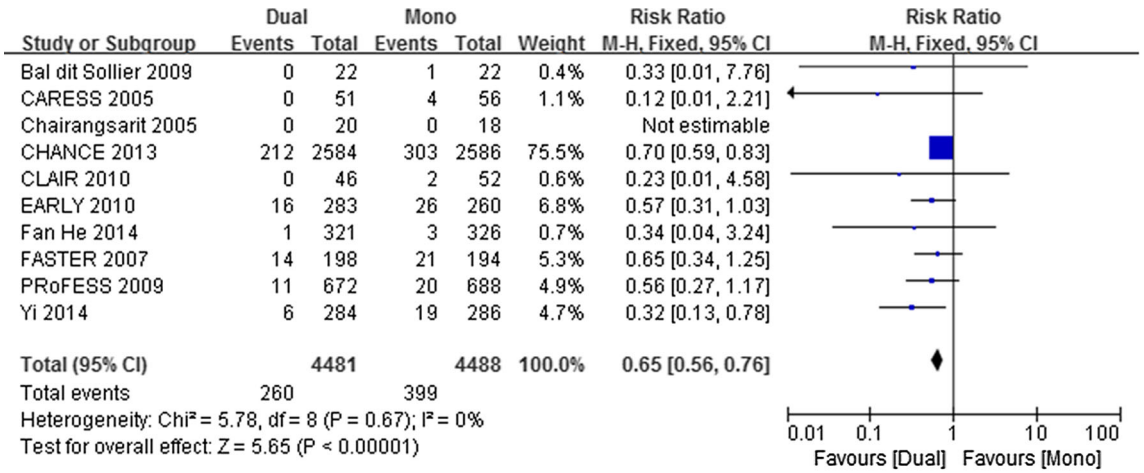

Fig. 3 Individual and summary risk ratios (RRs) with 95 % CIs of recurrent stroke

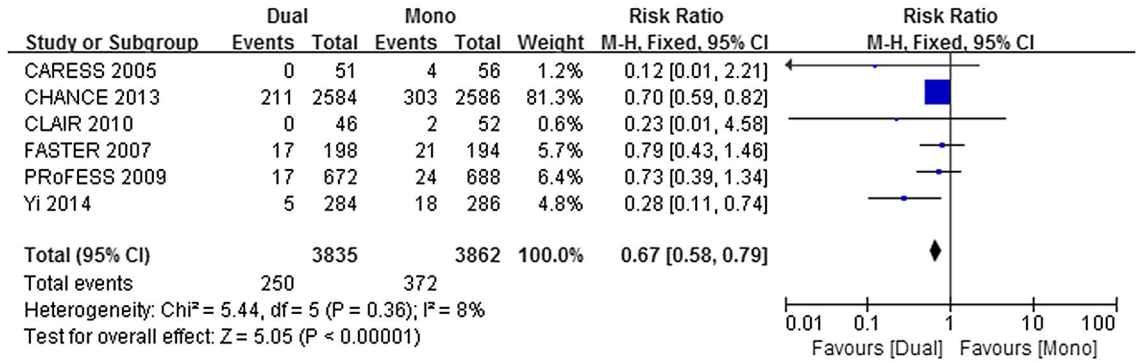

Fig. 4 Individual and summary risk ratios (RRs) with 95 % CIs of the net clinical outcome

