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Dual Antiplatelet Therapy Role in Acute Ischemic Stroke

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ABSTRACT

Stroke is the second greatest cause of mortality and one of the top causes of long-term disability. The fatality rate and age-adjusted prevalence of stroke have decreased globally over the past quarter-century. However, the absolute number of stroke cases has climbed, as populations have grown older. Initiating antiplatelet medications early in patients with acute ischemic stroke (AIS) is essential for preventing stroke recurrence. Aspirin, clopidogrel, and dipyridamole are the most commonly used antiplatelet medications worldwide. Combining antiplatelet drugs is associated with an increased risk of bleeding when used for long-term prophylaxis. The use of Dual antiplatelet treatment (DAPT) for a shorter duration is associated with a lower risk than long-term usage. The best period of treatment for transient ischemic attack (TIA) and mild ischemic stroke appears to be between 21 and 30 days.

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Introduction

Globally, stroke is the second greatest cause of mortality and one of the top causes of long-term disability [1]. The fatality rate and age-adjusted prevalence of stroke have decreased globally over the past quarter-century, but the absolute number of stroke cases has climbed as populations have grown older [1]. Ischemic stroke is by far the most prevalent cause of stroke worldwide, accounting for 10 times more strokes than hemorrhagic strokes in countries with higher incomes, but with a significantly smaller difference in countries with lower incomes [2, 3]. It is believed that up to fifty percent of stroke-related deaths are linked to inadequately manage modifiable risk factors, despite the fact that the stroke mortality rate is decreasing [4]. The management of hypertension, hypercholesterolemia, diabetes, smoking, and cardiac arrhythmias such as atrial fibrillation are all supported by a substantial body of data for reducing the incidence and recurrence of stroke [5]. Studies have found a recurrence rate of 1.1–15% within 30 days after a stroke and up to 17% after a transient ischemic attack (TIA) [6, 7]. Although one-third of patients with fast resolving impairments are at high risk for repeat vascular incidents, they are not considered for thrombolytic therapy [8]. Therefore, interventions that minimize this early risk can have a significant effect on morbidity and death. Initiating antiplatelet medications early in patients with acute ischemic stroke (AIS) is essential for preventing stroke recurrence and lowering the mortality rate in the acute period and over the long term [9]. The primary medical treatment for AIS is intravenous thrombolytic therapy. Aspirin, clopidogrel, and dipyridamole are the most commonly used antiplatelet medications worldwide [10, 11]. All have substantial evidence for the prevention of recurrent stroke. Sadly, some people display "resistance" to these drugs (have ischemia episodes while on an antiplatelet agent), have deleterious consequences from treatment, or develop allergic responses [12]. Combining antiplatelet is associated with an increased risk of bleeding when used for long-term prophylaxis; however, this increased risk is frequently outweighed by a reduction in stroke recurrence in the near term [13, 14]. As a result, the treatment provider is presented with a tough option regarding how best to treat a patient who has already received one antiplatelet medication yet is experiencing more stroke occurrences. Regarding the safety and efficacy of single or dual antiplatelet therapy (DAPT) for the treatment of AIS, there remains debate. Both aspirin and

clopidogrel are superior to aspirin alone for reducing the risk of stroke within the first 90 days, and neither increases the risk of bleeding [15]. DAPT with aspirin and ticagrelor or clopidogrel taken within 24 hours of a high-risk TIA or noncardioembolic mild to moderate stroke lowers the risk of recurrent stroke and MACE more effectively than aspirin monotherapy. While the risk of death from any cause remains same, DAPT is associated with an increased risk of bleeding events. In selecting whether or not to utilize DAPT with the addition of clopidogrel or ticagrelor to aspirin, therefore, the patient's underlying thrombotic and bleeding risk profile must be considered as a guide [16].

