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CARDIOVASCULAR DISEASE AND STROKE (S PRABHAKARAN, SECTION EDITOR)

Dual Antiplatelet Therapy in Acute Ischemic Stroke

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Abstract Stroke recurrence is common in the early period after a cerebral ischemic event. Treatment with an antiplatelet agent is recommended to reduce recurrent stroke and death in patients with a non-cardioembolic ischemic stroke and transient ischemic attack. Compared to monotherapy, dual antiplatelet therapy has more robust inhibition of platelet activation but a higher risk of systemic bleeding and intracranial hemorrhage. Randomized controlled trials and meta-analyses suggest that short-term use of dual antiplatelet treatment initiated early after ischemic stroke and TIA reduces the risk of recurrent stroke and major vascular events without significantly increasing the hemorrhagic complication rates, particularly in those with large-vessel disease, while long-term dual antiplatelet treatment increases the risk of systemic and intracranial hemorrhage over time, offsetting any potential benefit. Until further data becomes available, clinicians should carefully assess this risk and benefit in each case and continually reevaluate the need for prolonged dual antiplatelet therapy.

Keywords Antiplatelet therapy · Aspirin · Cerebral infarction · Clopidogrel · Ischemic stroke · Transient ischemic attack

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Introduction

It has long been known that patients at high risk for vascular disease benefit from antiplatelet therapy. The progressive decreases in stroke incidence and mortality observed over the last decades in developed countries [1] have been attributed at least in part to the widespread use of these antiplatelet and other preventive agents [2].

About 25 % of all incident strokes are recurrent events [3], and the first days after an ischemic stroke or transient ischemic attack (TIA) constitute a high-risk period for recurrence. Studies have reported a 30-day recurrence rate of 1.1 to 15 % after stroke [4] and as high as 17 % after a TIA [5]. Therefore, early initiation of antiplatelet agents in ischemic stroke and TIA patients is important to prevent stroke recurrence and is tracked as a quality measure by organizations that accredit stroke centers [6].

The majority of the data for aspirin use in acute ischemic stroke of arterial origin comes from two large studies that found a small benefit of aspirin in early stroke recurrence and death, and a slight increase in hemorrhagic stroke, for an overall benefit of aspirin of 0.9 % for early stroke or death [7], with a number needed to treat of 79 to prevent 1 death or dependency [8]. Treatment with aspirin is therefore recommended for patients with ischemic stroke and TIA in the first 24–48 h (American Heart Association (AHA) class I recommendation, level A evidence) [9].

Combination antiplatelet therapy is considered a more robust method to prevent platelet activation by simultaneously blocking different platelet activation pathways. In fact, the combination of aspirin and clopidogrel is considered a standard treatment in patients with acute coronary syndrome and those undergoing percutaneous coronary intervention [10, 11]. However, combination antiplatelet therapy with aspirin and clopidogrel is associated with a greater risk of major

hemorrhage [12]. Consequently, uncertainty regarding the safety and efficacy of short- and long-term dual antiplatelet treatment in patients with ischemic stroke and TIA persists. In this review, we will briefly examine the current evidence for combination oral antiplatelet therapy for secondary prevention of acute ischemic stroke, focusing mainly on the recent published literature. We have categorized early antiplatelet use when initiated within 3 days of symptom onset.

Long-Term Use of Dual Antiplatelet Therapy in Stroke

A number of large randomized controlled trials have been conducted to evaluate the effect of combination antiplatelet therapy in secondary prevention. Table 1 outlines the characteristics and results of studies that employed *long-term* dual antiplatelet use. The use of aspirin plus extended-release dipyridamole (ER-DP) has shown superior results compared to aspirin alone. However, large randomized controlled studies have not shown that combination antiplatelet therapy with aspirin and clopidogrel is superior to monotherapy for secondary stroke prevention. Significant limitations of prior studies include a lack of distinction between different ischemic stroke mechanisms, initiation of treatment beyond the acute period, and prolonged treatment that increased the risk of complications, particularly hemorrhagic events. As noted in Table 1, the majority of patients in these studies were not enrolled in the acute period. Even when only patients enrolled within 3 days of symptoms were considered, the individual trials did not show a statistical benefit of dual antiplatelet therapy but meta-analysis indicated a possible benefit in reducing stroke recurrence [20].

