School of Basic Medicine and Clinical Pharmacy[1], China Pharmaceutical University, Nanjing, China; Department of Clinical Pharmacology[2], Nanjing First Hospital, Nanjing Medical University, Nanjing, China; Faculty of Science[3], Melbourne University, Melbourne, Australia; Institute for Laboratory Medicine[4], NO.900 Hospital of the Joint Logistics Team of PLA, Fuzhou, China

Efficacy and safety of dual versus mono antiplatelet therapy in patients with stroke or transient ischemic attack: An updated meta-analysis of 18 randomized controlled trials

Wang Fu-Sang[1,2,#], Zheng Xiao-Han[1,2,#], Zou Yang[3,#], Chen Ting-Ting[1,2], Sun Chao[1,2], Ling Jing-Yi[4*], Zou Jian-Jun[2*]

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**Corresponding authors: Zou Jian-Jun, Department of Clinical Pharmacology, Nanjing First Hospital, Nanjing Medical University, Nanjing 210006, China*
zoujianjun100@126.com
Ling Jing-Yi, Institute for Laboratory Medicine, NO. 900 Hospital of the Joint Logistics Team of PLA, Fuzhou, China
Joy901115@163.com
#These authors contributed equally to this work and should be considered as joint first authors.

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The optimal duration of dual antiplatelet therapy (DAPT) as a routine treatment in stroke patients is still controversial. The efficacy and safety of DAPT may vary with different regiments, initiating treatment time and race. Our study assessed the efficacy and safety of DAPT in patients with stroke and to determine the factors influencing the efficacy and safety of DAPT. Relevant studies published up to May 2019 from PubMed, Embase, Web of Science and the Cochrane Library. Randomized controlled trials comparing DAPT with mono antiplatelet therapy (MAPT) for stroke secondary prevention were included. The primary endpoints were stroke recurrence, ischemic stroke recurrence and all-cause death. Subgroup analysis was made according to regiment, initiating treatment time and race. Eighteen studies (n=33353) were included. Comparing with MAPT, short-term DAPT reduced stroke recurrence (RR = 0.68, 95% CI = 0.60-0.77) and ischemic stroke recurrence (RR = 0.67, 95% CI = 0.59-0.77) but increased major bleeding (RR = 1.82, 95% CI = 1.11-2.98). Long-term DAPT had no superiority compared with MAPT. Aspirin plus clopidogrel comparing with aspirin and early initiating treatment time comparing with MAPT decreased stroke recurrence (RR = 0.74, 95% CI = 0.67-0.83; RR = 0.69, 95% CI = 0.61-0.78) and ischemic stroke recurrence (RR = 0.71, 95% CI = 0.64-0.79; RR = 0.68, 95% CI = 0.59-0.77) but also increased major bleeding (RR = 1.70, 95% CI = 1.38-2.09; RR = 1.75, 95% CI = 1.07-2.85). DAPT reduced stroke and ischemic stroke recurrence in non-Asian group but only reduced ischemic stroke recurrence in Asian group. As stroke secondary prevention, short-term DAPT rather than long-term DAPT could be a better choice. Patients could benefit more from aspirin plus clopidogrel or given DAPT within 72 h after symptoms onset. Race may be a factor influencing the efficacy of DAPT.

1. Introduction

Stroke is a major cause of mortality and disability worldwide (Lloyd-Jones et al. 2009). In China, there are 1.6 million people dead for stroke approximately every year (Wu et al. 2013). Timely and effective secondary prevention is crucial to patients with ischemic stroke (IS) or transient ischemic attack (TIA). Dual antiplatelet therapy (DAPT) is a common used therapy for stroke patients. Previous studies have proved that DAPT could decrease the risk of stroke recurrence more effectively than mono antiplatelet therapy (MAPT) (Ge et al. 2016; Liu et al. 2016; Wang et al. 2015).

However, there is still some controversy about the use of DAPT such as the choice of treatment duration and different drug combinations, etc. Although many studies have focused on determining the treatment duration of DAPT, their results are inconsistent (Liu et al. 2016; Wang et al. 2015; Pugliese et al. 2019; Benavente et al. 2012). The combination of the P2Y12 receptor antagonist clopidogrel and aspirin is the most common combination of DAPT in the secondary prevention of stroke. Nevertheless, the other combinations such as aspirin plus cilostazol or dipyridamole also showed great clinical efficacy (Barlas et al. 2018; Toyoda et al. 2019). In addition, some meta-analyses concluded the efficacy and safety of DAPT influenced by race of patients and initiating treatment time after symptoms onset (Ge et al. 2016; Liu et al. 2016; Tan et al. 2015; Ding and Peng 2018). Thus, the efficacy and safety of DAPT is affected by many factors and have not been determined yet.

In this study, we aimed to evaluate the efficacy and safety of short-term and long-term DAPT for secondary stroke prevention and make a subgroup analysis to determine the factors influencing the efficacy and safety of DAPT to provide more evidence-based medical evidence for clinical using.

