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Dual Antiplatelet Therapy (DAPT) Versus Single Antiplatelet Therapy (SAPT) in Patients with Stroke Under 12 Hours: Meta-analysis and Systematic Review

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ABSTRACT

Background: Patients with ischemic stroke under 12 hours are typically treated with antiplatelet therapy. Combining two antiplatelet medicines agents with differing actions and antithrombotic efficacy increases the risk of hemorrhage. Among 1000 patients with ischemic stroke, dual-antiplatelet therapy was associated with 1 to 7 more ICH events than clopidogrel monotherapy and seemed to provide no significant additional benefit in reducing ischemic stroke events. ***Method:*** Search in PubMed, EMBASE, and the Cochrane Central Register about dual antiplatelet therapy versus monotherapy. The research method used was PRISMA guidelines followed by literature exclusions. The inclusion criteria in this literature search were medicinal, literature from 2013-2023. ***Results:*** There is 5 literatures discussing the advantages of DAPT with the results obtained DAPT was not associated with a significant reduction in recurrent ischemic stroke [pooled RR 0.79 (95%CI 0.67-0.92)] but was associated with a higher risk of major bleeding [pooled RR 1.86 (95%IC 1.86-3.32)]. ***Conclusion:*** Immediate administration of DAPT <12 hours after ischemic stroke can reduce recurrent stroke compared with antiplatelet monotherapy despite the increased risk of hemorrhage.

Keywords: antiplatelet; antithrombotic; dual antiplatelet therapy (DAPT); ischemic stroke; single antiplatelet therapy (SAPT)

INTRODUCTION

The most important aspect of secondary stroke prevention for noncardioembolic ischemic stroke and transient ischemic attack (TIA) is antiplatelet treatment [1]. Because dual antiplatelet therapy (DAPT) inhibits platelet activation pathways more potently than single antiplatelet therapy (SAPT), it may reduce the risk of stroke even more [2]. Clinical investigations comparing SAPT and DAPT for secondary prevention, however, have not consistently demonstrated a decrease in recurrent stroke and frequently find an increase in the risk of bleeding [3].

An effective intervention for the short- and long-term secondary prevention of stroke and transient ischemic attack following an index event is single antiplatelet treatment with aspirin or clopidogrel [4,5]. Physicians occasionally employ dipyridamole and aspirin together or as substitutes for cilostazole; both are referred to in this recommendation as single-agent therapy [6].

The advantages of DAPT over SAPT in short-term trials, but not in long-term trials, might be related to when treatment is started. Randomized treatment was started in the short-duration studies shortly after the stroke, either in 12 or 24 hours for the two larger trials or in 72 hours or 7 days for the smaller trials. Within three or six months of the stroke onset, randomized treatment was started in the long-term trials (mean time to randomization was 27 days for the former and 62 days for the latter). Since there is a small increase in the absolute risk of recurrent stroke in the initial months following a stroke, trials that start treatment shortly after the stroke may find it easier to uncover benefits in reducing the risk of recurrent stroke. In a similar vein, the lengthier DAPT [7].

The efficacy of DAPT administered <12 hours (aspirin and clopidogrel) compared with aspirin monotherapy in patients with minor stroke or TIA was found to reduce the incidence of recurrent stroke despite the greater risk of bleeding. The safety of combined aspirin and clopidogrel in preventing recurrent stroke in mild stroke (National Institutes of Health Stroke Scale score ≤3) or high-risk TIA (ABCD2 score≥4) has been established by 2 large-scale multicenter studies [2,3,7]. This meta-analysis and systematic review were used to determine the relative risk of recurrence of ischemic stroke and the risk of intracerebral hemorrhagic stroke.

MATERIALS AND METHODS

PubMed, EMBASE, and the Cochrane Central Register data sources until December 2023. The terms used in the search were "dual antiplatelet", "antiplatelet", "ischemic stroke", and "stroke attack <12 hours", PRISMA criteria were followed by literature exclusions as the study methodology.

The exclusion criteria for this review were animal samples, non-research literature, literature from 2013-2023, discontinuity/irrelevant topics between the abstract and the review material, and other reviews. The inclusion criteria for this literature search were medical, literature from 2013-2023, and if it didn't have data on the relative risk of recurrent ischemic stroke.

RESULTS

A total of 176 literatures were obtained which were then reviewed and screened based on inclusion and exclusion criteria resulting in 5 literatures to be reviewed which can be seen in figure 1. Study Designs, Treatment Protocols, and Baseline Characteristics at Table 1. The relative risk of recurrent ischemic events in the use of DAPT compared to SAPT in Table 2. Overall RR this study got RR 0.79 (95%CI 0.67-0.92) which means that the risk of recurrent stroke events in the use of DAPT is not up to 1 time increase so this shows that DAPT is better in stroke recurrence rates compared to SAPT. The results of bleeding risk were found to increase with an RR value of 1.86 (95%IC 1.86-3.32) which means that the risk of bleeding using DAPT increased more than 1.86 times the incidence compared to SAPT.