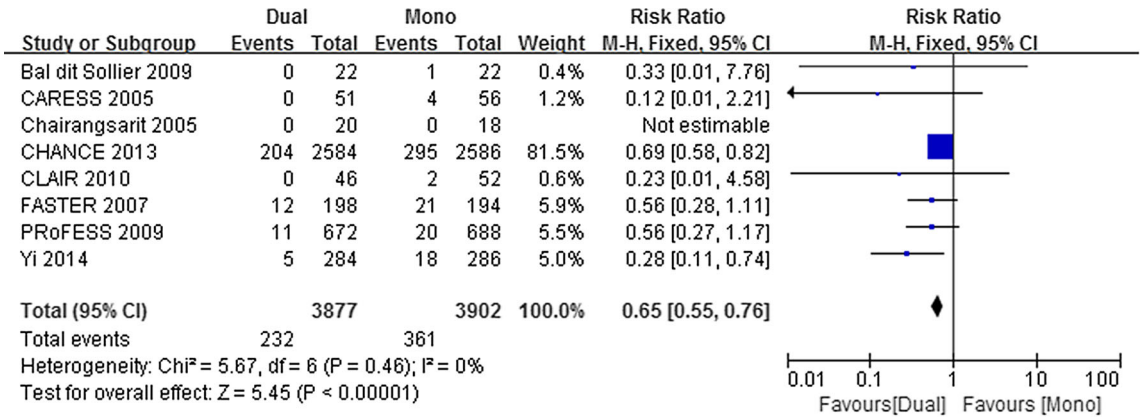

Fig. 5 Individual and summary risk ratios (RRs) with 95 % CIs of ischemic stroke recurrence

DAPT can lead to a significant increase in bleeding episodes compared with monotherapy (RR 1.66, 95 % CI 1.19–2.30). No statistical heterogeneity was found in all three safety outcomes.

Through sensitive analysis conducted by STATA software, we found similar overall results for primary outcome after excluding each individual study shown in Fig. 11.

Discussion

The meta-analysis of 8969 participants provided evidence about the efficacy and safety of short-term DAPT in treating IS or TIA. A sensitivity analysis on three main outcomes generated similar results, which indicated that results of the present meta-analysis were generalizable. In

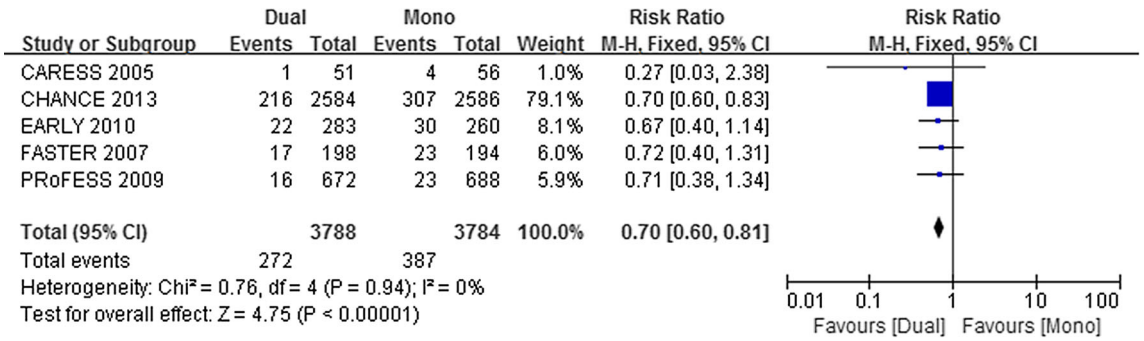

Fig. 6 Individual and summary risk ratios (RRs) with 95 % CIs of composite outcome of major vascular events

