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Combination Aspirin and Clopidogrel for Secondary Prevention of Ischemic Stroke

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Introduction

Stroke is the leading cause of adult-acquired disability in most places in the world and the second-leading cause of death worldwide [2–4]. In the era of contemporary secondary prevention strategies patients, approximately one in seven patients will have a recurrent event within one year of their first stroke or TIA (Transient Ischemic Attack) [5]. Though antiplatelet therapy remains the mainstay of antithrombotic treatment for secondary prevention of non-cardioembolic stroke, accounting for a 20 % reduction of all recurrent stroke [6], the roles for combination aspirin and clopidogrel for secondary stroke prevention have yet to be fully determined.

Previous trials investigating the role of another antiplatelet combination, aspirin plus dipyridamole (ASA-DP), found a benefit in favor of the combination over either agent alone for secondary stroke prevention [7, 8]. However, the combination agent was less well tolerated compared with clopidogrel in a non-inferiority trial, PROFESS (Prevention Regimen for Effectively avoiding Second Strokes), where ASA-DP was associated with a higher risk of major hemorrhages, including intracranial hemorrhages (HR, 1.15; 95 % CI, 1.00–1.32), and higher rates of discontinuation (29 % vs 23 %; absolute difference 7 %; 95 % CI, 5.3–7.7), mainly because of headache [9]. More recent trials investigating the efficacy of combination antiplatelet therapy have focused on combination aspirin/clopidogrel.

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Conflict of Interest

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Whereas previous secondary prevention trials of aspirin alone vs aspirin/clopidogrel (CHARISMA [Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance], MATCH [Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients], FASTER [Fast assessment of stroke and transient ischemic attack to prevent early recurrence]) examined the role of monotherapy vs combination antiplatelet for secondary prevention of all non-cardioembolic stroke subtypes, more recent randomized trials — SPS3 (Secondary Prevention of Small Subcortical Strokes Trial), SAMMPRIS (Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis), and CLAIR (Clopidogrel plus aspirin vs aspirin alone for reducing embolization in patients with acute symptomatic cerebral or carotid artery stenosis) — have investigated the role for dual antiplatelet therapy for secondary prevention of specific stroke mechanisms (Table 1).

This review will examine the current evidence for combination aspirin/clopidogrel therapy for secondary stroke prevention with an emphasis on the most recently published literature.

Short-term dual antiplatelet therapy after ischemic stroke/TIA

The risk of recurrent ischemic events after ischemic stroke and TIA is as high as 10 % at 30 days; the majority of which occur within the first 24 hours [5, 10].

No significant trends from the MATCH and FASTER trials have suggested that there may be a potential beneficial effect of dual antiplatelet therapy in the acute phase post-stroke [1•, 12]. In the MATCH trial, which randomized 7599 patients within three months of ischemic stroke or TIA to aspirin 81–162 mg daily/clopidogrel 75 mg daily vs clopidogrel 75 mg, there was no overall benefit for dual antiplatelet use over monotherapy for the primary endpoint, a composite of ischemic stroke, myocardial infarction, vascular death, or hospitalization for cerebral or systemic ischemia (15.7 % vs 16.7 % stroke recurrence, RRR 6.4 %, 95 % CI –4.6–16.3). The median time from index event to enrollment in MATCH was 15 days. Though non-significant, the subset of patients randomized within seven days showed a trend towards a benefit of combination over mono antiplatelet therapy (15.6 % vs 18.7 %, RR 0.83, 95 % CI 0.63–1.09). There was no excess of bleeding in those allocated to dual therapy during the first month of treatment; though an increased bleeding risk in the aspirin/clopidogrel group became apparent after three months of therapy.