Short-Term Use of Dual Antiplatelet Therapy in Stroke

Two earlier small studies evaluated the early use of short-term dual antiplatelet therapy within 24 h of symptom onset. The Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) study evaluated 376 patients with TIA or minor stroke and compared aspirin plus clopidogrel to aspirin alone for 90 days. Combination therapy was associated with a statistically non-significant trend towards a decrease in early recurrent events at 90 days (absolute risk reduction 3.8 %, p=0.19), at the expense of a small increase in intracranial hemorrhage (absolute risk increase 1 %, p=0.5) [21]. The early treatment with aspirin plus extended-release dipyridamole for transient ischemic attack or ischemic stroke (EARLY) trial evaluated 543 patients with ischemic stroke and compared aspirin plus extended-release dipyridamole versus aspirin alone for 7 days, followed by aspirin plus extended-release dipyridamole up to day 90. No difference was noted in disability or the combined endpoint of vascular events and major bleeding; however, there was a trend for relative risk reduction for stroke recurrence at 7 days (relative risk (RR) 0.57; 95 % confidence interval (CI) 0.31, 1.03) [22].

Based on this experience, the Clopidogrel and Aspirin versus Aspirin Alone for the Treatment of High-risk Patients with Acute Non-disabling Cerebrovascular Event (CHANCE) trial [23•], a randomized placebo-controlled double-blind study, was designed to answer the question of whether the combination of aspirin and clopidogrel administered early after a cerebral ischemic event was superior to aspirin alone in preventing early recurrence. The CHANCE trial evaluated 5170 Chinese individuals with non-disabling stroke (NIHSS 0–3) or TIA with a high risk of recurrence (ABCD>4) [24] within 24 h of symptom onset. Participants were randomized to clopidogrel for 90 days (with a loading dose) plus aspirin for 3 weeks versus aspirin alone for 90 days. The primary outcome of any stroke at 90 days occurred in 8.2 % with combination therapy and in 11.7 % on aspirin (hazard ratio (HR) 0.68; 95 % CI 0.57, 0.81), ischemic stroke recurrence in 7.9 versus 11.4 % (HR 0.67; 95 % CI 0.56, 0.81), and moderate or severe bleeding in 0.3 % in each arm. Despite the significant findings of the CHANCE study, questions remain regarding the generalizability of its results. East Asians may have different CYP2C19 loss-of-function allele frequencies that may impact the efficacy and safety of clopidogrel in this population [25]. In addition, intracranial large-vessel atherosclerosis accounts for 33 to 50 % of all strokes and >50 % of TIAs in Chinese populations [26], but only 1–11 % in the USA [27]. Therefore, it is unclear from the CHANCE study if the effects of dual antiplatelet therapy are driven by the probable high prevalence of large-vessel atherosclerosis in this population.

Short-Term Use of Dual Antiplatelet Therapy in Large-Vessel Atherosclerotic Stroke

It is not surprising that more intense antithrombotic therapy would be effective in large-vessel disease. Atherosclerosis is the main pathological process in large-vessel disease-related stroke, which can affect the aortic arch, extracranial vessels, and large intracranial vessels. Plaque destabilization results in disruption of the fibrous cap and exposure of its thrombogenic content to the bloodstream, thus leading to local platelet-rich thrombus formation with distal embolization and consequent cerebral ischemia [28]. Moreover, plaque instability is a dynamic process, with stabilization of the plaque occurring over 12 weeks [29]. Therefore, short-term dual antiplatelet therapy may be more effective during this period, while longer administration may result in a higher risk of hemorrhage.

Table 1 Randomized controlled studies of *long-term* dual antiplatelet therapy versus monotherapy for stroke prevention