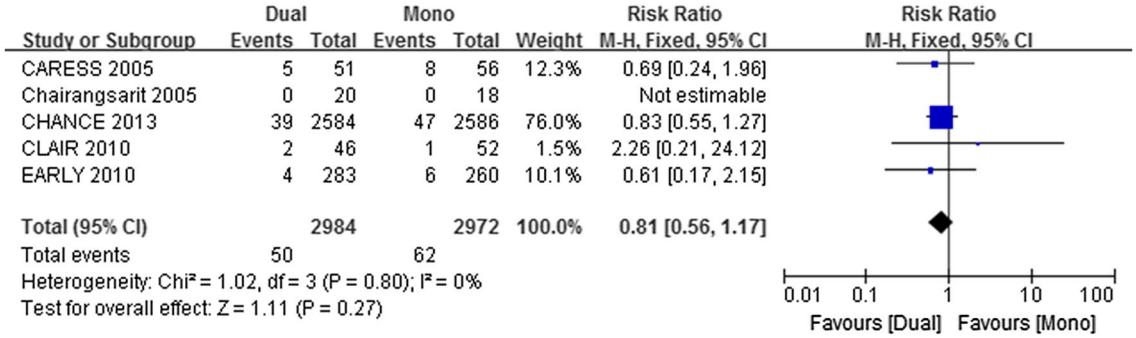

Fig. 7 Individual and summary risk ratios (RRs) with 95 % CIs of TIA

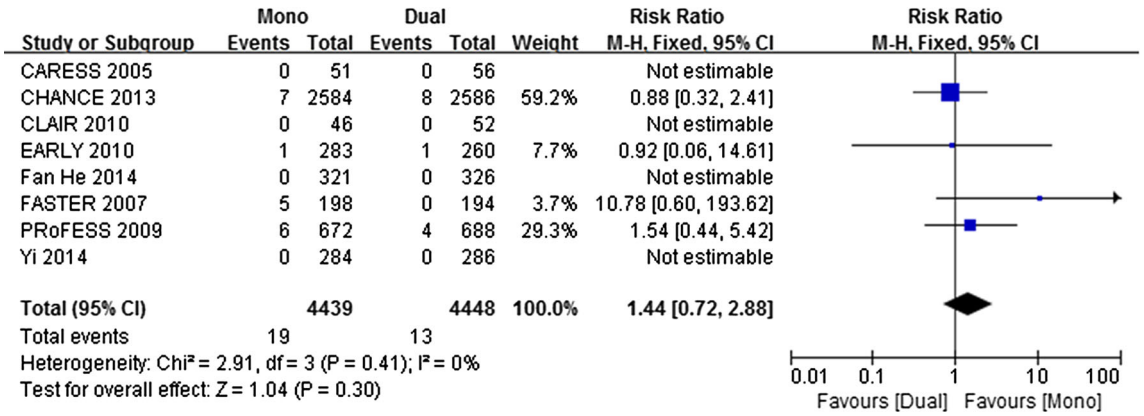

Fig. 8 Individual and summary risk ratios (RRs) with 95 % CIs of major bleeding

the subgroup analysis of clopidogrel plus aspirin or dipyridamole plus aspirin, significant reductions were found in the risks of stroke recurrence, the net clinical outcome, composite outcome of vascular events and IS recurrence (Table 4). We also performed an acute phase (<72 h) and non-acute phase subgroup analysis of eight outcomes. The data indicated that either in acute IS or non-acute phase of IS, DAPT brought more beneficial outcomes without increasing the risk for major bleeding and intracranial hemorrhage. In addition, subgroup analysis based on different races was also carried out. Both arms have similar effect outcomes, whereas non-Asian have more bleeding risk compared with Asian which may be due to different physiology character and stroke type.

Although many clinical trials such as MATCH [25] or SPS3 [26] and meta-analyses [27, 28] have shown that treatment with DAPT offers no better clinical outcomes while having more bleeding danger, many participants in these trials were given long-term treatment of DAPT which may increase risks of bleeding. Three network meta-analyses [29–31] were published recently which compared different antiplatelet therapy for treating IS. All three analyses concluded that cilostazol has advantages over DAPT. Whereas the conclusions lack credibility for they

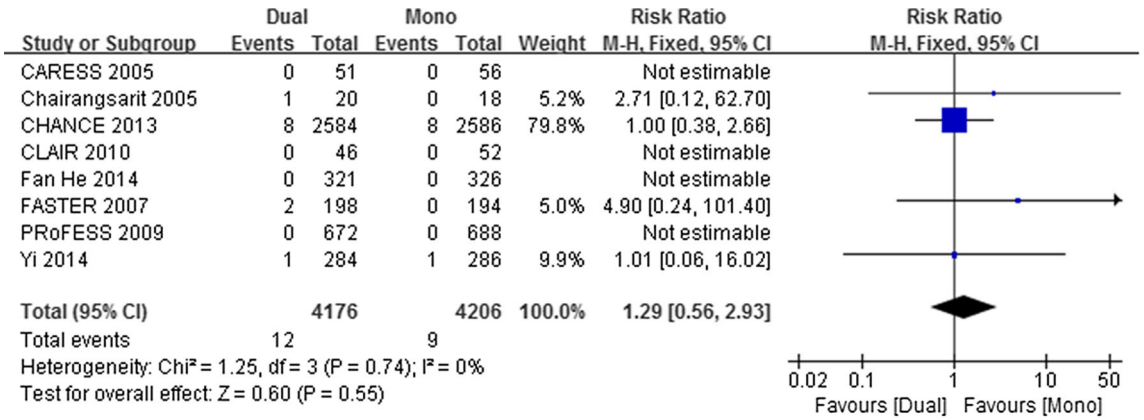

Fig. 9 Individual and summary risk ratios (RRs) with 95 % CIs of intracranial hemorrhage