2. Investigations and results

A total of 18 studies (Wang et al. 2015; Benavente et al. 2012; Hong et al. 2016; Johnston et al. 2018; Bal Dit Sollier et al. 2009; Markus et al. 2005; Uchiyama et al. 2015; Hankey et al. 2011; Wong et al. 2010; Dengler et al. 2010; Halkes et al. 2006; Kennedy et al. 2007; He et al. 2015; Uchiyama et al. 2011; Diener et al. 2004; Nakamura et al. 2012; Bath et al. 2010; Yi et al. 2014) with 33353 patients were included, of whom 16667 patients were in the experimental group and 16686 patients were in the control group. The study selection procedure is shown in Fig. 1. The outcomes of study quality assessment are presented in Fig. 2. The baseline characteristics of included studies are given in Table 1. Only two evaluation indicators achieved a low risk of bias in the

Table 1: Baseline characteristics of included studies

Included studies	Country/Region	Patients	Sample size	Interventions		Treatment Duration	Follow-up
				DAPT	MAPT		
Bal dit sollier 2009	France	IS, TIA	44	aspirin + clopidogrel	aspirin	10 d	10 d
CARESS 2005	France, Germany, Switzerland, UK	IS, TIA	107	aspirin + clopidogrel	aspirin	7 d	7 d
CATHARSIS 2015	Japan	IS	163	aspirin + cilostazol	aspirin	2 y	2 y
CHANCE 2013	China	IS, TIA	5170	aspirin + clopidogrel	aspirin	21 d	3 m
CHARISMA 2006	Worldwide	IS, TIA	4320	aspirin + clopidogrel	aspirin	2.5 y	2.5 y
CLAIR 2010	Hong Kong, Singapore, China, Thailand, Malaysia	IS, TIA	98	aspirin + clopidogrel	aspirin	7 d	7 d
COMPRESS 2016	Korea	IS	358	aspirin + clopidogrel	aspirin	30 d	30 d
EARLY 2010	Germany	IS, TIA	543	aspirin + dipyridamole	aspirin	3 m	3 m
ESPRIT 2006	Worldwide	IS, TIA	2763	aspirin + dipyridamole	aspirin	42 m	42 m
FASTER 2007	Canada	IS, TIA	392	aspirin + clopidogrel	aspirin	3 m	3 m
Fan He 2014	China	IS, TIA	690	aspirin + clopidogrel	aspirin	14 d	14 d
JASAP 2010	Japan	IS	1294	aspirin + dipyridamole	aspirin	1 y	1 y
MATCH 2004	Worldwide	IS, TIA	7599	aspirin + clopidogrel	clopidogrel	18 m	18 m
Nakamura 2012	Japan	IS	76	aspirin + cilostazol	aspirin	6 m	6 m
POINT 2018	North America, Europe, Australia, New Zealand	IS, TIA	4881	aspirin + clopidogrel	aspirin	3 m	3 m
PRoFESS 2009	Worldwide	IS	1360	aspirin + dipyridamole	clopidogrel	3 m	3 m
SPS3 2012	North America, Latin America, Spain	lacunar stroke	3020	aspirin + clopidogrel	aspirin	3.4 y	3.4 y
Yi 2014	China	IS	570	aspirin + clopidogrel	aspirin	30 d	30 d

IS, ischemic stroke; TIA, transient ischemic attack.

CATHARSIS trial (Uchiyama et al. 2015) and only three achieved in the JASAP trials (Uchiyama et al. 2011). Therefore, the two studies were defined as low-quality studies. The quality of other included references was generally high with more than four evaluation indexes stating a low risk of bias.

2.1. Result of meta analysis

The results of DAPT versus MAPT in short-term subgroup and long-term subgroup are shown in Fig. 3. Compared to MAPT, short-term DAPT decreased the risk of stroke recurrence and ischemic stroke recurrence by 32% and 33%, respectively (RR = 0.68, 95% CI = 0.60-0.77; RR = 0.67, 95% CI = 0.59-0.77), but long-term DAPT had no advantage. However, both two duration groups were not accompanied by a reduction of all-cause death, but heterogeneity was shown in long-term DAPT ($P = 0.02$, $I^2 = 67\%$). Neither the short-term DAPT nor long-term DAPT decreased the risk of myocardial infarction and increased the risk of intracranial hemorrhage. The short-term DAPT rather than long-term DAPT increased the risk of major bleeding (RR = 1.82, 95% CI = 1.11-2.98), and significant heterogeneity was shown in long-term DAPT ($P < 0.0001$, $I^2 = 80\%$).

2.2. Subgroup analysis

The results of DAPT versus MAPT in five regiments subgroups are presented in Fig.4. Only the DAPT of group A was associated with a reduction of stroke recurrence and ischemic stroke recurrence compared to MAPT (RR = 0.74, 95% CI = 0.67-0.83; RR = 0.71, 95% CI = 0.64-0.79) and significant heterogeneity was observed in group B ($P = 0.01$, $I^2 = 77\%$; $P = 0.05$, $I^2 = 73\%$). As for the reduction the risk of all-cause death and myocardial infarction, no DAPT group showed superiority. The DAPT of group D increased the risk of intracranial hemorrhage and major bleeding (RR = 1.88, 95% CI = 1.05- 3.39; RR = 2.38, 95% CI = 1.81-3.13) and group A only increased the risk of major bleeding (RR = 1.70, 95% CI = 1.38-2.09).