Study Eligibility Number enrolled	Treatment	Symptom onset to randomization	Therapy duration	Primary outcome (DAPT vs. SAPT)	Stroke recurrence (DAPT vs. SAPT)	Major or severe hemorrhage (DAPT vs. SAPT)	Number (%) enrolled=<3 days of stroke/TIA [13•]	Relative risk (95 % CI) for stroke recurrence (DAPT vs. SAPT) in those enrolled within 3 days [13•]
•ESPS [14] •IS, TIA •*N*=6602	ASA 25 mg+ER-DP 200 mg BID vs. ASA 25 mg or ER-DP 200 mg BID vs. placebo	3 months	24 months	Stroke or death, 17.4 % ASA+ER-DP vs. 19.9 % ASA vs. 19.4 % ER-DP vs. 23 % placebo (p<0.001)	9.9 vs. 12.9 % (RRR 23.1 %; p=0.006)	1.6 % ASA/DP vs. 1.2 % ASA vs. 0.3 % DP	221 (3.3 %)	1.22 (0.23, 6.33) vs. ASA 1.23 (0.24, 6.41) vs. DP
•ESPRIT [15] •IS, TIA •*N*=2739	ASA+ER-DP 200 mg BID vs. ASA 30–325 daily	6 months	3.5 years	Stroke, MI, vascular death, major hemorrhage, 12.7 vs. 15.7 % (HR 0.80; 95 % CI 0.66, 0.98)	10.3 vs. 12.6 % (HR 0.84; 95 % CI 0.64, 1.10)	2.6 vs. 3.9 % (HR 0.67; 95 % CI 0.44, 1.03)	95 (3.5 %)	1.21 (0.08, 18.77)
•MATCH [16] •IS, TIA •*N*=7599	Clopidogrel 75 mg+ASA 75 mg vs. clopidogrel 75 mg daily	3 months	18 months	Ischemic stroke, MI, vascular death, 15.7 vs. 16.7 % (RRR 6.4 %; 95 % CI −4.6 to 16.3)	8.1 vs. 8.8 % (RRR 7.1 %; 95 % CI −8.5, 20.4)	4.5 vs. 1.9 %	491 (6.5 %)	0.83 (0.36, 1.93)
•CHARISMA [17] •IS, TIA, PVD, CAD, or vascular risk factors •*N*=15,603	Clopidogrel 75 mg+ASA 75–162 mg vs. ASA 75–162 mg daily	5 years for stroke/TIA (36.5 % of study population)	28 months (median)	MI, stroke, vascular death, 6.8 vs. 7.3 % (p=0.22)	1.7 vs. 2.1 % (HR 0.81; 95 % CI 0.64, 1.02)	2 vs. 1.6 %	216 (1.4 %)	2.41 (0.22, 26.16)
•PRoFESS [18] •IS •*N*=20,332	ASA 25 mg+ER-DP 200 mg BID vs. clopidogrel 75 mg daily	90 days	2.5 years (mean)	Stroke, 9 vs. 8.8 % (HR 1.01; 95 % CI 0.92–1.11)	7.7 vs. 7.9 % (HR 0.97; 95 % CI 0.88, 1.07)	4.1 vs. 3.6 % (HR 1.15; 95 % CI 1, 1.32)	1360 (6.7 %)	0.56 (0.27, 1.17)
•SPS3 [19] •Lacunar IS •*N*=3020	ASA 325 mg+clopidogrel 75 mg vs. ASA 325 mg daily	>14 and <180 days	3.4 years (mean)	Stroke, 8.2 vs. 9.2 % (HR 0.92; 95 % CI 0.72, 1.16)	6.6 vs. 8.3 % (HR 0.82; 95 % CI 0.63, 1.09)	6.9 vs. 3.7 % (HR 1.97; 95 % CI 1.41, 2.71)	0	NA

ASA aspirin, *DP* dipyridamole, *ER-DP* extended-release dipyridamole, *DAPT* dual antiplatelet therapy, *SAPT* single antiplatelet therapy, *IS* ischemic stroke, *TIA* transient ischemic attack, *MI* myocardial infarction, *PVD* peripheral vascular disease, *CAD* coronary artery disease, *HR* hazard ratio, *RR* relative risk, *RRR* relative risk reduction, *CI* confidence interval

The effects of dual antiplatelet therapy have been studied in large-vessel disease-related stroke. Two small randomized controlled trials compared the efficacy of combination antiplatelet treatment versus monotherapy in patients with a recently symptomatic large-artery atherosclerotic disease and evaluated the reduction of microembolic signals (MES) on transcranial Doppler (TCD) ultrasound as a surrogate marker for a decreased risk of future stroke and TIA [30, 31].

The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis (CARESS) study was a randomized, double-blind study of 110 patients with symptomatic carotid artery stenosis of ≥50 % within the preceding 3 months [30]. Patients were included if they had ≥1 MES on the screening TCD study and were randomized to either clopidogrel (75 mg daily after a 300-mg loading dose) and aspirin (75 mg daily) or aspirin alone (75 mg daily). Patients were excluded if they were scheduled to receive carotid endarterectomy in the ensuing 2 weeks from the initial assessment. A total of 40 and 77 % had experienced symptoms within the past 7 and 30 days of randomization, respectively. In the intention-to-treat analysis, the primary outcome of presence of asymptomatic MES on day 7 was significantly reduced in patients on dual therapy relative to monotherapy (43.8 vs. 72.7 %, relative risk reduction (RRR) 39.8 %; 95 % CI 13.8–58; p=0.0046). There was no difference in the major hemorrhage rates or early stroke recurrence between the two groups during the short period of therapy.