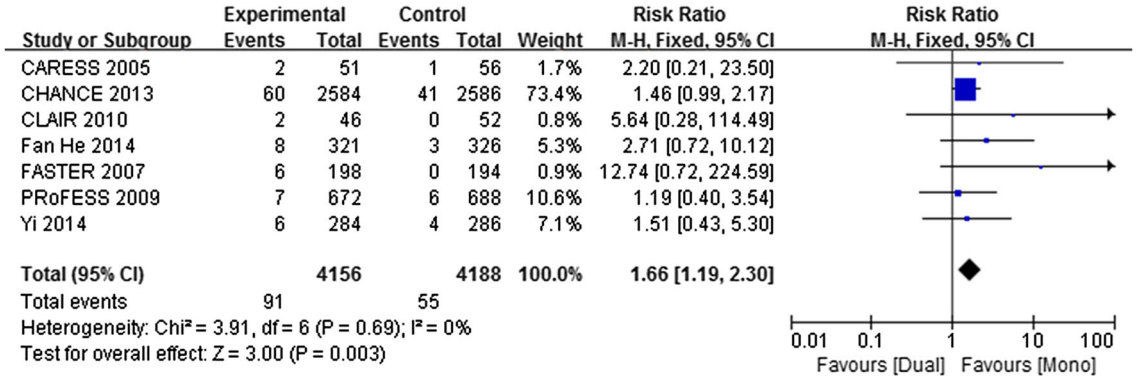

Fig. 10 Individual and summary risk ratios (RRs) with 95 % CIs of bleeding episodes

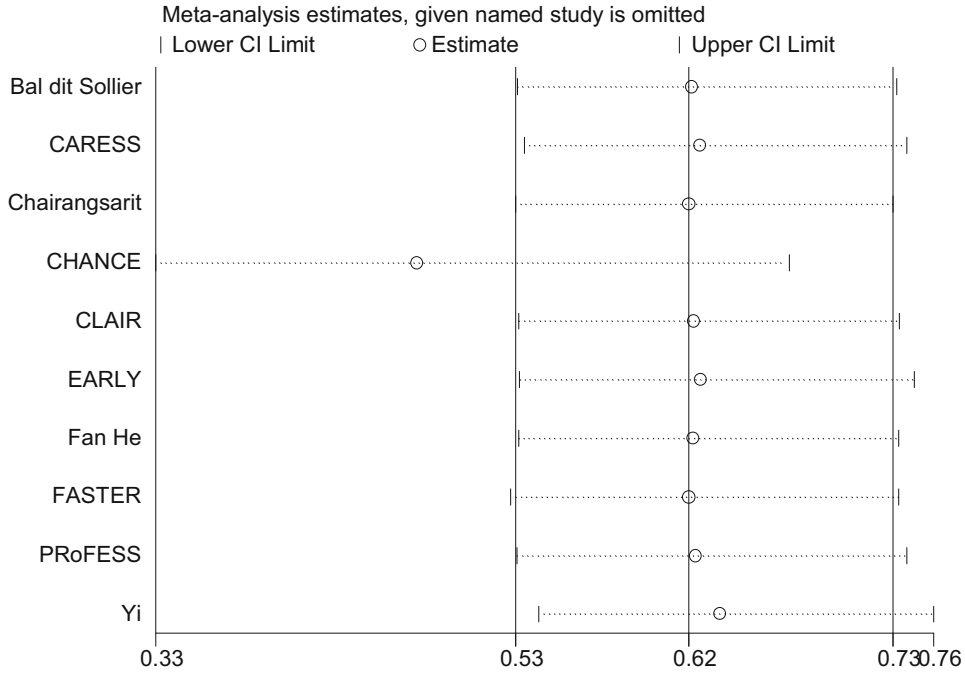

Fig. 11 Sensitivity analysis of primary outcome

Table 4 Subgroup analysis of eight outcomes on baseline characteristics (treatment initiation time, races, different DAPT combination)