The analysis of initiating treatment time and race is depicted in Table 2. Compared with MAPT, early initiating DAPT decreased the risk of stroke recurrence and ischemic stroke recurrence (RR = 0.69, 95% CI = 0.61-0.78; RR = 0.68, 95% CI = 0.59-0.77) but did not reduce the risk of myocardial infarction and all-cause death. Besides, early initiating DAPT increase the risk of major bleeding (RR = 1.75, 95% CI = 1.07-2.85) but not the risk of intracranial hemorrhage. However, late initiating DAPT was not significantly

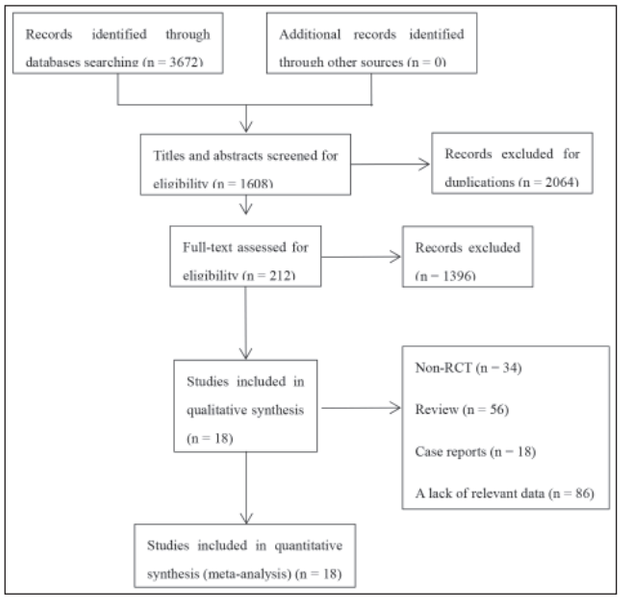
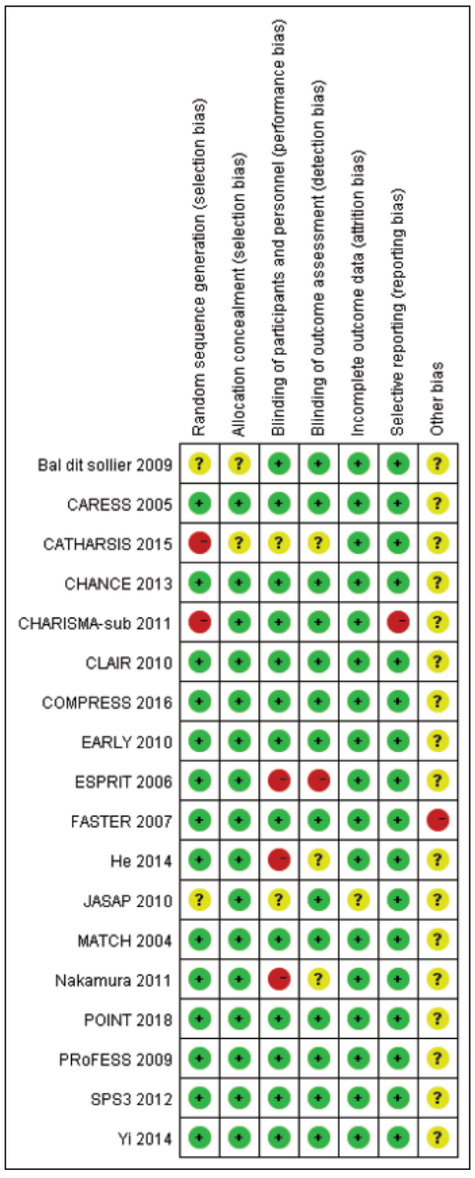


Fig. 1: Flowchart of study selection process according to PRISMA guidelines



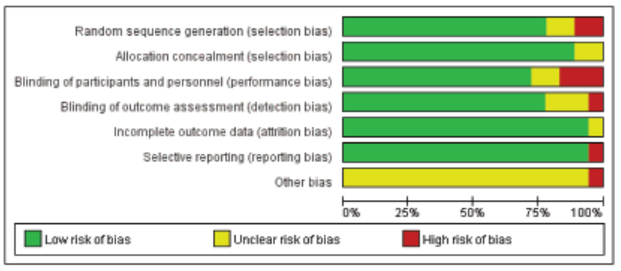
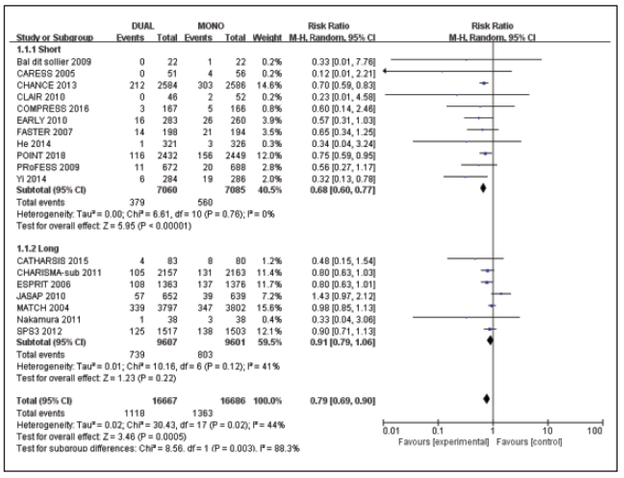
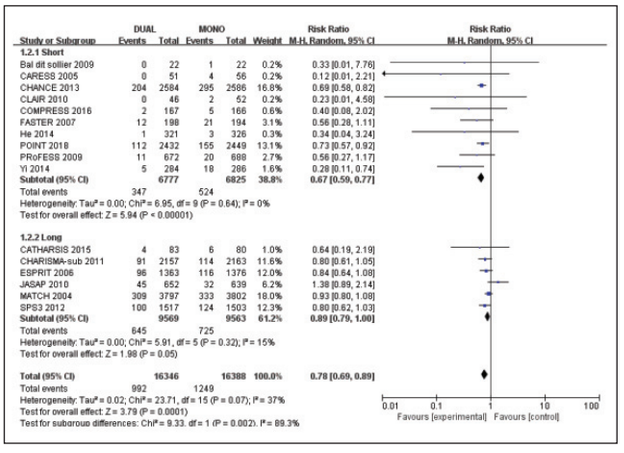
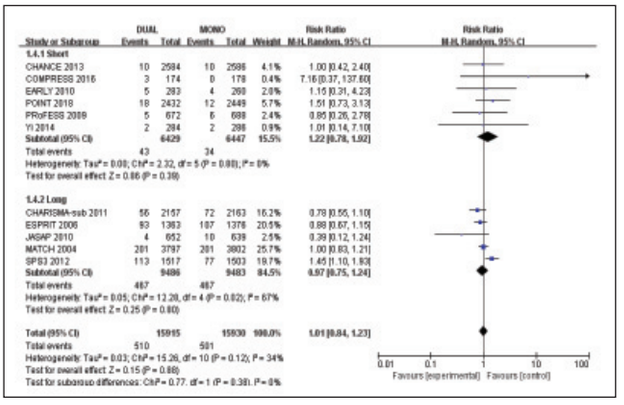
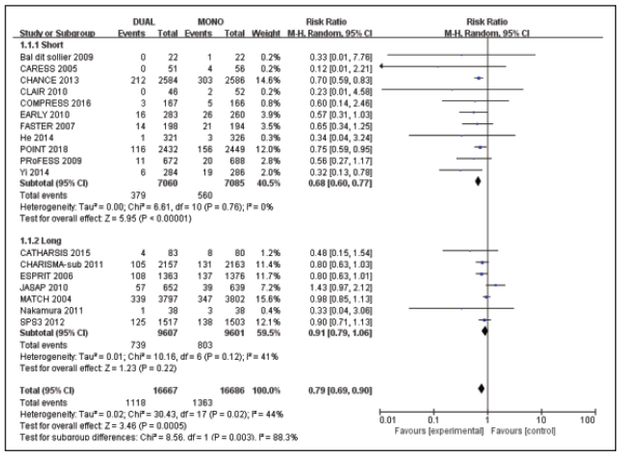


