Dual or Mono Antiplatelet Therapy for Patients With Acute Ischemic Stroke or Transient Ischemic Attack

Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background and Purpose—Antiplatelets are recommended for patients with acute noncardioembolic stroke or transient ischemic attack. We compared the safety and efficacy of dual versus mono antiplatelet therapy in patients with acute ischemic stroke or transient ischemic attack.

Methods—Completed randomized controlled trials of dual versus mono antiplatelet therapy in patients with acute (≤3 days) ischemic stroke/transient ischemic attack were identified using electronic bibliographic searches. The primary outcome was recurrent stroke (ischemic, hemorrhagic, unknown; fatal, nonfatal). Comparison of binary outcomes between treatment groups was analyzed with random effect models and described using risk ratios (95% CI).

Results—Twelve completed randomized trials involving 3766 patients were included. In comparison with mono antiplatelet therapy, dual therapy (aspirin+dipyridamole and aspirin+clopidogrel) significantly reduced stroke recurrence, dual 58 (3.3%) versus mono 91 (5.0%; risk ratio, 0.67; 95% CI, 0.49–0.93); composite vascular event (stroke, myocardial infarction, vascular death), dual 74 (4.4%) versus mono 106 (6%; risk ratio, 0.75; 95% CI, 0.56–0.99); and the combination of stroke, transient ischemic attack, acute coronary syndrome, and all death, dual 100 (1.7%) versus mono 136 (9.1%; risk ratio, 0.71; 95% CI, 0.56–0.91); dual therapy was also associated with a nonsignificant trend to increase major bleeding, dual 15 (0.9%) versus mono 6 (0.4%; risk ratio, 2.09; 95% CI, 0.86–5.06).

Conclusions—Dual antiplatelet therapy appears to be safe and effective in reducing stroke recurrence and combined vascular events in patients with acute ischemic stroke or transient ischemic attack as compared with mono therapy. These results need to be tested in prospective studies. (Stroke. 2012;43:00-00.)