The Clopidogrel plus Aspirin for Infarction Reduction in Acute Stroke or Transient Ischemic Attack Patients with Large Artery Stenosis and Microembolic Signals (CLAIR) study randomized 100 TIA and stroke patients within 7 days of symptom onset to receive either clopidogrel (300-mg loading dose then 75 mg daily) plus aspirin (75–160 mg daily) or aspirin alone (75–160 mg daily) for 7 days [31]. Patients were eligible to be enrolled if they had symptomatic large-artery stenosis in the cerebral or carotid arteries and ≥1 MES on screening TCD; 93 % of patients had intracranial stenosis in either the internal carotid artery or the middle cerebral artery. The primary outcome of presence of MES was significantly lower in the dual antiplatelet arm at day 2 relative to the monotherapy group (31 vs. 54 %, RRR=42.4 %; 95 % CI 4.6–65.2; p=0.025). Adverse events were similar in both arms with no significant hemorrhage (intracranial or systemic) cases in either group. However, two patients had minor hemorrhages in the combination therapy arm.

The results of both studies were encouraging, but the small sample size did not allow for an adequate statistical power to determine a clinical efficacy of reducing subsequent stroke or TIA with combination antiplatelet therapy in this population.

The Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial included only patients with symptomatic intracranial stenosis (70–99 %) within 30 days of symptom onset [32]. Patients were randomized to either aggressive medical management (including aspirin 325 mg daily and clopidogrel 75 mg daily for 90 days) or aggressive medical therapy plus percutaneous transluminal angioplasty and stenting. The primary outcome was stroke or death within 30 days after enrollment or after a revascularization procedure or stroke within the territory of the qualifying artery beyond 30 days. The study was halted prematurely after 451 patients underwent randomization, due to a significantly higher rate of the stroke and death at 30 days in the interventional arm-relative medical group (14.7 %, 95 % CI 10.7–20.1 vs. 5.8; 95 % CI 3.4–9.7; p=0.002). Endovascular intervention did not offer delayed benefits in the SAMMPRIS trial; beyond 30 days, 10 % of patients in each group had a primary endpoint. At a final follow-up, the absolute differences in the primary endpoint rates between the two groups were 7.1 % at year 1 (95 % CI 0.2, 13.8; p=0.0428), 6.5 % at year 2 (95 % CI −0.5, 13.5; p=0.07), and 9.0 % at year 3 (95 % CI 1.5, 16.5; p=0.0193) [33•]. The good result in the medical arm of the SAMMPRIS trial was surprising. In the Warfarin and Aspirin for the Prevention of Recurrent Ischemic Stroke (WASID) trial [34], the subgroup of patients ≤80 years of age with 70–99 % symptomatic stenosis and enrolled within 30 days from symptom onset, a similar population to that enrolled in the SAMMPRIS trialt had 14 % and 29 % rate of the primary outcome at 3 months and 2 years, respectively. This difference in the early recurrent rates can be attributed at least in part to the addition of clopidogrel to medical management in the SAMMPRIS trial, although it is possible that the greater adherence to other stroke prevention medications and lifestyle changes played a role.

Ongoing Studies

The ongoing Platelet-Oriented Inhibition in New TIA (POINT) trial [35] is anticipated to expand the results of the CHANCE trial in a non-Asian population. Patients with a minor stroke or TIA within 12 h of symptom onset are randomized to clopidogrel (600-mg loading dose followed by 75 mg daily) plus aspirin versus aspirin alone for 90 days. The primary outcomes are the 90-day occurrence of the combined endpoint of stroke, myocardial infarction or ischemic vascular death, or major hemorrhage.