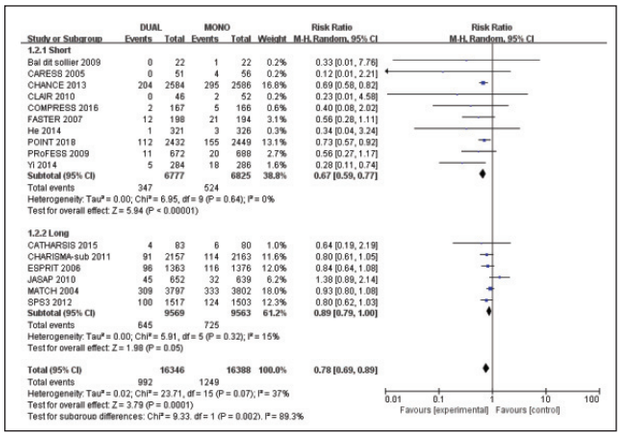
Fig. 2: Risk of bias graph and summary for included studies.











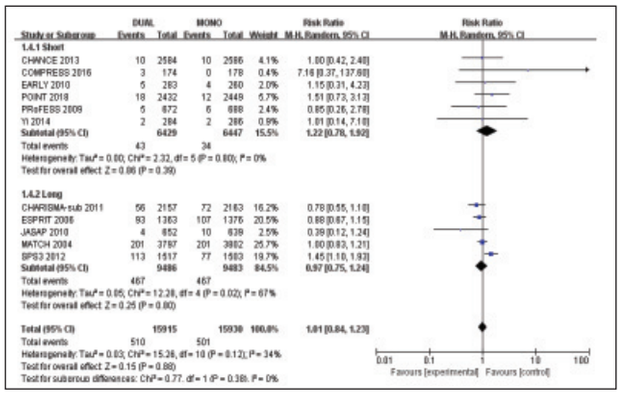
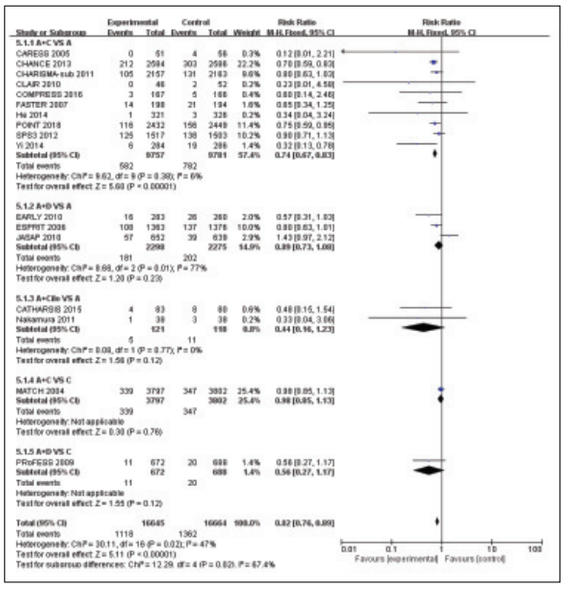
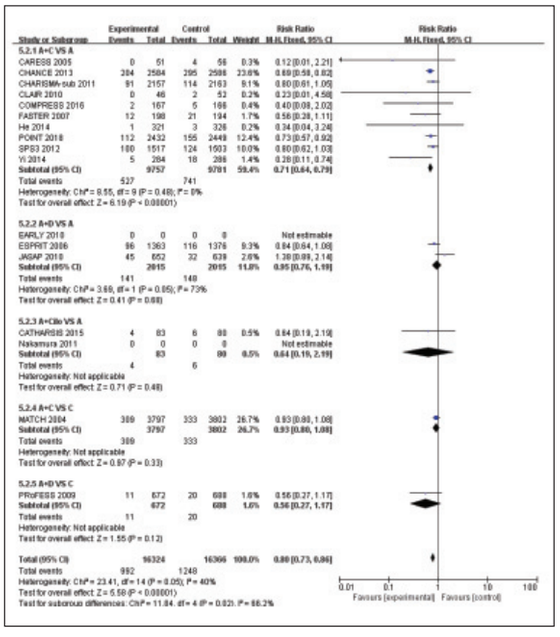
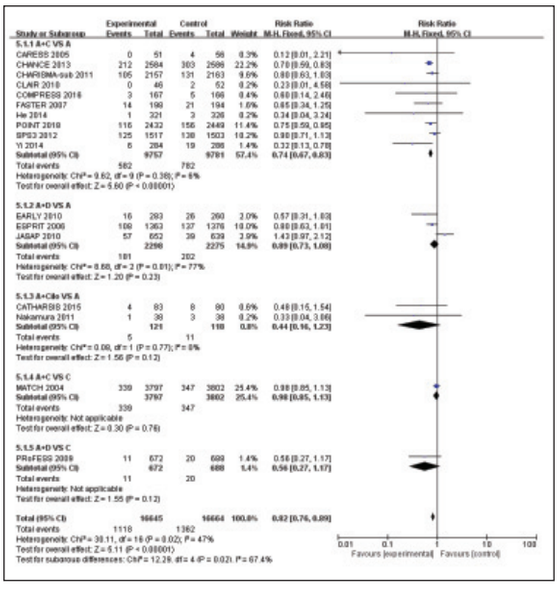