Key Words: acute ischemic stroke • antiplatelet therapy • cardiovascular prevention • transient ischemic attack
Table 1. Design and Baseline Characteristics of Included Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Groups and Dose</th>
<th>Patients</th>
<th>Treatment Onset, D</th>
<th>Treatment Duration, Mo</th>
<th>Age, Y</th>
<th>Male, %</th>
<th>Blinding</th>
<th>Completeness of Follow-Up</th>
<th>Intention-to-Treat Analysis</th>
<th>Study Quality</th>
<th>Size (≤3 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESPS 2 1996</td>
<td>Asp (25 mg bd) + Dip (200 mg bd) vs Asp vs Dip</td>
<td>IS, TIA</td>
<td>≤3</td>
<td>24</td>
<td>67</td>
<td>58</td>
<td>Double-blind</td>
<td>42 lost to follow-up</td>
<td>Intention-to-treat</td>
<td>A</td>
<td>221</td>
</tr>
<tr>
<td>ESPRIT 2006</td>
<td>Asp (30–325 mg od) + Dip (200 mg bd) vs Asp</td>
<td>IS, TIA</td>
<td>≤3</td>
<td>42</td>
<td>63</td>
<td>66</td>
<td>Open nonblind</td>
<td>106 lost to follow-up</td>
<td>Intention-to-treat</td>
<td>A</td>
<td>95</td>
</tr>
<tr>
<td>FASTER 2007</td>
<td>Asp (162-mg load then 81 mg od) + Clop (300-mg load then 75 mg od) vs Asp</td>
<td>IS, TIA</td>
<td>≤1</td>
<td>3</td>
<td>68</td>
<td>53</td>
<td>Double-blind</td>
<td>7 lost to follow-up</td>
<td>Intention-to-treat</td>
<td>A</td>
<td>392</td>
</tr>
<tr>
<td>EARLY 2009</td>
<td>Asp (25 mg) + Dip (200 mg bd) vs Asp (100 mg od)</td>
<td>IS, TIA</td>
<td>≤1</td>
<td>7</td>
<td>69</td>
<td>62</td>
<td>Blinded outcomes</td>
<td>Not given</td>
<td>Analyzed as treated</td>
<td>A</td>
<td>543</td>
</tr>
<tr>
<td>PRoFESS 2009</td>
<td>Asp (25 mg bd) + Dip (200 mg bd) vs Clop (75 mg od)</td>
<td>IS</td>
<td>=3</td>
<td>30</td>
<td>66.1</td>
<td>64</td>
<td>Double-blind</td>
<td>125 lost to follow-up</td>
<td>Intention-to-treat</td>
<td>A</td>
<td>1360</td>
</tr>
<tr>
<td>CHARISMA 2006</td>
<td>Asp (75–162 mg od) + Clop (75 mg od) vs Asp</td>
<td>IS, TIA</td>
<td>≤1</td>
<td>28</td>
<td>64</td>
<td>70</td>
<td>Double-blind</td>
<td>Lost to follow-up ≥0.5%</td>
<td>Intention-to-treat</td>
<td>A</td>
<td>216</td>
</tr>
<tr>
<td>MATCH 2004</td>
<td>Asp (75 mg od) + Clop (75 mg od) vs Clop</td>
<td>IS, TIA</td>
<td>≤3</td>
<td>18</td>
<td>66</td>
<td>63</td>
<td>Double-blind</td>
<td>323 lost to follow-up</td>
<td>Intention-to-treat</td>
<td>A</td>
<td>491</td>
</tr>
<tr>
<td>CARESS 2005</td>
<td>Asp (75 mg od) + Clop (300-mg load then 75 mg od) vs Asp</td>
<td>IS, TIA</td>
<td>≤3</td>
<td>7</td>
<td>65</td>
<td>69</td>
<td>Double-blind</td>
<td>None</td>
<td>Intention-to-treat</td>
<td>A</td>
<td>25</td>
</tr>
<tr>
<td>CLAIR 2010</td>
<td>Asp (75–160 mg od) + Clop (300-mg load on then 75 mg od) vs Asp</td>
<td>IS, TIA</td>
<td>≤3</td>
<td>7</td>
<td>58</td>
<td>78</td>
<td>Blinded outcomes</td>
<td>1 lost to follow-up</td>
<td>Intention-to-treat</td>
<td>A</td>
<td>98</td>
</tr>
<tr>
<td>Matthews Gui 1984</td>
<td>Asp (50 mg od) + Dip (100 mg qds) vs Dip</td>
<td>TIA</td>
<td>≤3</td>
<td>21</td>
<td>55</td>
<td>77</td>
<td>Open</td>
<td>11 lost to follow-up</td>
<td>Not described</td>
<td>B</td>
<td>109</td>
</tr>
<tr>
<td>Kaye 1989</td>
<td>Asp (900 mg od) + Dip vs Asp</td>
<td>IS</td>
<td>≤3</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>B</td>
<td>178</td>
</tr>
<tr>
<td>Chairangsrirat 2005</td>
<td>Asp (300 mg od) + Dip (225 mg od) vs Asp</td>
<td>IS</td>
<td>≤2</td>
<td>6</td>
<td>64</td>
<td>53</td>
<td>Open</td>
<td>Unclear</td>
<td>Not described</td>
<td>A</td>
<td>38</td>
</tr>
</tbody>
</table>

Quality scale: A, true randomization and allocation concealed; B, process of randomization not given and concealment of allocation unclear.

ESPS indicates European Stroke Prevention Study; ESPRIT, European/Australasian Stroke Prevention in Reversible Ischemia Trial; FASTER, Fast Assessment of Stroke Treatment Duration; MATCH, Management of ATherothrombosis with Clopidogrel in High-risk patients; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CARESS, Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis; CLAIR, Clopidogrel plus aspirin vs aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis; Asp, aspirin; Dip, dipyridamole; Clop, clopidogrel; bd, twice daily; od, once daily; qds, 4 times daily; IS, ischemic stroke; TIA, transient ischemic attack.