The FASTER trial randomized patients in a 2×2 factorial design to aspirin (162 mg loading if aspirin-naïve, then 81 mg daily)/clopidogrel (300 mg loading dose then 75 mg daily) vs aspirin alone and simvastatin vs placebo within 24 hours of ischemic stroke or TIA. The study was terminated prematurely due to lack of recruitment. There was a non-significant reduction in recurrent stroke in the dual antiplatelet group (7.1 % vs 10.8 %, RR 0.7, 95 % CI 0.3–1.2). There were two intracranial hemorrhages, both in the dual antiplatelet group (risk difference 1 %, 95 % CI –0.4–2.4, $P=0.5$) and six symptomatic extracranial hemorrhages, one of which was severe, all in the dual antiplatelet group (risk difference 3 %, 95 % CI 0.6–5.4, $P=0.03$).

The pooled effects of treatment with dual vs single antiplatelet therapy in the acute phase after an ischemic event were examined in a recent meta-analysis [13•]. Twelve randomized trials including 3766 subjects (149 recurrent strokes in total) were analyzed. Participants were assigned to receive single or dual antiplatelet agents within 72 hours of stroke or TIA and continued therapy for seven days–42 months. Five studies compared aspirin/clopidogrel (FASTER [12], CHARISMA [14], MATCH [11], CARESS [Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis] [15], CLAIR [16]), and seven compared aspirin/dipyridamole (ESPS-2 [7], ESPRIT [8], EARLY [17], PRoFESS [9], and

three other small studies, one of which was unpublished [18, 19]) to a single antiplatelet agent. Twenty-four percent of patients used the combination of aspirin/clopidogrel as their dual antiplatelet therapy. Stroke recurrence was significantly reduced in the dual vs the single antiplatelet group (3.3 % vs 5.0 %, RR 0.67, 95 % CI 0.56–0.91); as were total major vascular events (4.4 % vs 6 %, RR 0.75, 95 % CI, 0.56–0.99). There was no difference with regards to overall mortality. Dual therapy was associated with a non-significant increase in major bleeding (0.9 % vs 0.4 %, RR 2.09, 95 % CI 0.86–5.06).

The nonsignificant trends from MATCH and FASTER as well as the meta-analysis data suggested that there may be a beneficial effect of dual antiplatelet therapy in the acute phase following cerebral ischemic events. The preliminary results of the CHANCE (Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events) trial (clinicaltrials.gov identifier: NCT00979589) suggests a large benefit in stroke reduction at 90 days with use of combination aspirin/clopidogrel within 24 hours of minor stroke or TIA. There other ongoing trials examining the use of early combination antiplatelet therapy after ischemic events that may help to better clarify these issues. Further prospective trials may help to clarify if patients on dual antiplatelet therapy may benefit from reduced rates of recurrent stroke without an excess of bleeding, as well whether there is an optimal duration for length of dual antiplatelet therapy.

CHANCE, which was based in China, randomized 5100 patients within 24 hours of stroke or TIA to aspirin/clopidogrel for 21 days, followed by clopidogrel alone, vs aspirin alone [20]. The preliminary results of the trial, announced in February 2013 at the International Stroke Conference, showed that the hazard ratio at 90 days for the primary endpoint of ischemic or hemorrhagic stroke was 0.68 (95 % CI 0.57–0.81; $P<0.001$) for the combination group [1•]. For the secondary endpoint of stroke, MI, and vascular death, the 90-day hazard ratio was 0.69 (95 % CI 0.58–0.82; $P<0.001$). There was no difference between groups with regards to incidence of hemorrhagic stroke (0.3 %) or severe bleeding (0.2 %). There was a non-significant increase in minor bleeding (1.2 % vs 0.7 %) in the combination group.

Other ongoing studies will determine if these results are replicable in other populations. Implementation of other optimal secondary prevention strategies is not standardized in China or in the CHANCE population, and post-stroke care may differ from North American standards [21]. Whether differences with regards to stroke subtype or other genetic, environmental, or undetermined factors may also affect the benefit-risk ratio of combination antiplatelet therapy in other ongoing trials has yet to be determined.

The POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial is enrolling patients in North America and Europe. Investigators plan to randomize 4200 participants to aspirin/clopidogrel or aspirin alone within 12 hours after stroke or TIA and assessing vascular event rate at 90 days (NCT00991029). So far, more than 1000 patients are enrolled and the results are anticipated by 2015. The recently completed COMPRESS (Combination of Clopidogrel and Aspirin for Prevention of Early Recurrence in Acute Atherothrombotic Stroke) study (NCT00814268) is assessing whether aspirin plus clopidogrel vs aspirin alone within 48 hours of stroke will help to reduce new diffusion-weighted lesions on MRI at 30 days. The TARDIS (Triple Antiplatelets for Reducing Dependency after Ischemic Stroke) trial is enrolling patients within 48 hours of noncardioembolic ischemic events to aspirin/dipyridamole/clopidogrel vs aspirin/dipyridamole and assessing stroke severity at 90 days as the primary outcome and recurrent stroke amongst the secondary outcomes. Results are still pending.

Combination antiplatelet therapy for cerebral small vessel disease

Approximately one-quarter of ischemic strokes are due to small vessel disease, also referred to as lacunar, or small subcortical, strokes. Intrinsic cerebral small vessel disease, based on previous pathological series, has multiple mechanisms, the commonest being lipohyalinosis, which involves chronic fibrin and collagen deposition in the walls of penetrating vessels and microatheroma which can either be occlusive or embolic in and of itself or secondary to plaque rupture with subsequent thrombotic occlusion or embolization [22]. Intrinsic endothelial dysfunction has also been proposed as a possible mechanism [23]. Lacunar strokes account for approximately 50 % of subjects enrolled in antiplatelet secondary prevention trials and antiplatelet monotherapy is effective for secondary prevention in this population. However, classification of strokes due to small vessel disease in these trials was vaguely defined without neuroimaging confirmation in most cases [24]. In addition, the mechanism of antiplatelet therapy for stroke prevention in this stroke subtype is not completely elucidated.

The recently completed SPS3 trial enrolled subjects with MRI-proven small subcortical ("lacunar") infarcts within six months of the index event to daily aspirin 325 mg/placebo vs aspirin 325 mg/clopidogrel 75 mg and more aggressive (<130 mm Hg) vs less aggressive (130–149 mm Hg) systolic blood pressure targets in a 2×2 factorial design [25•]. Primary outcomes were all recurrent stroke, secondary outcomes included acute myocardial infarction, and death (vascular, non-vascular or unknown), and primary safety outcome was major extracranial hemorrhage. The antiplatelet arm of the trial was double-blinded. There were 3020 participants enrolled (mean age=63, 63 % male) and mean follow-up was 3.4 years.

Analyses were based on an intention-to-treat paradigm. Over the follow-up period, 8.7 % had recurrent stroke (85 % ischemic; 13 % intracranial hemorrhage). There was no significant difference in overall risk of recurrent stroke between the single vs dual antiplatelet groups (2.7 %/years vs 2.5 %/years, HR 0.92, 95 % CI 0.72–1.16, $P=0.48$). A nonsignificant reduction of recurrent ischemic events (RRR 18 %) was offset by a nonsignificant increase (RR 70 %) of intracranial hemorrhage in the dual antiplatelet group. The rate of major systemic hemorrhage in the dual antiplatelet group was nearly twice that of the aspirin-only group (1.1 %/years vs 2.1 %, HR 1.97, 95 % CI 1.41–2.71, $P<0.001$). There was an excess of all-cause mortality in the dual antiplatelet group (77 vs 113, HR 1.52, 95 % CI 1.14–2.04, $P=0.004$). When mortality was subdivided by cause, there was a significant increase with respect to probable vascular death (HR 3.09, 95 % CI 1.23–7.80, $P=0.02$) and a non-significant trend towards increased mortality in the dual antiplatelet groups compared with the aspirin-only group.