The use of multiple concurrent antithrombotic agents is a common practice in patients with acute coronary syndrome. Furthermore, patients with atrial fibrillation are often prescribed anticoagulants, aspirin, and clopidogrel after coronary stents. However, the risk of systemic bleeding increases with addition of antithrombotics to anticoagulants with no significant benefit in reduction of thromboembolic events [36]. The Triple Antiplatelets for Reducing Dependency after Ischaemic

Stroke (TARDIS) [37] study is evaluating the short-term use of combined aspirin, clopidogrel (with a loading dose), and extended-release dipyridamole versus standard antiplatelet therapy (aspirin plus extended-release dipyridamole or clopidogrel alone) in patients with ischemic stroke or TIA within 48 h from symptom onset.

Mechanisms of Action of Antiplatelet Agents and Testing for Resistance

Genetic influences the efficacy of antiplatelet therapy, but agent choice and dosing decisions are not usually guided by platelet function tests. The prevalence of laboratory evidence of aspirin resistance is reported to be between 5 and 30 % [38], although non-adherence and non-steroidal anti-inflammatory agent use may explain a proportion of adverse cardiovascular events misclassified as aspirin resistance [39], while other studies have not found a correlation between aspirin resistance tests or genetic polymorphisms that underlie aspirin resistance and vascular events [40, 41]. Clopidogrel is metabolized to its active metabolite by the P450 enzyme CYP2C19. Individuals with the loss-of-function allele of CYP2C19, reported in one in four Caucasians [42], are at increased risk for vascular events [43]. However, trials that used platelet function tests to guide therapy after coronary revascularization did not show a benefit from this strategy [44, 45]. Therefore, laboratory testing to guide selection and dosage of antiplatelet agents in acute ischemic stroke is not supported by the literature at the current time.

Current Use of Dual Antiplatelet Therapy in Acute Stroke

At the time of the writing of this manuscript, while awaiting results of ongoing studies, the authors would use dual antiplatelet agents with aspirin and clopidogrel in the acute period and for a total of 12 weeks in patients with stroke related to large-vessel atherosclerosis in mild stroke and TIA. Those with a larger stroke are at higher risk of hemorrhagic transformation and may require further surgical interventions for which dual antiplatelet agents may be precluded. This recommendation is summarized in Table 2 and is based on the following factors: (a) there is a well-established benefit of dual antiplatelet therapy in recently symptomatic and presumably unstable plaques in the coronary circulation [10, 11]; (b) studies of dual antiplatelet therapy in recently symptomatic carotid or large intracranial artery atherosclerotic disease have shown a reduction in clinical events or microembolic signals, a surrogate marker of plaque instability [30–32, 33•]; (c) the positive results of the CHANCE study may be explained by the high prevalence of intracranial large-vessel atherosclerotic disease in the Chinese population [23•]; and (d) the longer-term use of dual antiplatelet therapy after ischemic stroke has not shown benefit in stroke recurrence but resulted in higher risk of hemorrhagic events; in these studies, a small proportion was enrolled in the early period, but no benefit was found in that subgroup (see Table 1).

Conclusions

The current literature points to a potential benefit from short-term dual antiplatelet therapy over a single antiplatelet agent in acute ischemic stroke patients, while extended therapy with aspirin and clopidogrel beyond 3 months does not appear to confer additional benefit but increases the risk of hemorrhagic complications. It is possible that this benefit applies mostly to those with atherosclerotic large-artery disease. Ongoing studies will clarify if the findings of recent trials favoring dual antiplatelet therapy are valid and should determine if this conduct should be restricted to certain stroke subtypes such as large-vessel disease. Therapeutic decisions based on platelet function testing are not currently supported by clinical data.

Table 2 Recommendation for the use of dual antiplatelet therapy in acute ischemic stroke

	Dual antiplatelet therapy	Single antiplatelet therapy
Severity	Minor stroke[a] Transient ischemic attack	Major stroke
Mechanism	Large-vessel extracranial or intracranial disease	Small-vessel disease Cryptogenic Early cardioembolic[b]
Duration	12 weeks followed by single antiplatelet therapy	Indefinite (except for cardioembolic)

[a] The definition of minor stroke varies, but most clinical trials have used NIHSS between 0 and 5 to define minor strokes

[b] It is usual to wait at least a few days after a major cardioembolic stroke before initiating anticoagulation, given the low risk of early recurrence and concern for hemorrhagic transformation. Randomized controlled data for early oral anticoagulant use are lacking, but recent guidelines are recommended against urgent anticoagulation in moderate to severe strokes [9]

Compliance with Ethics Guidelines

Conflict of Interest N Asdaghi and JG Romano both declare no conflicts of interest.

Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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