In acute ischemic stroke, 2 megatrials established the efficacy of Asp. However, whether more intensive antiplatelet therapy should be given remains unclear. The Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial compared the combination of Asp+Clop versus Asp monotherapy (with or without simvastatin) in patients with TIA or minor stroke within 24 hours of symptom onset. Although this trial was stopped early because of slow recruitment, a trend to less stroke recurrence was present with Asp+Clop in comparison with Clop alone. The early treatment with aspirin plus extended-release dipyridamole for transient ischemic attack or ischemic stroke (EARLY) trial compared the safety and efficacy of Asp+Dip initiated within 24 hours of stroke or TIA with that of Asp+Dip initiated after 7 days of Asp monotherapy. Although there was no difference in functional status at 90 days, a trend to lower recurrence was present with dual therapy. A similar pattern of findings was seen for Asp+Dip versus Clop in patients randomized early into the PRoFESS trial. Although not reported separately, some secondary prevention trials such as Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA), European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), and Management of ATherothrombosis with Clopidogrel in High-risk patients (MATCH) have recruited patients during the acute stage of ischemic stroke and TIA.

The present study aimed to compare the safety and efficacy of early dual antiplatelet versus monotherapy in acute (within 3 days from onset to randomization) ischemic stroke or TIA using data from completed randomized trials. Because different pairs of antiplatelets appear to be superior to single agents, we hypothesized that the composition of agents would be less important than their number in determining safety and efficacy.

Methods

Eligibility Criteria

Randomized controlled trials assessing dual versus mono antiplatelet therapy in noncardioembolic ischemic stroke or TIA were considered if they included patients within 72 hours of ictus. Trials involving adult patients (age ≥18 years) of either sex were considered for inclusion, whether published (irrespective of language) or unpublished. Noncontrolled trials, observational studies, trials comparing dual or mono versus no therapy, and trials with no acute data or where it was not possible to obtain acute data were excluded.
Search Strategy
Published studies fulfilling these eligibility criteria were identified from electronic searches of the Cochrane Library, MEDLINE, EMBASE, and Science Citation Index (last searched in April 2011). Trials were also identified from reference lists of relevant trial publications and existing review articles of antiplatelet therapy in stroke.23–31

Search
Key search words included: “antiplatelet therapy,” “aspirin,” “dipyridamole,” “clopidogrel,” “ticlopidine,” “prasugrel,” “cilostazol,” “triflusal,” “glycoprotein IIb/IIIa receptor antagonists,” “stroke,” “cerebral ischemia,” “transient ischemic attack,” and “randomized control trial.” The search strategy for MEDLINE is given as an example in the online supplement (http://stroke.ahajournals.org).

Selection
The search results were screened for randomized controlled trials by 2 authors (C.M.G., M.W.B.). Identified full-text articles were screened for these eligibility criteria. Trials that met the eligibility criteria and reported outcome data were selected for systematic review and meta-analysis. Where duplicate publications were identified, data from the primary report were used. If the primary trial publication did not provide the relevant data, principal investigators of identified trials were approached and asked to share outcome data for patients randomized within 3 days of stroke/TIA onset.

Data Collection Process
Two authors (C.M.G., M.W.B.) independently recorded information from publications and discrepancies were resolved through discussion with another author (P.M.W.B.). For trials in which the Principal Investigator was contacted, data were provided by them or another person (usually statistician) with access to the data.

Data Items
The primary outcome was stroke recurrence (as defined in individual trials: ischemic, hemorrhagic, unknown; fatal or nonfatal). Secondary outcomes included: the combination of stroke, TIA, acute coronary syndrome, and death; the composite of nonfatal stroke, nonfatal myocardial infarction (MI), and vascular death; MI (fatal or nonfatal); severe stroke (modified Rankin Scale 2–6); TIA; intracerebral hemorrhage; major bleeding; all-cause death; vascular death; and all death.

Quantitative Data Synthesis
Interobserver agreement between the authors collecting trials was assessed as observed percent agreement and Cohen’s k coefficient. Data were entered into and analyzed using the Cochrane Collaboration Review Manager software (Version 5 for Mac). Outcomes up to and including 90 days of enrollment were obtained for each trial by treatment group. Events were recorded for each potential comparison of dual versus mono antiplatelet. Risk ratio (RR) and 95% CIs were calculated using random effects models because the interventions, event rates, and trial designs were expected to vary. Significance was set at P<0.05. The presence of heterogeneity was quantified using χ² and I² statistics.32 Egger test and Begg funnel plot were performed to assess any publication bias in the included trials.33,34 The methodological quality of trials was assessed in relation to randomization and concealment of allocation as recommended by the Cochrane collaboration.32 A quality scale was used to assess the trials: A: true randomization and allocation concealed, B: process of randomization not given and concealment of allocation unclear. When a trial compared >1 control against a common treatment group, the treatment group patients were divided equally between control groups to prevent treatment subjects getting counted more than once and thereby artificially narrowing the CIs. In addition, trials were also assessed for blinding, completeness of follow-up, and intention-to-treat analysis.