Method

This study reviwed efficacy of DAPT with aspirin and a P2Y12 inhibitor in acute ischemic every articles published between January 1980 and September 2022. Eligible articles were retrieved from Medline, EMBASE, Web of Science, and Cochrane Central using the terms "ischemia", "stroke", "cerebral infarction", "transient ischemic attack", "aspirin", "clopidogrel", "ticagrelor", "prasugrel", and "antiplatelets". In addition, the references of the listed research were combed for any further investigations. Observational studies were not included for the purposes of this study. Two reviewers examined the titles and abstracts of the retrieved studies to determine which fulfilled the inclusion criteria. If there was any disagreement, a third reviewer (A.Q.) assisted achieve a consensus.

Result

Several previous trials have demonstrated that dual antiplatelet medication for the secondary prevention of ischemic stroke over the long run is dangerous. Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) trial demonstrated in 2004 that adding aspirin to clopidogrel increased the risk of life-threatening or significant bleeding in high-risk patients who had recently suffered an ischemic stroke or transient ischemic attack (TIA). 1 In 2008, the PRoFESS trial compared aspirin and extended-release dipyridamole. The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) study examined whether dual antiplatelet medication may be more effective in the short term than in the long term for patients with recent mild ischemic stroke or TIA. In 2012, the Secondary Prevention of Small Subcortical Strokes (SPS3) trial indicated that the addition of clopidogrel to aspirin improved outcomes for individuals with recent symptomatic lacunar stroke.

In the weeks following an index mild ischemic stroke and a transient ischaemic attack with a high risk of recurrence, the risk of recurrent stroke and other vascular events ranges from 5 to 11.7%. Dual antiplatelet treatment (DAPT), which includes aspirin and clopidogrel, is a successful method for minimizing recurrence. Dual antiplatelet medication following a stroke has not been proved to be superior to a single drug. In recent years, acute antiplatelet treatment trials have evaluated the efficacy and safety of more extensive treatment to prevent recurrent stroke following mild ischemic stroke or high-risk transient ischaemic attack [17].

The BMJ and Sorcery group concluded, based on a new randomized controlled trial followed by an effective survey, that double antiplatelet medication for a limited time after a mild stroke is beneficial. Low-dose aspirin and clopidogrel (Plavix), when started as soon as feasible after a high-risk transient ischemic attack (TIA) or mild ischemic stroke without persistent debilitating neurologic damage and sustained for 10 to 21 days, prevent recurrent stroke and disability compared to aspirin alone. Long-term (22 to 90 days) continuation of dual antiplatelet medication after stroke is not associated with any improvement in stroke-related outcomes and is associated with an increased risk of bleeding. Patients should continue taking a single agent for the foreseeable future. Dual antiplatelet therapy should not be administered to individuals suffering from a large stroke due to the increased risk of cerebral hemorrhage.

DAPT may treat patients with symptomatic large vessel high-grade cerebral atherosclerosis. In the SAMMPRIS trial, patients with high-grade intracranial stenosis who had a TIA or ischemic stroke within 30 days were randomly randomized to either stenting or aggressive medical therapy, including aspirin 325 mg daily and clopidogrel 75 mg daily, for 90 days (Stenting Versus Aggressive Medical Therapy for Intracranial Atherosclerosis). 1 The experiment was terminated early due to significantly higher rates of stroke and death in the stenting group. All SAMMPRIS patients got DAPT in addition to rigorous therapy of stroke risk factors. Importantly, in SAMMPRIS, both stented and control patients exhibited reduced incidence of recurrent ischemic strokes than in previous intracranial atherosclerosis clinical trials. Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis (WASID) patients who satisfied SAMMPRIS inclusion criteria had a 30-day stroke/death rate of 10.7% and a 1-year stroke/death rate of 25%, compared to 5.8% and 12.5%, respectively, in SAMMPRIS patients. This shows that intensive medical therapy, including DAPT, may be advantageous for individuals with cerebral atherosclerosis in the first 90 days following a stroke. 2

CLAIR (Clopidogrel plus Aspirin Versus Aspirin Alone for Reducing Embolization in Patients with Acute Symptomatic Cerebral or Carotid Artery Stenosis) and CARESS (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis) demonstrate reduced microembolic signals with transcranial Doppler in the first week after ischemic stroke. Despite the paucity of data beyond seven days after the initial stroke and the small number of occurrences in both groups, there were no differences in the number of recurrent stroke events between the two trials. The frequency of recurrent strokes has decreased by 6%, according to a meta-analysis.