Fig. 3: Meta-analysis results of dual versus mono in short-term subgroup and long-term subgroup.

different from MAPT about all endpoints. Significant heterogeneity was shown in the outcome of all-cause death and major bleeding about late initiating DAPT group (P = 0.02, I^2 = 67%; P < 0.00001, I^2 = 86%). Compared with MAPT, DAPT reduced the risk of stroke recurrence in the non-Asian group (RR = 0.78, 95% CI = 0.67-0.91) but not in the Asian group, and decreased the risk of ischemic stroke recurrence in both Asian group and non-Asian group (RR = 0.68, 95% CI = 0.47-0.98; RR = 0.74, 95% CI = 0.63-0.87). However, the DAPT of two subgroups failed to reduce the risk of myocardial infarction and did not increase the risk of intracranial hemorrhage. In addition, DAPT contributed to an increase of all-cause death (RR = 1.45, 95% CI = 1.12-1.87) and major bleeding (RR = 1.94, 95% CI = 1.45-2.58) in the non-Asian group. High heterogeneity was observed in the outcome of stroke recurrence in Asian group (P = 0.02, I^2 = 58%).







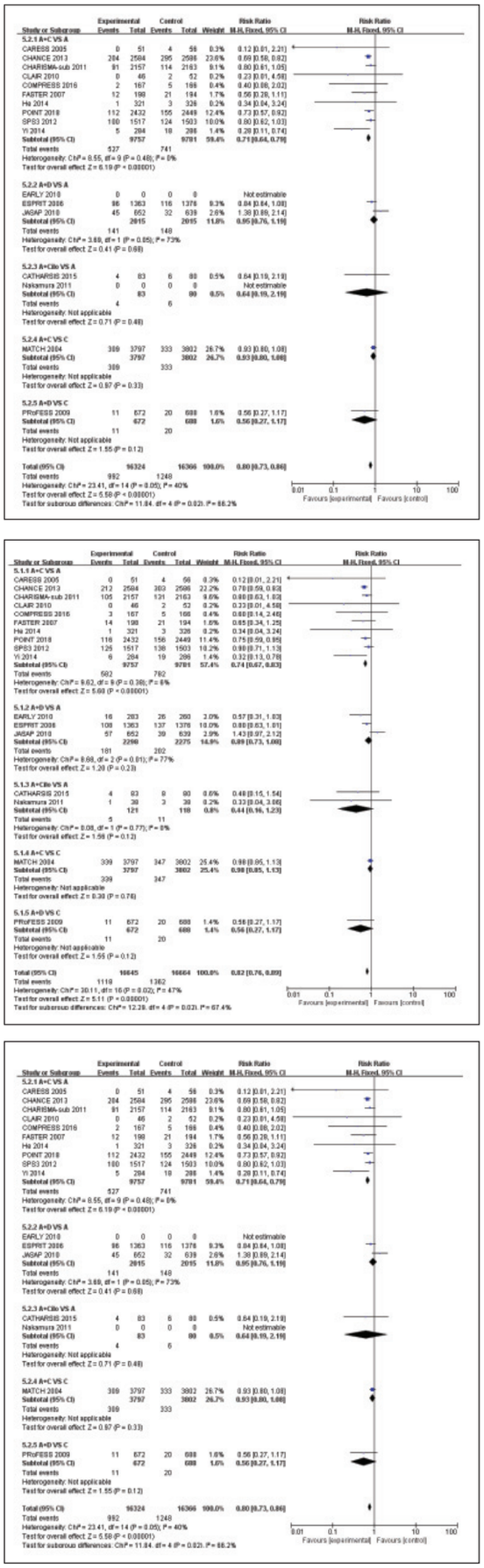


Fig. 4: Meta-analysis results of dual versus mono in five regiments subgroup. A, aspirin; C, clopidogrel; Cilo, cilostazol; D, dipyridamole.