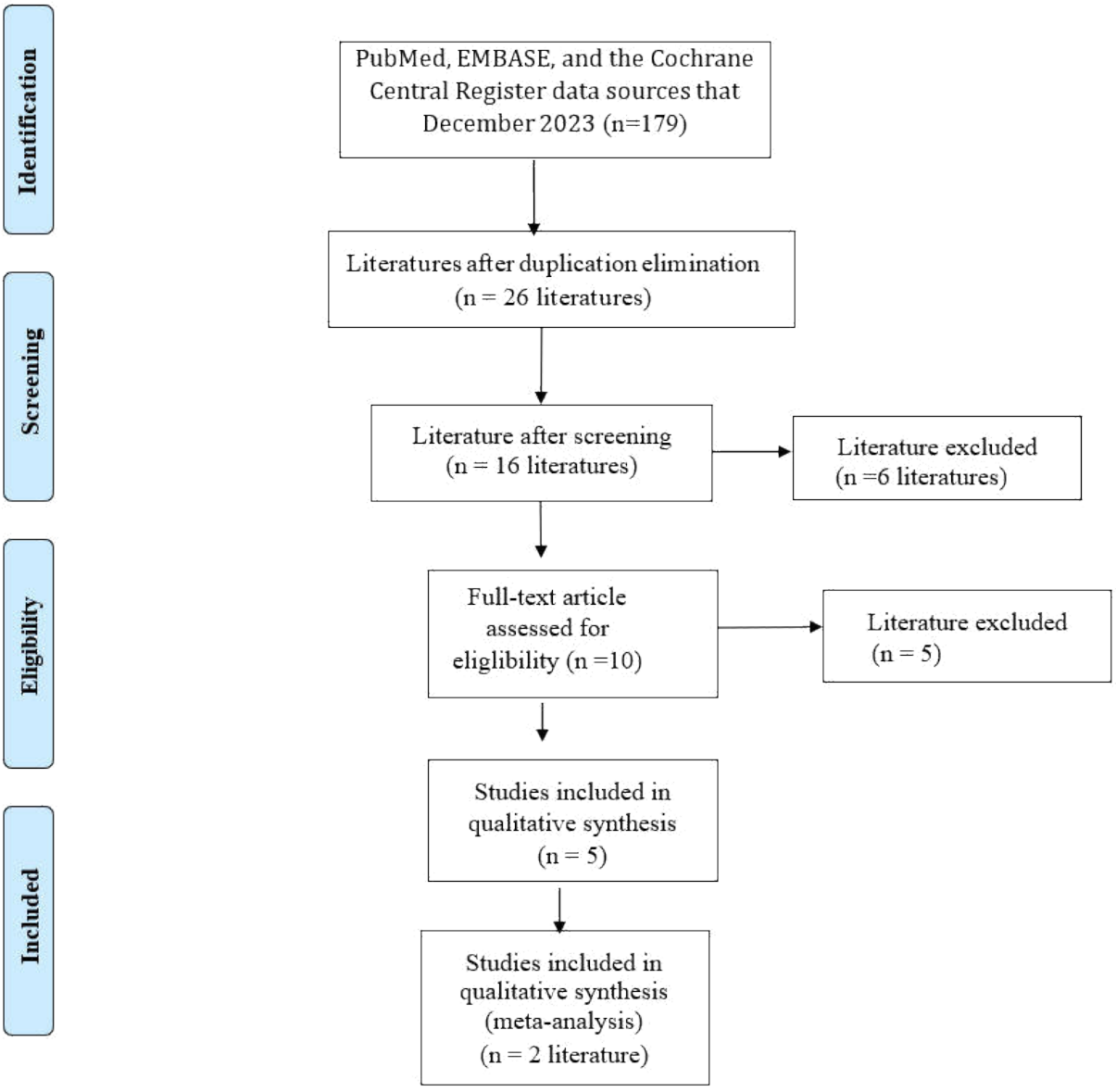

FIGURE 1: PRISMA flow diagram which illustrates the process of selection of the literature.

TABLE 1: Study designs, treatment protocols, and baseline characteristics.