Subgroup	Studies	Participants	Statistical method	RR (95 % CI)	P for interaction
Recurrent stroke					
Acute stroke or TIA (≤72 h)	7	8720	RR (M–H, fixed, 95 % CI)	0.66 [0.57, 0.77]	0.16
Non-acute stroke or TIA	3	249	RR (M–H, fixed, 95 % CI)	0.19 [0.03, 1.07]	
Asian	5	6523	RR (M–H, fixed, 95 % CI)	0.67 [0.57, 0.79]	0.43
Non-Asian	4	1086	RR (M–H, fixed, 95 % CI)	0.56 [0.36, 0.86]	
A + C	7	7006	RR (M–H, fixed, 95 % CI)	0.66 [0.57, 0.77]	0.52
A + D	3	1941	RR (M–H, fixed, 95 % CI)	0.56 [0.36, 0.90]	
The net clinical outcome					
Acute stroke or TIA (≤72 h)	4	7492	RR (M–H, random, 95 % CI)	0.68 [0.59, 0.80]	0.17
Non-acute stroke or TIA	2	205	RR (M–H, random, 95 % CI)	0.16[0.02,1.26]	
Asian	3	5838	RR (M–H, random, 95 % CI)	0.67 [0.57, 0.79]	0.96
Non-Asian	2	499	RR (M–H, random, 95 % CI)	0.68 [0.38, 1.22]	
A + C	5	6337	RR (M–H, random, 95 % CI)	0.67 [0.57, 0.79]	0.81
A + D	1	1360	RR (M–H, random, 95 % CI)	0.73 [0.39, 1.34]	
Ischemic stroke recurrence					
Acute stroke or TIA (≤72 h)	5	7530	RR (M–H, fixed, 95 % CI)	0.66 [0.56, 0.77]	0.16
Non-acute stroke or TIA	3	249	RR (M–H, fixed, 95 % CI)	0.19 [0.03, 1.07]	
Asian	4	5876	RR (M–H, fixed, 95 % CI)	0.67 [0.56, 0.79]	0.33
Non-Asian	3	543	RR (M–H, fixed, 95 % CI)	0.48 [0.25, 0.91]	
A + C	6	6359	RR (M–H, fixed, 95 % CI)	0.65 [0.55, 0.76]	0.71
A + D	2	1398	RR (M–H, fixed, 95 % CI)	0.56 [0.27, 1.17]	
TIA					
Acute stroke or TIA (≤72 h)	3	5751	RR (M–H, fixed, 95 % CI)	0.80 [0.54, 1.20]	0.90
Non-acute stroke or TIA	2	205	RR (M–H, fixed, 95 % CI)	0.86 [0.34, 2.19]	
Asian	3	5306	RR (M–H, fixed, 95 % CI)	0.86 [0.57, 1.30]	0.55
Non-Asian	2	650	RR (M–H, fixed, 95 % CI)	0.65 [0.29, 1.46]	
A + C	3	5375	RR (M–H, fixed, 95 % CI)	0.83 [0.57, 1.23]	0.64
A + D	2	581	RR (M–H, fixed, 95 % CI)	0.61 [0.17, 2.15]	
Composite outcome of major vascular events					
Acute stroke or TIA (≤72 h)	4	7465	RR (M–H, fixed, 95 % CI)	0.70 [0.61, 0.82]	0.39
Non-acute stroke or TIA	1	107	RR (M–H, fixed, 95 % CI)	0.27 [0.03, 2.38]	
Asian	1	5170	RR (M–H, fixed, 95 % CI)	0.70 [0.60, 0.83]	0.80
Non-Asian	3	1042	RR (M–H, fixed, 95 % CI)	0.67 [0.45, 0.98]	
A + C	3	5669	RR (M–H, fixed, 95 % CI)	0.70 [0.60, 0.82]	0.94
A + D	2	1903	RR (M–H, fixed, 95 % CI)	0.69 [0.46, 1.03]	
Bleeding episodes					
Acute stroke or TIA (≤72 h)	5	8139	RR (M–H, fixed, 95 % CI)	1.61 [1.15, 2.25]	0.44
Non-acute stroke or TIA	2	205	RR (M–H, Fixed, 95 % CI)	3.33 [0.54, 20.69]	
Asian	4	6485	RR (M–H, Fixed, 95 % CI)	1.59 [1.11, 2.26]	0.15
Non-Asian	2	499	RR (M–H, Fixed, 95 % CI)	5.85 [1.02, 33.56]	
A + C	6	6984	RR (M–H, Fixed, 95 % CI)	1.71 [1.21, 2.42]	0.54
A + D	1	1360	RR (M–H, Fixed, 95 % CI)	1.19 [0.40, 3.54]	
Major bleeding					
Acute stroke or TIA (≤72 h)	6	8682	RR (M–H, fixed, 95 % CI)	1.44 [0.72, 2.88]	Not estimable
Non-acute stroke or TIA	2	205	RR (M–H, fixed, 95 % CI)	Not estimable	
Asian	4	6485	RR (M–H, fixed, 95 % CI)	0.88 [0.32, 2.41]	0.13
Non-Asian	3	1042	RR (M–H, fixed, 95 % CI)	4.14 [0.71, 23.97]	