Results
Flow of Included Studies
Twelve completed randomized trials fulfilled the selection criteria (Table 1); these enrolled 3766 patients within 3 days.
of stroke/TIA onset (Figure 1; Table 1). Fourteen studies (3879 patients) were excluded, in most cases because they had no acute patient data (Figure 1; Supplemental Table I). When approached, all but 1 chief investigator or their deputy shared data. The observed percent agreement between the authors (C.M.G., M.W.B.) was 85% with Cohen \(\kappa\) coefficient 0.91.

**Study Characteristics**

The baseline characteristic of included patients by trial are summarized in Table 1. The trials studied the following antiplatelets: Asp vs Clop versus Asp (4 trials, 731 patients); Asp vs Clop versus Clop (1 trial, 491 patients); Asp vs Dip versus Asp (5 trials, 964 patients); Asp vs Dip versus Dip (2 trials, 220 patients); and Asp vs Dip versus Clop (1 trial, 1360 patients). No studies of dual versus monotherapy involving cilostazol, prasugrel, ticagrelor, or triflusal were identified. Of the 12 randomized trials, 6 were double-blind, 8 were intention-to-treat, and 10 had concealed allocation; the method of randomization and allocation concealment was unclear in 2 studies (Table 1).

**Synthesis of Results**

**Stroke Recurrence**

Dual antiplatelet therapy significantly reduced stroke recurrence in comparison with monotherapy in acute ischemic stroke/TIA, dual 58 (3.3%) versus mono 91 (5.0%; RR, 0.67; 95% CI, 0.49–0.93; Figure 2; Table 2). No heterogeneity was present between the comparisons of different pairs of antiplatelets. There was no evidence of publication bias assessed using Egger test (\(P\) for bias 0.37) nor asymmetry on visual inspection of the Begg funnel plot (not shown).
Table 2. Effects of Dual vs Mono Antiplatelet Therapy in Acute Ischemic Stroke/TIA*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Asp+Clop vs Asp</th>
<th>Asp+Clop vs Clop</th>
<th>Asp+Dip vs Asp</th>
<th>Asp+Dip vs Dip</th>
<th>Asp+Dip vs Clop</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke recurrence</td>
<td>0.67 (0.37–1.23)</td>
<td>0.83 (0.36–1.93)</td>
<td>0.64 (0.37–1.10)</td>
<td>1.23 (0.24–6.41)</td>
<td>0.56 (0.27–1.17)</td>
<td>0.67 (0.49–0.93)</td>
</tr>
<tr>
<td>Stroke, TIA, ACS, all death</td>
<td>0.68 (0.45–1.03)</td>
<td>0.81 (0.41–1.59)</td>
<td>0.67 (0.42–1.07)</td>
<td>...</td>
<td>0.76 (0.46–1.25)</td>
<td>0.71 (0.56–0.91)</td>
</tr>
<tr>
<td>Stroke, MI, vascular death</td>
<td>0.68 (0.39–1.17)</td>
<td>0.78 (0.35–1.70)</td>
<td>0.76 (0.44–1.31)</td>
<td>1.48 (0.38–5.84)</td>
<td>0.71 (0.38–1.34)</td>
<td>0.75 (0.56–0.99)</td>
</tr>
<tr>
<td>mRS 2–6</td>
<td>0.98 (0.47–2.06)</td>
<td>1.11 (0.87–1.43)</td>
<td>0.92 (0.76–1.10)</td>
<td>...</td>
<td>1.04 (0.90–1.20)</td>
<td>1.01 (0.91–1.12)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>3.61 (0.15–87.54)</td>
<td>0.31 (0.01–7.48)</td>
<td>0.18 (0.01–3.81)</td>
<td>...</td>
<td>1.02 (0.14–7.25)</td>
<td>0.74 (0.20–2.81)</td>
</tr>
<tr>
<td>TIA</td>
<td>1.75 (0.30–10.27)</td>
<td>0.61 (0.10–3.63)</td>
<td>0.61 (0.17–2.15)</td>
<td>0.77 (0.18–3.28)</td>
<td>1.13 (0.48–2.63)</td>
<td>0.92 (0.53–1.63)</td>
</tr>
<tr>
<td>MI</td>
<td>0.37 (0.06–2.41)</td>
<td>0.31 (0.01–7.48)</td>
<td>1.36 (0.20–9.19)</td>
<td>...</td>
<td>1.02 (0.14–7.25)</td>
<td>0.71 (0.25–2.03)</td>
</tr>
<tr>
<td>ICH</td>
<td>2.94 (0.31–28.02)</td>
<td>0.31 (0.01–7.48)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1.39 (0.22–8.75)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.77 (0.62–22.98)</td>
<td>3.67 (0.41–32.62)</td>
<td>0.92 (0.06–14.61)</td>
<td>...</td>
<td>1.54 (0.44–5.42)</td>
<td>2.09 (0.86–5.06)</td>
</tr>
<tr>
<td>Death</td>
<td>1.07 (0.16–7.21)</td>
<td>0.92 (0.19–4.50)</td>
<td>1.61 (0.73–3.52)</td>
<td>4.94 (0.46–52.56)</td>
<td>0.85 (0.26–2.78)</td>
<td>1.34 (0.76–2.34)</td>
</tr>
<tr>
<td>Death vascular</td>
<td>0.60 (0.06–6.54)</td>
<td>0.31 (0.03–2.92)</td>
<td>1.43 (0.39–5.30)</td>
<td>12.12 (0.60–245.70)</td>
<td>1.71 (0.41–7.11)</td>
<td>1.31 (0.59–2.93)</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack; Asp, aspirin; Clop, clopidogrel; Dip, dipiridamole; ACS, acute coronary syndrome (includes MI); MI, myocardial infarction; mRS, modified Rankin Scale; ICH, intracerebral hemorrhage.