2.3. Publication bias

We plotted inverted funnel plots for the six endpoints. By visual inspection, the funnel plots of myocardial infarction, all-cause death, major bleeding and intracranial hemorrhage were approximately symmetrical, suggesting the absence of significant publication bias. However, stroke recurrence and ischemic stroke recurrence were asymmetrical, suggesting the possibility of publication bias. (Figure 5A, Figure 5B) The results of the Egger regression test indicated no obvious publication bias for stroke recurrence (P = 0.14) and ischemic stroke recurrence (P = 0.22) in the included studies (Table 3).

3. Discussion

In this meta analysis, we evaluated the efficacy and safety of DAPT in stroke patients. The most important finding of our study was that short-term DAPT reduces the risk of stroke and ischemic stroke recurrence but increases the risk of major bleeding. In addition, the DAPT of aspirin plus clopidogrel appeared to be the most effective among five regiments although increasing the risk of major bleeding. Early initiating DAPT is important for patients with stroke and race may be one of the factors contributing to the efficacy of DAPT.

Ge et al. (2016) concluded that short-term DAPT appears to be superior to MAPT in reducing the risk of stroke recurrence and ischemic stroke recurrence but did not significantly increase the risk of major bleeding. Liu et al. (2016) recommended short-term DAPT for IS or TIA which showed a significant protection effects against stroke recurrence without increasing the risk of major bleeding (Liu et al. 2016). These results were not consistent with ours. One possible explanation was that, the CHANCE trial (Wang et al. 2015) accounted for a large proportion in the meta analyses of Ge et al. (2016) and Liu et al. (2016). Firstly, the low loading dose of aspirin and clopidogrel may result in a relatively low risk of major bleeding in that trial. Secondly, the duration of DAPT in that trail was only 21 days. A study indicated that the therapeutic benefits of aspirin and clopidogrel were mainly concentrated in the first month while the risk of bleeding remained relatively constant throughout the sequential treatment (Johnston et al. 2018). Furthermore, the enrolled patients in the CHANCE trial (Wang et al. 2015) also had lower stroke severity at admission (NIHSS ≤ 3), and these patients had a lower risk of bleeding. Finally, clopidogrel was used in both the CHANCE trail and our study and it has a wide interindividual variability during the therapy due to the need of cytochrome P450 (CYP)2C19 isoenzymes in metabolic transformation (Mallouk et al. 2012; Kazui et al. 2010). The patients enrolled in the CHANCE trial were Chinese. Carriers of the CYP2C19 allele loss-of-function (LOF) account for approximately 25% of the white race but up to 59% in the Asians (Pan et al. 2017). A meta-analysis showed that the rate of bleeding was significantly lower in carriers of CYP2C19 LOF compared with non-carriers (Xi et al. 2019). Therefore, the gene polymorphism of clopidogrel may lead to the higher risk of major bleeding in the non-Asian group rather than the Asian group in our study. These reasons may lead the CHANCE trial (Wang et al. 2015) to believe that short-term dual antiplatelet therapy does not increase the risk of major bleeding, and may also explain why the meta analysis conclusions of Ge et al. (2016) and Liu et al. (2016) are inconsistent with the current study.

Current guideline suggested that clopidogrel and aspirin could contribute to secondary stroke prevention if applied within 24 hours of stroke and then continued for 21 to 90 days (Powers et al. 2018). In the subgroup of regiment of our study, the DAPT of aspirin plus clopidogrel was accompanied with an increasing of major bleeding, although it reduced the risk of stroke and ischemic stroke recurrence. However, the two studies (Benavente et al. 2012; Hankey et al. 2011) which influenced our result significantly both used the long-term DAPT of aspirin plus clopidogrel. Many studies also proved that long-term combination of aspirin and clopidogrel would increase the risk of bleeding compared to short-term DAPT (Watanabe et al. 2019; Rahman et al. 2019). Moreover, a clinical practice guideline indicated that DAPT with

Table 2: Subgroup analysis of stroke recurrence, ischemic stroke recurrence, intracranial hemorrhage, myocardial infarction, all-cause death and major bleeding with initiating treatment time and race