This trial, which has the largest series in the literature to date of radiologically proven small subcortical infarcts, showed no benefit for long-term use of combination antiplatelet therapy for secondary prevention of this particular stroke mechanism. The higher mortality rate in the dual antiplatelet group was unanticipated and not due to an excess of fatal hemorrhage. The authors suggested that the difference may have been due to chance, or possibly due to a detrimental effect of combination therapy on patients with the distinct vascular risk profile of patients with cerebral small-vessel disease.

In a recent meta-analysis, the authors drew attention to subgroup analyses for the CHARISMA trial for those participants with asymptomatic vascular disease, who also experienced an excess of mortality with dual antiplatelet therapy [14, 26•]. Given that those at risk for death were found to have moderate bleeding [27] or were diabetic [28] with nephropathy [29], the authors posited that the SPS3 patients, who were not typical large-

artery vasculopathies, may possibly have been at risk with combination antiplatelet therapy for similar reasons. Mortality was not increased in those assigned to dual antiplatelet therapy [26•]. In the meta-analysis, twelve trials were retrieved (four “short-term” studies with a follow-up of 14 days–3 months and eight “long term” studies with follow-up >3 months) with a total of 90,934 subjects. Three of the long-term trials (SPS3, CHARISMA, and ACTIVE A [Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular events]) included patients with previous stroke; SPS3 was excluded from pooled analysis due to significant heterogeneity. The results showed a decrease in mortality associated with dual antiplatelet therapy in short-term studies (follow-up 14 days–3 months; OR 0.93, 95 % CI 0.87–0.99) and no excess mortality in long-term studies (>3 months; HR 0.97, 95 % CI 0.91–1.04) studies. Combination antiplatelet therapy was associated with an increased risk of fatal hemorrhage (OR 1.35, 95 % CI 0.97–1.90) and a decreased risk of myocardial infarction (OR 0.82, 95 % CI 0.74–0.91).

Combination antiplatelet therapy for large-vessel disease

Of all the stroke mechanisms, atherothrombotic large-vessel disease has the highest risk of early recurrence rate after stroke or TIA [30]. Carotid endarterectomy and stenting are superior to best medical therapy alone (including antiplatelet therapy) for secondary prevention for symptomatic extracranial carotid stenosis. However, for patients with intracranial stenosis, neither stenting [31••], extracranial-intracranial artery bypass [32, 33], nor dose-adjusted warfarin [32] have been shown to be superior to best medical therapy including antiplatelets for prevention of recurrent events. Whether dual antiplatelet therapy confers additional protection against recurrent events for intracranial large-vessel disease is still unclear.

The SAMMPRIS [31••] trial enrolled patients with symptomatic stenosis 70 % of a major intracranial artery within 30 days of their index event to receive percutaneous intervention with a Wingspan stent vs best medical therapy, which consisted of aspirin 325 mg daily, clopidogrel 75 mg daily (discontinued 90 days after enrollment), and risk factor management (treatment of elevated systolic blood pressure and LDL and enrollment in a “lifestyle modification program” to improve diet and management of diabetes, and to encourage exercise, smoking cessation, and weight loss).

Recruitment was terminated after 451 participants were enrolled due to an excess of stroke and death at 30 days in the stenting arm (14.7 %, 95 % CI 10.7 %–20.1 %, vs 5.8 %, 95 % CI 3.4 %–9.7 %, $P=0.002$), an effect that persisted at one year follow-up (20.0 %, 95 % CI 15.2 %–26.0 %, vs 12.2 %, 95 % CI 8.4 %–17.6 %, $P=0.009$). However, participants in the medical arm experienced a lower rate of recurrent stroke than in previous series of symptomatic intracranial stenosis treated with a single antiplatelet agent (10.1 % ipsilateral stroke at the end of follow-up compared with 12 % ipsilateral stroke in the WASID (Warfarin-Aspirin Symptomatic Intracranial Disease) trial at the end of the first year [34], 13.7 % all stroke in an observational study [35], and 22.3 % ipsilateral stroke in the COSS [Carotid Occlusion Surgery Study] trial [32]).