*The results are shown as risk ratio (95% CI) with the no. of trials (N), patients (n), and events (E).

Secondary Outcomes
Dual antiplatelet therapy significantly reduced composite vascular events (stroke, MI, and vascular death), dual 74 (4.4%) versus mono 106 (6%); RR, 0.75; 95% CI, 0.56–0.99; Table 2); and combined stroke, TIA, acute coronary syndrome, and all death, dual 100 (1.7%) versus mono 136 (9.1%; RR, 0.71; 95% CI, 0.56–0.91; Figure 3; Table 2). Dual antiplatelet therapy was also associated with a nonsignificant trend to increase major bleeding, dual 15 (0.9%) versus mono 6 (0.4%; RR, 2.09; 95% CI, 0.86–5.06; Figure 4). The number of patients with a poor functional outcome (modified Rankin Scale 2–6) did not differ between dual and monotherapy. Fatal stroke, TIA, MI, intracerebral hemorrhage, death, and vascular death did not differ between mono and dual antiplatelet therapy (Table 2), although the number of events was small (<60) in each case; the corresponding 95% CIs were wide. In each case, no heterogeneity was present between different antiplatelet regimes.

Discussion
The present systematic review and meta-analysis compared the safety and efficacy of dual versus mono antiplatelet therapy in patients with acute ischemic stroke or TIA. In comparison with mono antiplatelet therapy, dual antiplatelets were associated with reduced early stroke recurrence, composite vascular events (stroke, MI, and vascular death), and combined stroke, TIA, acute coronary syndrome, and all death. Dual therapy was also associated with a trend to increase major bleeding. Other outcomes did not differ between the antiplatelet strategies, including fatal stroke.
(modified Rankin Scale 6), severe stroke (modified Rankin Scale 2–6), TIA, MI, intracerebral hemorrhage, all death, or vascular death, although these latter outcomes were few in number. No individual comparison of specific dual versus mono antiplatelet combinations altered stroke or any other outcome.