Endpoints	Subgroup	Trials	*N*	Statistical method	RR (95% CI)	P for interaction	I-squared
Stroke recurrence	≤ 72 h	9	13972	M-H, random	0.69 (0.61, 0.78)	<0.00001	0%
	> 72 h	8	19218	M-H, random	0.92 (0.79, 1.06)	0.25	38%
	Asian	8	8348	M-H, random	0.67 (0.42, 1.04)	0.08	58%
	Non-Asian	6	8987	M-H, random	0.78 (0.67, 0.91)	0.002	0%
Ischemic stroke recurrence	≤ 72 h	7	13353	M-H, random	0.68 (0.59, 0.77)	<0.00001	0%
	> 72 h	8	19218	M-H, random	0.88 (0.77, 1.00)	0.06	19%
	Asian	7	8272	M-H, random	0.68 (0.47, 0.98)	0.04	39%
	Non-Asian	5	8444	M-H, random	0.74 (0.63, 0.87)	0.0004	0%
Intracranial hemorrhage	≤ 72 h	5	11660	M-H, random	1.40 (0.69, 2.85)	0.36	0%
	> 72 h	5	18969	M-H, random	1.18 (0.77, 1.80)	0.45	46%
	Asian	4	7678	M-H, random	1.03 (0.58, 1.82)	0.92	0%
	Non-Asian	3	8293	M-H, random	1.75 (0.96, 3.20)	0.07	0%
Myocardial infarction	≤ 72 h	6	12857	M-H, random	1.25 (0.65, 2.42)	0.50	0%
	> 72 h	5	16337	M-H, random	1.00 (0.76, 1.32)	1.00	24%
	Asian	4	7364	M-H, random	0.68 (0.36, 1.32)	0.25	0%
	Non-Asian	4	8551	M-H, random	0.91 (0.55, 1.49)	0.70	9%
All-cause death	≤ 72 h	6	12876	M-H, random	1.22 (0.78, 1.92)	0.39	0%
	> 72 h	5	18969	M-H, random	0.97 (0.75, 1.24)	0.80	67%
	Asian	4	7383	M-H, random	0.84 (0.38, 1.87)	0.67	23%
	Non-Asian	3	8444	M-H, random	1.45 (1.12, 1.87)	0.005	0%
Major bleeding	≤ 72 h	7	12774	M-H, random	1.75 (1.07, 2.85)	0.03	0%
	> 72 h	5	18969	M-H, random	1.38 (0.90, 2.12)	0.14	86%
	Asian	5	7052	M-H, random	1.06 (0.69, 1.63)	0.78	0%
	Non-Asian	4	8836	M-H, random	1.94 (1.45, 2.58)	<0.00001	0%

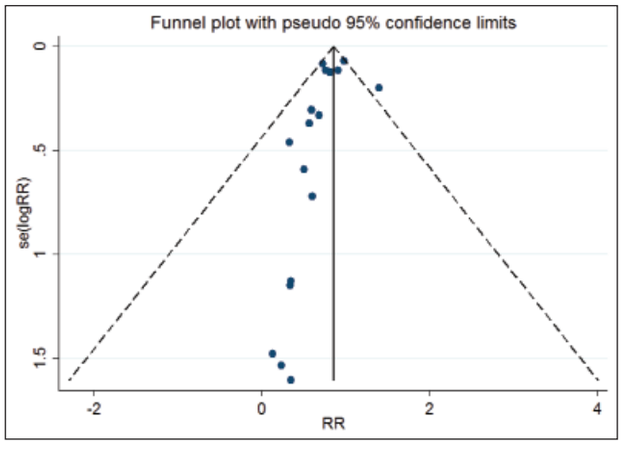


Fig. 5A: Funnel plot of stroke recurrence

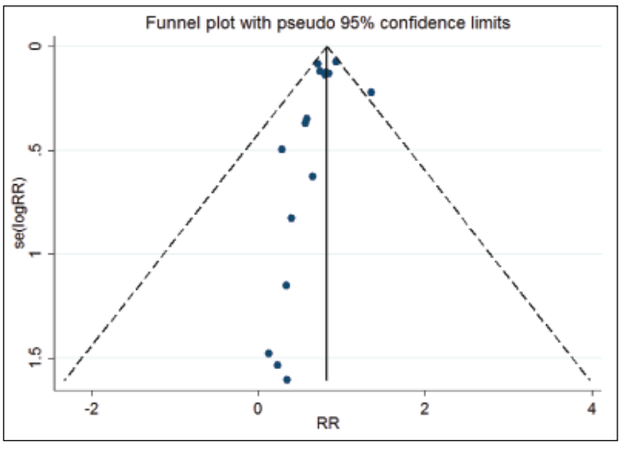


Fig. 5B: Funnel plot of ischemic stroke recurrence

aspirin and clopidogrel continued for 10-21 days could decreased 0.3% moderate to major bleeding events compared to 22-90 days and the maximum benefit was concentrated in the first 10 days (Prasad et al. 2018). Therefore, it is obvious that the short-term regiment of aspirin and clopidogrel is more beneficial for patients than long-term as stroke secondary prevention. The remaining four DAPT regiments did not show any efficacy compared with MAPT in our study. However, the DAPT such as aspirin plus cilostazol and aspirin plus dipyridamole both showed great efficacy in other studies when compared with aspirin or clopidogrel (Barlas et al. 2018; Toyoda et al. 2019). Hence, more effective DAPT combinations need to be further explored and studied.

Most recurrent strokes occurred in the initial 48 h after symptom onset (Johnston et al. 2000). Previous studies have shown that DAPT initiated within 72 h of symptom onset could provide more favorable stroke protection without increasing the risk of major bleeding (Liu et al. 2016; Wong et al. 2013; Geeganage et al. 2012). The enrolled patients had passed the very early high-risk period already when treated with DAPT beyond 72 h, which might partly explain our result that late initiating DAPT did not alter

Table 3: Statistical analysis of publication bias

Endpoints	Funnel Plot	Egger's test (P-value)
Stroke recurrence	asymmetrical	P = 0.14 > 0.05
Ischemic stroke recurrence	asymmetrical	P = 0.22 > 0.05
Intracranial hemorrhage	symmetrical	P = 0.38 > 0.05
Myocardial infarction	symmetrical	P = 0.49 > 0.05
All-cause death	symmetrical	P = 0.38 > 0.05
Major bleeding	symmetrical	P = 0.89 > 0.05

stroke outcomes compared to MAPT. Significant heterogeneity was found in our study. By analyzing the baseline data of each study, it was found that the possible source of heterogeneity was the combination difference of DAPT among different studies. The DAPT regiment in ESPRIT (Halkes et al. 2006) and JASAP (Uchiyama et al. 2011) which had great impact on heterogeneity was aspirin plus dipyridamole while other studies used aspirin plus clopidogrel.