Whether the use of dual antiplatelet therapy contributed significantly to the decreased event rate is unclear given that there was no single-platelet medical comparison group in the SAMMPRIS trial. Thus, the role for dual antiplatelet therapy for symptomatic intracranial stenosis remains unclear.

Two small randomized trials, CLAIR and CARESS, have compared single vs dual antiplatelet therapy to reduce microembolic signals on transcranial Doppler after recent symptomatic large artery disease. The use of microemboli as a clinically relevant proxy to

assess secondary prevention is controversial. It is unclear whether the number of detectable microemboli, or their presence or timing, serves as a reliable harbinger of a recurrent clinical ischemic event. Thus, it is difficult to apply the results of either trial to one's clinical secondary prevention strategy.

In the CLAIR study, 100 participants with symptomatic large artery disease (93 of whom had intracranial disease localized to the intracranial internal carotid artery or the middle cerebral artery) were randomized within seven days of the index event to aspirin (75–160 mg daily)/clopidogrel (300 mg loading dose then 75 mg daily) vs aspirin alone [16]. Patients were monitored at two and seven days for microembolic signals on transcranial Doppler. Analysis was a modified intention-to-treat and primary outcome was the proportion of patients with microembolic signals on day two. There were significantly fewer patients on dual antiplatelet therapy who experienced detectable microemboli on day two (14 % vs 27 %, RRR 42.4 %, 95 % CI 4.6–65.2, $P=0.025$). In addition, there were no significant differences between groups with regards to new DWI lesions between baseline MRI and repeat MRI on day 7, nor was there a significant difference between groups with respect to baseline or follow-up NIHSS score, MMSE score, or mRS. There were no major hemorrhages overall, though there were two minor bleeding events in the dual antiplatelet group and none in the monotherapy group.

The CARESS trial randomized 107 subjects with recently symptomatic carotid disease with 50 % stenosis and microembolic signals on TCD screening within three months of their event to aspirin (75 mg daily)/clopidogrel (300 mg loading dose then 75 mg daily) vs aspirin alone for seven days [15]. Patients were assessed for microembolic signals at two and seven days after enrollment. The primary endpoint was the proportion of patients with microembolic signals on day seven. Analysis was by intention-to-treat. There was a significant reduction proportion of patients with detectable microemboli on day seven (43.8 % vs 72.7 %, RRR 39.8 %, 95 % CI 13.8–58.0, $P=0.0046$). There was a nonsignificant trend towards a benefit on day 2. There was also a significant decrease in number of microemboli per hour on days two and seven. There were no major bleeding events in either group, though there were two minor bleeding events in the dual antiplatelet group and one in the monotherapy group.

There is a suggestion that optimized secondary prevention measures are beneficial in secondary stroke prevention for symptomatic intracranial stenosis, and there is evidence that microembolic signals may be reduced with dual antiplatelet therapy. Still, the clinical benefits of dual over single antiplatelet therapy for secondary prevention of symptomatic large artery disease have yet to be definitely demonstrated in randomized trials.

Combination antiplatelet therapy for stroke prevention in atrial fibrillation

Cardioembolism is responsible for approximately 1/6 of cerebrovascular events and nonvalvular atrial fibrillation is the commonest cause of cardioembolic stroke [36]. The average risk of stroke for all comers with atrial fibrillation is 3 %–4 % per year, however those with prior cerebrovascular events and atrial fibrillation have more than double the risk of stroke than other AF patients and annualized risk may vary considerably depending on other risk factors.