Table 4 continued

Subgroup	Studies	Participants	Statistical method	RR (95 % CI)	P for interaction
A + C	6	6984	RR (M–H, fixed, 95 % CI)	1.46 [0.61, 3.50]	0.96
A + D	2	1903	RR (M–H, fixed, 95 % CI)	1.41 [0.45, 4.41]	
Intracranial hemorrhage					
Acute stroke or TIA (≤72 h)	6	8177	RR (M–H, fixed, 95 % CI)	1.29 [0.56, 2.93]	Not estimable
Non-acute stroke or TIA	2	205	RR (M–H, fixed, 95 % CI)	Not estimable	
Asian	5	6523	RR (M–H, fixed, 95 % CI)	1.10 [0.46, 2.63]	0.35
Non-Asian	2	499	RR (M–H, fixed, 95 % CI)	4.90 [0.24, 101.40]	
A + C	6	6984	RR (M–H, fixed, 95 % CI)	1.21 [0.51, 2.85]	0.63
A + D	2	1398	RR (M–H, fixed, 95 % CI)	2.71 [0.12, 62.70]	

A aspirin, *C* clopidogrel, *D* dipyridamole, *TIA*: transient ischemic attack, *RR* risk ratio, *CI* confidence interval, *M–H* Mantel–Haenszel

are indirect comparisons of different antiplatelet therapy; large head-to-head RCTs are needed to further confirm their conclusions.

To our knowledge, there are two recently published meta-analyses that mentioned the comparison of short-term DAPT and monotherapy. They also recommended short-term DAPT for IS or TIA which is consistent with our results. Compared with these two analyses, first we focused on the short-term application of DAPT. Second, we included more dual-antiplatelet combinations and made subgroup analysis according to different combinations. Third, quality of the included studies in the meta-analyses by Zhang et al. [22] and Ge et al. [21] was only assessed with Jadad scoring system, which is explicitly discouraged in Cochrane reviews because it has a strong emphasis on reporting rather than conducting and does not cover one of the most important potential biases in randomized trials (allocation concealment). Fourth, we used Cochrane collaboration's tool for assessing the risk of bias, which is recommended in Cochrane reviews. Moreover, our meta-analysis is the first study of this subject to assess the quality of evidence with the GRADE system, which was used to ensure the reliability of our results.