Characteristics	Wang et al., 2013[4]	Johnston et al., 2018[5]	Johnston et al, 2020 [8]	Bhatia et al, 2021 [2]	Brown, 2021[7]
Study characteristics					
No. of patients randomized	5170	4881	11016	21.459	17896
Study design	Double-blind	Double-blind	Double-blind	Meta-analysis	Meta-analysis
Treatment	Aspirin+ clopidogrel vs aspirin	Aspirin+ clopidogrel vs aspirin	Aspirin+ ticagrelor vs aspirin	DAPT vs aspirin	DAPT vs aspirin
Inclusion NIHSS score	0-3	0-3	0-3	0-5	0-5
Primary outcome	Recurrent stroke (ischemic or hemorrhagic)	Major ischemic events	Composite of stroke or death	recurrent stroke at the expense of a higher risk of major bleeding.	prevention of secondary ischemic stroke
Baseline characteristics					
Mean age (SD)	62.8 (12.6)	64.8 (13.7)	65.2 (11.0)	65,2 (12.4)	65,1 (11,4)
Females	33.9%	45 %	38.8%	41,22%	40,2%
Hypertension	65.7%	69.4%	69.4%	68,1%	68,0%
Diabetes	21.1%	27.5%	28.6%	25,7%	26,5%
Dyslipidemia	11.1%	-	-	9,1%	10,5%
Current or previous smoker	42.9%	20.6%	26.6%	29,1%	23,5%

TABLE 2: Relative risk of recurrent ischemic events in the use of DAPT versus SAPT.

Literature	RR	95% IK	P-value
Wang et al., 2013[4]	0,70	0,59-0,83	<0,001
Johnston et al., 2018[5]	0,75	0,59-0,95	<0,001
Johnston et al, 2020 [8]	0,81	0,70-0,95	<0,001
Bhatia et al, 2021[2]	0,76	0,68-0,83	<0,001
Brown et al 2021[7]	0,89	0,79-1,02	<0,001
Overall	**0,79**	**0,67-0,92**	

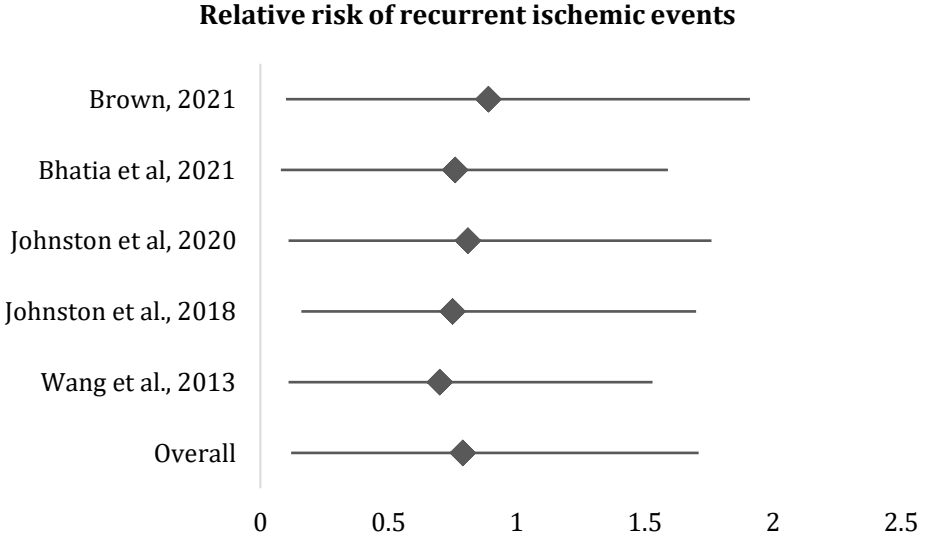

FIGURE 1: Fores plot the relative risk of recurrent ischemic events using DAPT versus SAPT.

TABLE 3: Relative risk of intracranial hemorrhage in the use of DAPT compared to SAPT.

Literature	RR	95% IK	P-value
Wang et al., 2013[4]	1,00	0,38-2,66	<0,001
Johnston et al., 2018[5]	1,68	0,40-2,01	<0,001
Johnston et al, 2020 [8]	3,25	1,66-4,95	<0,001
Bhatia et al, 2021[2]	2,22	1,14-4,34	<0,02
Brown et al., 2021[7]	1,18	0,53-2,65	<0,001
Overall	**1,86**	**0,82-3,32**	