Both the ACTIVE-A and the ACTIVE-W trials investigated the use of dual antiplatelet therapy for non-valvular atrial fibrillation. In ACTIVE-A, 7554 subjects deemed unsuitable for warfarin were randomized to aspirin 75–100 mg daily/clopidogrel 75 mg daily vs aspirin alone [37]. There was an overall reduction of combined vascular events (6.8 % vs 7.6 %, RR 0.89, 95 % 0.81–0.98, $P=0.01$), though the benefit of dual antiplatelet therapy for stroke

prevention (2.4 % vs 3.3 %, RR 0.72, 95 % CI 0.62–0.83) was marginal when rates of major bleeding were taken into account (2.0 % vs 1.3 % per year, RR 1.57, 95 % CI 1.29–1.92). On the other hand, dual antiplatelet therapy had a significantly increased incidence of major bleeding (2.0 % vs 1.3 % per year, RR 1.57, 95 % CI 1.29–1.92). ACTIVE-W assigned 6706 participants to aspirin 75–100 mg daily/clopidogrel 75 mg daily vs dose-adjusted warfarin (target INR 2.0–3.0) [38]. The trial was halted after 1.3 years due to clear superiority in the warfarin group for reduction of combined vascular endpoints (3.9 % vs 5.6 %, RR 0.69, 95 % CI 0.57–0.85); stroke rates were also significantly reduced (2.39 % vs 1.40 %/years, RR= 1.72, 95 % CI 1.24–2.37, $P=0.001$). There was no significant difference in major bleeding (2.4 % vs 2.2 %, though there were significantly more bleeding events overall in the warfarin group (15.4 % vs 13.2 %).

Unless all anticoagulant options are untenable, there is no compelling reason to treat patients with an antiplatelet agent for secondary prevention of cardioembolic stroke. There is a marginal benefit of dual antiplatelet therapy over aspirin monotherapy for this indication, though it is nearly eclipsed by the corresponding increased risk of bleeding.

Combination antiplatelet therapy for aortic arch atheroma

Aortic arch atheroma with plaque thickness greater than 4–5 mm has been associated with increased risk of stroke. In one meta-analysis the odds of stroke in a patients with severe arch atheroma compared with without was 3.76 (95 % CI 2.58–5.48) [39]. Additional risk factors in the context of thick aortic plaque include plaque ulceration, non-calcified plaque, and plaque with mobile components [40]. It is unclear as to which antithrombotic therapy is best for stroke prevention in this context. The results of recently completed ARCH (Aortic Arch Related Cerebral Hazard) trial, which randomized 350 patients with atheroma 4 mm thick within six months of their event to combination aspirin 75–150 mg daily/clopidogrel 75 mg daily vs dose-adjusted warfarin (INR 2–3), should help to clarify this issue.

Conclusions

A definitive indication for long-term dual antiplatelet therapy for secondary stroke prevention has not yet been demonstrated in randomized trials. Moreover, current AHA/ASA (American Heart Association/American Stroke Association) guidelines for secondary stroke prevention do not support the routine use of combination aspirin/clopidogrel [41••]. However, the preliminary results of the CHANCE trial suggest that use of dual antiplatelet therapy in the acute post-ischemic period for a limited duration may be of benefit. The results from the POINT, COMPRESS, and TARDIS trials may help to better clarify the generalizability of these results and help to clarify the optimal duration of combination antiplatelet therapy.

Whether patients with symptomatic intracranial disease may benefit from dual antiplatelet therapy over monotherapy (and for what period of time) in addition to medical and lifestyle optimization will need to be addressed in future randomized trials.

A rational clinical approach that takes into account a patient's timing after their index event, stroke mechanism, comorbidities, and bleeding risks into account may help to guide decision-making with regards to initiating dual antiplatelet therapy in an individual patient where the current body of evidence can only offer incomplete guidance.

Clinical trial acronyms

ACTIVE	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular events
AHA/ASA	American Heart Association/American Stroke Association
ARCH	Aortic Arch Related Cerebral Hazard
CARESS	Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CHANCE	Clopidogrel in High-risk Patients With Acute Non-disabling Cerebrovascular Events
CLAIR	Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis
COMPRESS	COMbination of Clopidogrel and Aspirin for Prevention of Early REcurrence in Acute Atherothrombotic Stroke
COSS	Carotid Occlusion Surgery Study
EXPRESS	Effect of urgent treatment of transient ischemic attack and minor stroke on early recurrent stroke
FASTER	Fast assessment of stroke and transient ischaemic attack to prevent early recurrence
MATCH	Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke
PRoFESS	Prevention Regimen for Effectively avoiding Second Strokes
SAMMPRIS	Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis
SPS3	Secondary Prevention of Small Subcortical Strokes Trial
TIA	Transient Ischemic Attack
WASID	Warfarin-Aspirin Symptomatic Intracranial Disease study