There are two ongoing multicenter clinical trials [32, 33] which are relevant to our analysis. The double-blind POINT [32] (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke, ClinicalTrials.gov Identifier: NCT00991029) trial aims to assess the safety and efficacy of clopidogrel (75 mg od) plus aspirin (50–325 mg od) versus aspirin alone (50–325 mg od) for reducing risk of major ischemic vascular events at 90 days, in TIA or minor stroke patients within 12 h of symptom onset. It was initiated in October 2009 and aims to enroll 5840 patients until December 2018. Upon finished, the POINT trial will be included in our updated meta-analysis. In addition, the open-label, blinded end point TARDIS [33] (triple antiplatelets for reducing dependency after ischaemic stroke) trial (ISRCTN47823388) is investigating the efficacy and safety of more intensive antiplatelet therapy (combined aspirin, clopidogrel, and dipyridamole) in treating IS and TIA. Both these trials will bring fresh air to the establishment of future guidelines for treatment of acute IS and TIA.

We note several limitations in our study. First, our meta-analysis included studies that varied in relation to the study population, stroke severity, comparator, antiplatelet medications, onset-to-treatment interval, and treatment duration. All of these factors could be potential confounders for accurate inclusions. Second, CHANCE is a large trial which account for about 50 % of participants in the meta-analysis; therefore, its results drove much of the findings. Third, only published data were included, which may lead to a reporting bias by overestimating the effect of dual therapy. In addition, the majority of participants included in trials are from Asia; therefore, the application of our inclusions may have some limitations in whites. All these aspects reinforce the need to perform more large, well-designed trials involving the effects of short-term DAPT in the secondary prevention of IS to obtain more reliable conclusions.

Conclusions

In conclusion, the current study shows that short-term (≤1 year) DAPT offers protection effects against stroke recurrence and major vascular events without increasing the risk of hemorrhagic stroke and major bleeding events in patients with prior stroke or TIA. Either in acute phase or non-acute phase, DAPT will provide more beneficial outcomes for patients with IS or TIA. For both the combination of aspirin plus clopidogrel and aspirin plus dipyridamole, short-term DAPT is superior to monotherapy in treating IS or TIA. Results of ongoing large trials will provide more conclusive evidence on the use of DAPT for

stroke patients of other ethnic descents than Asian region and for IS patients.

Compliance with ethical standards

Funding No sources of funding were used to assist the preparation of this study.

Conflicts of interest Yang Liu, Zhaoxia Fei, Wei Wang, Jingxue Fang, Meijuan Zou and Gang Cheng have no conflicts of interest that are directly relevant to the content of this study.