Discussion

Both the treatment and prevention of acute ischemic stroke rely on antiplatelet medication. Patients with known symptomatic cerebrovascular illness and those at high risk for atherosclerosis benefit from antiplatelet medication, which lowers the risk of stroke. Our purpose was to investigate the effect of dual antiplatelet medication on patients with acute ischemic stroke. Dual antiplatelet medication has been demonstrated to reduce future ischemic events after a small stroke or TIA with high risk, but it also raises the risk of bleeding problems. Individual patient features, such as stroke pathology and the possibility of cytochrome P450 2C19 polymorphisms, must be taken into account when weighing the risk of a repeat ischemic episode vs the danger of significant bleeding for each individual patient. Prasugrel and ticagrelor, two more strong P2Y12 inhibitors, as well as intensive therapy with three antiplatelet drugs, may increase the risk of bleeding and should be avoided until additional data are available.

Dual antiplatelet treatment (DAPT) with aspirin and clopidogrel is not advised for secondary stroke prevention due to the risk of severe bleeding. In the CHANCE and POINT trials, published in 2013 and 2018, it was shown that short-term DAPT lowered the risk of early recurrent stroke following mild ischemic stroke

and transient ischemic attack. Consequently, from 2011 to 2019, short-term DAPT recommendations were incorporated into classifications with increasing levels of evidence in the American Heart Association/American Stroke Association guidelines.

Studies indicating DAPT effectiveness employed DAPT for a relatively short period of time. Benefit with long-term DAPT was countered by increased bleeding. The MATCH trial (Aspirin and Clopidogrel Compared with Clopidogrel Alone after Recent Ischaemic Stroke or Transient Ischaemic Attack in High-Risk Patients) compared DAPT to clopidogrel alone in stroke or TIA patients at high risk. The DAPT failed to prevent major vascular events and increased life-threatening bleeding consequences, primarily cerebral and gastrointestinal. 54% of patients in MATCH experienced lacunar stroke, while 34% had big artery stroke. These data along with the SPS3 trial (Effects of Clopidogrel Added to Aspirin in Patients With Recent Lacunar Stroke), which compared DAPT to aspirin in patients with subcortical, lacunar strokes, showed DAPT dramatically increased annual risk of hemorrhages and mortality. 5 SPS3 was prematurely terminated because to significant hemorrhage and death in the DAPT arm. The bulk of hemorrhages occurred within the brain, followed by the digestive system.

In MATCH and SPS3, the use of DAPT for a shorter duration is associated with a lower risk than long-term usage. Neither DAPT nor aspirin monotherapy significantly increased the risk of bleeding in the CHANCE study (2.3% versus 1.6%). POINT demonstrated a rise in severe hemorrhage (0.9% vs. 0.4%), but only between 8 and 90 days, with an overall advantage of DAPT through day 30. The prolonged duration of DAPT in POINT is likely to result in more bleeding. The best period of DAPT appears to be between 21 and 30 days in patients with TIA and mild ischemic stroke at high risk. SAMMPRIS results suggest 90 days of DAPT for individuals with intracranial atherosclerosis; nevertheless, the best duration of therapy for intracranial atherosclerosis has not been evaluated precisely.

Current guidelines advocate the use of DAPT for secondary prevention in individuals with cerebral ischemia who are at high risk for early recurrence strokes. The American Heart Association (2014) secondary prevention guideline supports DAPT for 90 days for individuals with significant intracranial stenosis (Class IIb). Level of Evidence B), whereas DAPT may be used to treat patients with atrial fibrillation-related ischemic stroke or transient ischemic attack who are unable to take oral anticoagulants (Class IIb; Evidence Level B). Class IIb; Evidence at Level B; However, the evidence level has been raised to Class I; In the 2019 update to the Early Management of Stroke, Level of Evidence A)10, studies that demonstrated the benefit of DAPT were conducted in patients who had no acute stroke (ACTIVE A), low NIHSS (CHANCE, POINT), or a nondisabling stroke (SAMMPRIS). These patients had a minimal risk of hemorrhagic conversion because they lacked or had minor infarct volumes.