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- Of importance
- Of major importance
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Opinion statement

Though antiplatelet agents are the mainstay of antithrombotic therapy for secondary prevention of noncardioembolic cerebral ischemic events, the efficacy of combination aspirin and clopidogrel has yet to be clarified by clinical trials. Current evidence suggests that there is no role for long-term combination of aspirin/clopidogrel for secondary stroke prevention. Recent preliminary data from the CHANCE (Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events) trial suggests that stroke recurrence at 90 days is reduced by a short course (21 days) of combination aspirin/clopidogrel initiated within 24 hours of minor stroke or TIA (Transient Ischemic Attack) compared with aspirin alone [1••] (Table 1). Other ongoing trials, which are also investigating the role of short-term combination antiplatelet therapy initiated immediately after minor stroke and TIA, will determine if these findings will be replicated.

Table 1

Completed clinical trials investigating aspirin/clopidogrel vs aspirin alone

Trial	n, patient population	Stroke mechanism	Time to enrollment after event	Follow-up	Intervention
MATCH 2004	7599 with recent IS or TIA and at least one additional vascular risk factor who were already taking daily clopidogrel	1.8 % CE 41.4 % Small vessel 26.8 % LA 0.9 % Other 7.8 % Unk	Within 3 mos. (median 15 d)	18 mos.	Clopidogrel 75 ASA-C 81-162/75
CHARISMA 2006	15,603 with clinically evident cardiovascular disease, documented cerebrovascular disease or multiple vascular risk factors	24 % of participants with prior stroke	—	28 mos.	ASA 75-162 ASA-C 75/162/75
FASTER 2007	392 with TIA or minor stroke	4.1 % CE 28.8 % Lac 24.0 % LA 0.5 % Other 36.7 % Unk	Within 24 h	90 d.	ASA 81 ASA-C 81/75
CHANCE 2013	5170 with TIA or minor stroke	NA	Within 24 h	90 d.	ASA 75 ASA-C 75/75
SPS3 2012	3020 with MRI-proven clinically evident subcortical stroke	Small vessel disease	180 d. (median 62)	Mean 3.4 y	ASA 81 ASA-C 81/75
SANMPRIS 2012	451 with recent stroke or TIA with due to symptomatic intracranial stenosis 70 %-99 %	Intracranial LA disease	Within 30d (Median 7)	90 d.	Aggressive medical management including ASA-C 325/75 ± PTAS
CARESS 2005	100 with 50 % symptomatic extracranial carotid stenosis	LA disease	Within 3 mos.	7 d.	ASA 75 ASA-C 75/75
CLAIR 2010	100 with 50 % symptomatic extracranial or intracranial carotid or MCA stenosis	LA disease	Within 7 d. (mean 2.5 d in ASA-C group, 3.2 in ASA)	7 d.	ASA 75-160 ASA-C 75-160/75
ACTIVE-A 2008	7554 with AF within 6 mos. plus one additional vascular RF	13 % with history of stroke or TIA	—	Mean 3.6 y	ASA 75-100 ASA-C 75-100/75
ACTIVE-W 2008	6706 with AF plus one additional vascular RF	15 % with history of stroke or TIA	—	1.3 y	ASA-C 75-100 Warfarin, INR 2.0-3.0

AF atrial fibrillation, ASA aspirin, ASA-C Aspirin and clopidogrel, CE Cardioembolic, ICH intracranial hemorrhage, IS ischemic stroke, LA Large artery, Lac Lacunar, MCA middle cerebral artery, MES microembolic signals, MI myocardial infarction, PTAS percutaneous transluminal angiography and stenting, RF risk factor, TIA Transient ischemic attack, Unk Unknown