Several advantages deserve to be mentioned for our study. Firstly, our analysis included a great sample from a large number of studies. Therefore, we were able to execute comprehensive subgroup analyses to evaluate any efficacy and safety outcomes thoroughly. Secondly, we included more DAPT combinations and performed subgroup analyses based on different combinations. Thirdly, the enrolled studies were RCTs, and quality evaluations demonstrated that the overall quality of evidence of our analysis was high, which enhanced our confidence in our pooled results and its further clinical application. However, our study has the following limitations. Firstly, only published English articles not all RCTs were included and the enrolled patients derived from RCTs may not represent community patients at large, which may lead to potential publication bias. Next, the included studies vary with study population, stroke severity, antiplatelet agents, onset-to-treatment interval and treatment course, all of these factors could be potential confounders for the efficacy and safety evaluation. Furthermore, the difference of definition of bleeding events among studies may lead to heterogeneity and influence the safety evaluation. Finally, only one study provided related information in the stratified analysis of aspirin plus clopidogrel versus clopidogrel alone or aspirin plus dipyridamole versus clopidogrel, which may result in imprecise estimations when applied in clinical service. Therefore, more high-quality studies are needed to determine clinical differences between antiplatelet regiments.

In conclusion, short-term DAPT was more effective for stroke prevention than MAPT although it was associated with a higher risk of bleeding. Long-term DAPT did not show superiority in efficacy. The DAPT with aspirin and clopidogrel may be a good alternative to prevent stroke recurrence, but the safety should be evaluated by further studies. More importantly, patients receiving DAPT with 72 h after symptoms onset could benefit more from DAPT and race may be one of the factors contributing to the efficacy of DAPT.

4. Experimental

4.1. Search strategy

PubMed, Embase, Web of Science and the Cochrane Library were searched to identify relevant articles published up to May 2019 concerning antiplatelet agents for secondary IS prevention, using the key words "antiplatelet therapy" , "aspirin" , "clopidogrel" , "dipyridamole" , "cilostazol" , "stroke" , "cerebral infarction" and "transient ischemic attack". The reference lists of included articles were also reviewed to supplement and identify relevant studies.

4.2. Study selection

Two independent researchers excluded irrelevant studies by screening titles and abstracts and then examined the full text in order to determine the final list of eligible studies. If there is a disagreement, they would settle it by discussion and consulting a third reviewer if necessary.

Studies met following criteria were includes: (1) RCTs published in English comparing DAPT (aspirin + clopidogrel or aspirin + dipyridamole or aspirin + cilostazol) with aspirin or clopidogrel MAPT for secondary stroke prevention; (2) patients with prior IS or TIA; (3) evaluated the efficacy and safety of outcomes after patients taking antiplatelet agents; (4) clinical data could be extracted.

Trails are excluded based on following criteria: (1) non-English study; (2) non-RCTs; (3) repeated publications; (4) summary or case report; (5) compared triple antiplatelet therapy with MAPT; (6) follow-up less than seven days; (7) clinical data insufficient or missing and unable to be extracted or calculated.

4.3. Endpoint

The primary endpoints: (1) stroke recurrence; (2) ischemic stroke recurrence; (3) all-cause death: including vascular, nonvascular or unknown cause.

The secondary endpoints: (1) myocardial infarction; (2) major bleeding; (3) intracranial hemorrhage: including epidural hematomas, subdural hematomas, subarachnoid hemorrhage, cerebral hemorrhage and intraventricular hemorrhage.

4.4. Data extraction

Two researchers independently extracted the following data: basic information of included studies (including title, first author, issuing time, country, region, et al.); basic characteristics of the research objects (including sample size of patients, age, gender, disease status, duration of follow-up, treatment dosages, duration of each antiplatelet therapy group, et al.); research data; primary and secondary outcome.

4.5. Quality assessment

With bias and risk assessment tools of Cochrane collaboration, we assessed 18 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 others forms of bias. The assessment outcomes are divided into the following three categories: '+' means low bias risk; '-' means high bias risk; '?' means unclear bias risk (Higgins et al. 2011).

4.6. Statistical analysis

Data were entered and analyzed using RevMan software (version 5.3) and Stata software (version 13.0). The statistical analyses were conducted based on the random-effect model. Results of relative ratio (RR) with 95% confidence intervals (CIs) were used as the analytical statistics and represented and explained by forest maps. The presence of heterogeneity between the results of each study was quantified by chi-square test and $I^2 > 50\%$ indicated significant heterogeneity. Publication bias was assessed by Egger's test and visual examination of funnel plots (Kicinski et al. 2015). Significance was set at $P < 0.05$. Subgroup analysis was performed according to duration of antiplatelet drugs treatment, different regiments, race and initiating treatment time. The detailed group was as follows: (1) duration: short-term group (≤ 3 months) and long-term group (> 3 months). (2) regiment: Group A (aspirin + clopidogrel versus aspirin), Group B (aspirin + dipyridamole versus aspirin), Group C (aspirin + cilostazol versus aspirin), Group D (aspirin + clopidogrel versus clopidogrel) and Group E (aspirin + dipyridamole versus clopidogrel). (3) initiating treatment time: early initiating DAPT group (≤ 72 h) and late initiating DAPT group (> 72 h). (4) race: Asian group and non-Asian group.

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