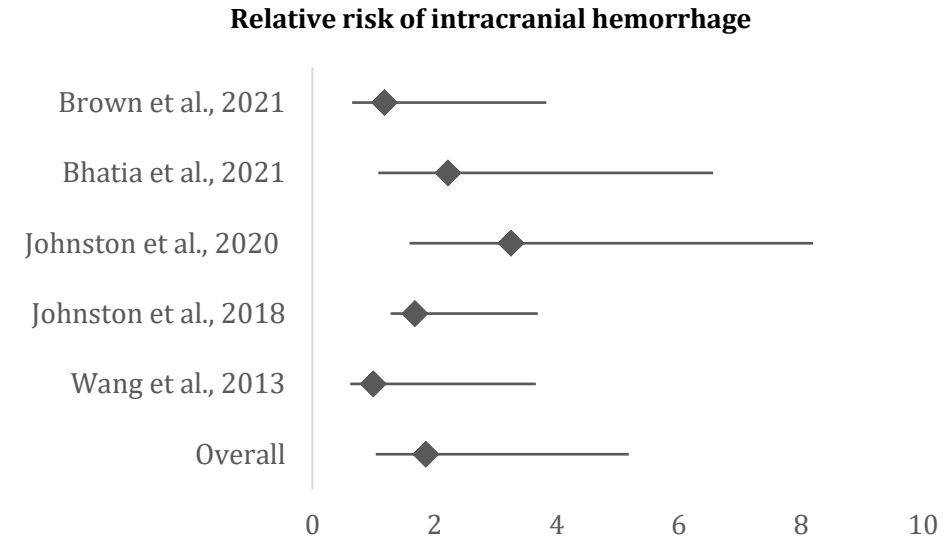

FIGURE 2: Fores plot the relative risk of recurrent ischemic events using DAPT versus SAPT.

DISCUSSION

The results of this study obtained 3 double-blind studies and 2 systematic reviews. The results showed that the use of DAPT was more effective than the use of SAPT. Globally, stroke is one of the main causes of death and disability. Major risk factors of stroke include age, ethnicity, hypertension, diabetes mellitus, smoking, metabolic syndrome, and atrial fibrillation [9]. There are many subtypes of example, atherosclerosis, atrial fibrillation, and small vessel disease. Moreover, elderly patients with ischemic stroke often have worse outcomes than younger patients. The results from the literature show that the age of stroke patients ranges from 60-66 years, this shows that stroke is a disease associated with aging. This nonmodifiable increases the incidence of cerebrovascular events, doubling it for each decade after the age of 55 years [10].

Hypertension was the most common risk factor and cardioembolic stroke was the most common stroke sub-type in the elderly and was associated with poor outcome. Thus, it is very important to detect atrial fibrillation among the elderly in order to secondary prevent stroke and manage the patient appropriately. [11]. Hypertension is the most prevalent risk factor for stroke, based on data from 30 studies, and has been reported in about 64% of patients with stroke. In low-income countries, the reported prevalence of risk factors among patients with stroke is lower, however, patients have the highest in-hospital mortality, probably due to delays in presentation for seeking acute stroke care, differences in health system response, and acute stroke management [12].

Blood pressure is a powerful determinant of risk for ischemic stroke and intracranial *hemorrhage* and there is evidence that controlling BP levels to < 150/90 mmHg reduces the risk of stroke. Evidence of the benefits is weaker for lower BP targets obtained with intensive BP lowering, especially in older patients.42,43 The management of BP in adults with stroke is complex and challenging due to its heterogeneous causes and hemodynamic consequences. Future studies should focus on optimal timing and targets for BP reduction, as well as ideal antihypertensive agent therapeutic class by patient type and event type. [12].

The use of DAPT (Clopidogrel + Aspirin) versus aspirin conducted by Wang et al., 2013 found that among patients with TIA or minor stroke who can be treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage [4]. In Johnston et al., 2018 study In patients with minor ischemic stroke or high-risk TIA, those who received a combination of clopidogrel and aspirin had a lower risk of major ischemic events but a higher risk of major hemorrhage at 90 days than those who received aspirin alone [5].

The use of DAPT with aspirin and P2Y12 inhibitors compared to aspirin monotherapy in patients with minor ischemic stroke or TIA is known to reduce the recurrence rate of ischemic stroke.

Research on the use of a combination of Aspirin + Ticagrelor vs aspirin obtained results among patients with a mild-to-moderate acute noncardioembolic ischemic stroke (NIHSS score ≤5) or TIA who were not undergoing intravenous or endovascular thrombolysis, the risk of the composite of stroke or death within 30 days was lower with ticagrelor-aspirin than with aspirin alone, but the incidence of disability did not differ significantly between the two groups. Severe bleeding was more frequent with ticagrelor Johnston et al, 2020 [8]. Ticagrelor is a direct antagonist of P2Y12 inhibitors and has a more consistent and potent antiplatelet effect compared to clopidogrel [13].

The results of 2 systematic review studies in 2021 conducted by Bhatia et al, and Brown, et al found that as compared to aspirin alone, short-term DAPT within 24 hours of high-risk transient ischemic attack or mild-moderate ischemic stroke reduces the risk of recurrent stroke at the expense of higher risk of major bleeding and DAPT was more effective than SAPT for prevention of secondary ischemic stroke when initiated early after stroke. the onset of minor stroke/high-risk transient ischemic attack and treatment duration was <90 days [2,7].

CONCLUSION

DAPT with aspirin and ticagrelor or clopidogrel given within 12 hours in high-risk TIA or mild to moderate noncardioembolic stroke effectively reduces the risk of recurrent stroke compared with aspirin monotherapy, although bleeding events are increased so guidance is needed by the patient's underlying thrombotic and bleeding risk profile.

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