References

1. Lozano R, Naghavi M, Foreman K et al (2012) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380(9859):2095–2128
2. Vos T, Flaxman AD, Naghavi M et al (2012) Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380(9859):2163–2196
3. Wong KS, Chen C, Ng PW et al (2007) Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. Lancet Neurol 6(5):407–413
4. Torbey MT, Bösel J, Rhoney DH et al (2015) Evidence-based guidelines for the management of large hemispheric infarction: a statement for health care professionals from the Neurocritical Care Society and the German Society for Neuro-intensive Care and Emergency Medicine. Neurocrit Care 22(1):146–164
5. Wu X, Zhu B, Fu L et al (2013) Prevalence, incidence, and mortality of stroke in the Chinese island populations: a systematic review. PLoS One 8(11):e78629
6. Krishnamurthi RV, Moran AE, Feigin VL et al (2015) Stroke prevalence, mortality and disability-adjusted life years in adults aged 20–64 years in 1990–2013: data from the global burden of disease 2013 study. Neuroepidemiology 45(3):190–202
7. Coull AJ, Lovett JK, Rothwell PM et al (2004) Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 328(7435):326
8. Petty GW, Brown RD Jr, Whisnant JP et al (1998) Survival and recurrence after first cerebral infarction: a population-based study in Rochester, Minnesota, 1975 through 1989. Neurology 50(1):208–216
9. Sandercock PA, Counsell C, Tseng MC et al (2014) Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev (3):CD000029
10. Piepoli MF, Hoes AW, Agewall S et al (2016) 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J pii:ehw106 **[Epub ahead of print]**
11. Markus HS, Droste DW, Kaps M et al (2005) Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) Trial. Circulation 111(17):2233–2240
12. Bal Dit Sollier C, Crassard I, Simoneau G et al (2009) Effect of the thromboxane prostaglandin receptor antagonist terutroban on arterial thrombogenesis after repeated administration in patients treated for the prevention of ischemic stroke. Cerebrovasc Dis 28(5):505–513
13. Wang Y, Wang Y, Zhao X et al (2013) Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 369(1):11–19
14. Wong KS, Chen C, Fu J et al (2010) Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurol 9(5):489–497
15. He F, Xia C, Zhang JH et al (2015) Clopidogrel plus aspirin versus aspirin alone for preventing early neurological deterioration in patients with acute ischemic stroke. J Clin Neurosci 22(1):83–86
16. Kennedy J, Hill MD, Ryckborst KJ et al (2007) Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. Lancet Neurol 6(11):961–969
17. Yi X, Lin J, Wang C et al (2014) A Comparative Study of Dual versus Monoantiplatelet Therapy in Patients with Acute Large-Artery Atherosclerosis Stroke. J Stroke Cerebrovasc Dis 23(7):1975–1981
18. Dengler R, Diener HC, Schwartz A et al (2010) Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY trial): a randomised, open-label, blinded-endpoint trial. Lancet Neurol 9(2):159–166
19. Chairangsarit P, Sithinamsuwan P, Niyasom S et al (2005) Comparison between aspirin combined with dipyridamole versus aspirin alone within 48 hours after ischemic stroke event for prevention of recurrent stroke and improvement of neurological function: a preliminary study. J Med Assoc Thai 88(Suppl 3):S148–S154
20. Bath PM, Cotton D, Martin RH et al (2010) Effect of combined aspirin and extended-release dipyridamole versus clopidogrel on functional outcome and recurrence in acute, mild ischemic stroke PRoFESS subgroup analysis. Stroke 41(4):732–738
21. Ge F, Lin H, Liu Y et al (2016) Dual antiplatelet therapy after stroke or transient ischaemic attack-how long to treat? The duration of aspirin plus clopidogrel in stroke or transient ischaemic attack: a systematic review and meta-analysis. Eur J Neurol 23(6):1051–1057
22. Zhang Q, Wang C, Zheng M (2015) Aspirin plus clopidogrel as secondary prevention after stroke or transient ischemic attack: a systematic review and meta-analysis. Cerebrovasc Dis 39(1):13–22
23. Wong KS, Wang Y, Leng X et al (2013) Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack an updated systematic review and meta-analysis. Circulation 128(15):1656–1666
24. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339:b2535
25. Diener HC, Bogousslavsky J, Brass LM et al (2004) MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 364(9431):331–337
26. Benavente OR, Hart RG, McClure LA et al (2012) Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med 367(9):817–825
27. Zhou YH, Wei X, Lu J et al (2012) Effects of combined aspirin and clopidogrel therapy on cardiovascular outcomes: a systematic review and meta-analysis. PLoS One 7(2):e31642
28. Lee M, Saver JL, Hong KS et al (2013) Risk-benefit profile of long-term dual- versus single-antiplatelet therapy among patients with ischemic stroke. Ann Intern Med 159(7):463–470

29. Niu PP, Guo ZN, Jin H et al (2016) Antiplatelet regimens in the long-term secondary prevention of transient ischaemic attack and ischaemic stroke: an updated network meta-analysis. BMJ Open 6(3):e009013
30. Huang HP, Lin WH, Chen SG et al (2016) Comparative efficacy and safety of nine anti-platelet therapies for patients with ischemic stroke or transient ischemic attack: a mixed treatment comparisons. Mol Neurobiol **[Epub ahead of print]**
31. Xie W, Zheng F, Zhong B et al (2015) Long-term antiplatelet mono- and dual therapies after ischemic stroke or transient ischemic attack: network meta-analysis. J Am Heart Assoc 4(8):e002259
32. Johnston SC, Easton JD, Farrant M et al (2013) Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. Int J Stroke 8(6):479–483
33. Krishnan K, Beridze M, Christensen H et al (2015) Safety and efficacy of intensive vs. guideline antiplatelet therapy in high-risk patients with recent ischemic stroke or transient ischemic attack: rationale and design of the triple antiplatelets for reducing dependency after ischaemic stroke (TARDIS) trial (ISRCTN47823388). Int J Stroke 10(7):1159–1165