The meta-analysis compared 2 different combinations of dual antiplatelet therapy—Asp/Clop and Asp/Dip—with 3 different single antiplatelets—Asp, Clop, and Dip. Importantly, there was no heterogeneity (as assessed by the $I^2$ statistic) for any of the analyses; this suggests that the composition of the dual and mono antiplatelet therapy may not be important, that is, it appears that the numbers of antiplatelets rather than their type that drove reductions in stroke and vascular events. This finding is analogous with antihypertensive agents in which it is the number of drugs rather than the drug class that drives blood pressure-lowering and, with it, stroke reduction. Like with antihypertensive agents, this hypothesis is dependent on the studied antiplatelets having differing and complementary modes of action, as present for Asp (cyclo-oxygenase inhibitor), Clop (adenosine 5'-diphosphate receptor antagonist), and Dip (adenosine uptake inhibitor and phosphodiesterase inhibitor) so that their effects are additive. In contrast, agents with the same mode of action such as using combined Clop and ticlopidine would not be expected to have an additive effect.

Supporting evidence for the superiority of dual over mono antiplatelet therapy comes from transcranial Doppler embolic signal studies. The presence of embolic signal on transcranial Doppler identifies a group with a high risk of recurrence in acute stroke/TIA and transcranial Doppler embolic signal also predicts risk in acute stroke and acute large artery atherosclerosis. The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis (CARESS) and Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR) studies have both shown that dual antiplatelet therapy with Asp and Clop reduces embolic signal more than Asp alone and this reduction correlates with clinical outcome events. Additionally, the AMBulatory Dual Treatment for Preventing Stroke (MATTERS) study compared dual antiplatelet therapy (Asp/Clop) versus single antiplatelet therapy (Asp) in patients with acute stroke/TIA. The MATTERS study showed a significant reduction in the combined endpoint of stroke recurrence or death at 90 days with dual antiplatelet therapy compared to single antiplatelet therapy (relative risk reduction 30%, 95% CI 20–40%).

**Figure 3.** Comparison of dual versus mono antiplatelet therapy in acute ischemic stroke/TIA on stroke, TIA, ACS, and all death. TIA indicates transient ischemic attack; ACS, acute coronary syndrome.
Anti-Platelet (AMDAP) trial suggested that Asp and Clop reduced embolization to a similar extent to Asp and Dip.39

Several limitations to this systematic review need to be highlighted. First, the included data came from trials recruiting patients within 3 days of stroke/TIA onset. The cutoff of 72 hours was chosen a priori because it allows inclusion of patients presenting on the second or third day after stroke or TIA, important because this sizable group is often neglected in acute stroke research. Nevertheless, 2 of the trial only recruited within 24 hours (FASTER and EARLY18,19). Second, the data included both complete trials, that is, all patients were recruited within 72 hours (FASTER and EARLY18,19) and those in which only a proportion, usually small, of patients were recruited acutely. Because this latter proportion of patients was not from a distinct stratum within the trials, it is unclear whether potential confounders were equally distributed across the 2 arms of each study. Therefore, the findings in trial subgroups have to be carefully interpreted to avoid bias but the choice of a predefined time limit will have reduced the potential for this. Third, a limited number of events occurred for some outcomes (fatal stroke, TIA, MI, intracerebral hemorrhage, all death, vascular death) thereby limiting any comment on the effect of dual versus mono antiplatelets on these. Nevertheless, the point estimate for the RRs for fatal stroke, TIA, and MI are all similar to those for recurrent stroke and vascular outcomes. Hence, it is likely that the presence of 2 antiplatelets rather than 1 also reduces these outcomes. Last, most trial publications did not give all the necessary data and we had to contact authors for additional data; all but 1 group of authors was willing to share data so bias from missing some data is minimal. There are no large randomized trials comparing dual antiplatelet therapies (aspirin/dipyridamole versus aspirin/clopidogrel) to resolve more definitively the question as to whether the number of agents, or the agent per se, drives the clinical benefit.

When considering using more intensive antiplatelet therapy, the balance between reducing recurrent stroke and vascular events, and increasing intracerebral hemorrhage and
major bleeding, needs to be considered. The much larger number of strokes (149) and combined vascular events (236) than major bleeding events (21) and significant reduction in vascular outcomes but only trend to increase in bleeding confirms that, overall, the balance lies in favor of using dual rather than mono antiplatelet therapy.