Conclusions

Patients with cerebral ischemia are at a significant risk for early recurrent stroke, and current guidelines recommend the use of DAPT for secondary prevention. Patients with ischemic stroke/TIA related to atrial fibrillation who are unable to take oral anticoagulation may be treated with DAPT if they are unable to take oral anticoagulation (Class IIb; Level of Evidence B). DAPT for 21 days after mild stroke might be considered (Class IIb; Level of Evidence B; however, the level of evidence is upgraded to Class I; Level of Evidence A in the 2019 update to the Early Management of Stroke). 10 studies demonstrating the efficacy of DAPT on patients with nondisabling stroke (SAMMPRIS), low NIHSS (CHANCE, POINT), or no acute stroke were completed (ACTIVE A). These patients had either no infarct volume or a minor infarct volume, and hence a minimal probability of hemorrhagic conversion. The use of DAPT in patients with a high NIHSS or big infarcts would be riskier and is therefore not advised.

The benefit appears to be greatest in the short term (within 7 days) after a stroke or TIA, although the risk of bleeding remains elevated during the extended course of treatment. Therefore, further research is required to identify the appropriate length of DAPT treatment. In addition, additional clinical trials are required to determine which treatment alternatives people with more severe ischemic strokes who are not candidates for thrombolysis prefer.

References

1. Feigin VL, Abajobir AA, Abate KH, Abd-Allah F, Abdulle AM, et al. (2017) Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Neurology 16: 877-97.
2. Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP (2009) Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. Stroke 40: 2068-2072.
3. Poon MT, Bell SM, Salman RA S (2016) Epidemiology of intracerebral haemorrhage. New Insights in Intracerebral Hemorrhage 37: 1-12.
4. Avan A, Digaleh H, Di Napoli M, Stranges S, Behrouz R, et al. (2019) Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden: an ecological analysis from the Global Burden of Disease Study 2017. BMC medicine 7: 1-30.
5. Boehme AK, Esenwa C, Elkind MS (2017) Stroke risk factors, genetics, and prevention. Circulation research 120: 472-495.
6. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, et al. (2011) Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke 42: 1489-1494.
7. Giles MF, Rothwell PM (2007) Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. The Lancet Neurology 6: 1063-1072.
8. Barber P, Zhang J, Demchuk A, Hill M, Buchan A (2001) Why are stroke patients excluded from TPA therapy?: An analysis of patient eligibility. Neurology 56: 1015-1020.
9. Fonarow GC, Reeves MJ, Smith EE, Saver JL, Zhao X, et al. (2010) Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in get with the guidelines-stroke. Circulation: Cardiovascular Quality and Outcomes 3: 291-302.
10. Disorders NIoN, Group Sr-PSS (1995) Tissue plasminogen activator for acute ischemic stroke. New England Journal of Medicine 333: 1581-1587.
11. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, et al. (2019) Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 50: e344-e418.
12. Topçuoglu MA, Arsava EM, Ay H (2011) Antiplatelet resistance in stroke. Expert review of neurotherapeutics 11:

251-263.

13. Malloy RJ, Kanaan AO, Silva MA, Donovan JL (2013) Evaluation of antiplatelet agents for secondary prevention of stroke using mixed treatment comparison meta-analysis. Clinical therapeutics 35: 1490-500. e7.
14. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, et al. (2018) Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. New England Journal of Medicine 379: 215-225.
15. Wang Y, Wang Y, Zhao X, Liu L, Wang D, et al. (2013) Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 369: 11-19.
16. Wiviott SD (2009) Antiplatelet therapy in ischemic heart disease. John Wiley & Sons. https://www.wiley.com/en-us/t+Therapy+In+Ischemic+Heart+Disease-p-9781405176262.
17. Wahlgren NG (1995) Thrombolytic therapy in acute ischemic stroke: Combination therapy with antiplatelet and anticoagulant agents. Thrombolytic Therapy in Acute Ischemic Stroke III, 165-173. https://doi.org/10.1007/978-4-431-68459-6_19.