In summary, dual antiplatelet therapy appears to be safe and effective in reducing stroke recurrence and vascular events in patients with acute ischemic stroke or TIA as compared with monotherapy. The ongoing Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT, www.pointtrial.org/) trial, which is comparing Asp+Clop versus Asp alone, will add more data to this question. In contrast, the ongoing Triple Antiplatelets for Reducing Dependency after Ischemic Stroke (TARDIS, www.tardistrial.org/) trial moves the question on by comparing more intensive antiplatelet therapy (Asp+Clop+Dip) and guideline-based dual antiplatelet therapy (Asp+Dip). The present study had relatively small numbers of outcome events; it is primarily only hypothesis-generating and should not lead to modification of treatment paradigms.

Acknowledgments
We thank Prof Lawrence Wong for providing CLAIR data. We also thank the following people for sharing data on behalf of trial Chief Investigators: Philip Bath (European Stroke Prevention Study [ESP5] 2, Matias Guin), Danielle Brennan (CHARISMA, Sanofi-Aventis), Deborah Bauer (MATCH, CARESS, Sanofi-Aventis); Christoph Eschenfelder (EARLY, Boehringer Ingelheim); Dan Cotton (PROFESS, Boehringer Ingelheim); and Jon Blatchford (Kaye 1989, Boehringer Ingelheim). The analyses, their interpretation, and the writing of this article were done independently of these pharmaceutical companies.

Disclosures
H.-C.D. was the national Principal Investigator (PI) for CHARISMA, PI of ESPS2 and MATCH, Co-PI of PROFESS, and was on the steering committee of EARLY. A.A. was chief investigator of ESRIPT trial. C.C. led the CLAIR trial in Singapore. E.J.T. was chief investigator of ESPS2 and MATCH, Co-PI of PROFESS, and was on the steering committee of EARLY. Matthias Guiu), Danielle Brennan (CHARISMA, Sanofi-Aventis), Deborah Bauer (MATCH, CARESS, Sanofi-Aventis); Christoph Eschenfelder (EARLY, Boehringer Ingelheim); Dan Cotton (PROFESS, Boehringer Ingelheim); and Jon Blatchford (Kaye 1989, Boehringer Ingelheim). The analyses, their interpretation, and the writing of this article were done independently of these pharmaceutical companies.

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Stroke. published online January 26, 2012;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Dual or mono antiplatelet therapy for patients with acute ischaemic stroke or TIA: systematic review and meta-analysis of randomised controlled trials

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Fax: 0115 823 1767
E-mail: philip.bath@nottingham.ac.uk
Search strategy: MEDLINE (OVID)

01 antiplatelet therapy/
02. antiplatelet$.tw.
03. combined antiplatelet/
04. combined antiplatelet.tw.
05. aggressive antiplatelet therapy/
06. aggressive antiplatelet therapy/
07. antiplatelet therapy/
08. antiplatelet therapy/
09. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. aspirin/
11. dipyridamole/
12. clopidogrel/
13. ticlopidine/
14. prasugrel/
15. cilostazol/
16. triflusal/
17. glycoprotein IIb/IIIa receptor antagonists/
18. abciximab/
19. tirofiban/
20. eptifibatide/
21. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 9 and 21
23. stroke/
24. TIA.tw.
25. transient ischaemic attack/
26. cerebral infarction/
27. cerebral ischaemia/
28. ischaemic stroke/
29. transient ischaemic attack/
30. acute cerebral ischaemia/
31. acute stroke/
32. acute ischaemic stroke/
33. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
34. 22 and 33
35. randomised controlled trials/
36. randomised-controlled-trial.pt.
37. controlled-clinical-trial.pt.
38. random allocation/
39. double-blind method/
40. single-blind method/
41. 35 or 36 or 37 or 38 or 39 or 40
42. exp clinical trials/
43. clinical-trial.pt.
44. (clin$ adj trial$).ti,ab.
45. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$)).ti,ab.
46. random$.ti,ab.
47. 42 or 43 or 44 or 45 or 46
48. research design/
49. comparative study/
50. exp evaluation studies/
51. follow-up studies/
52. prospective studies/
53. (control$ or prospective$ or volunteer$).ti,ab.
54. 49 or 50 or 51 or 52 or 53
55. 41 or 47 or 48 or 54
56. 34 and 55
Table S1. Excluded trials and reason for exclusion, ordered by date of publication.

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Size</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian cooperative</td>
<td>Asp + Sul v Sul v Asp</td>
<td>585</td>
<td>Unable to obtain data for patients &lt;3 days</td>
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<tr>
<td>1978</td>
<td></td>
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<td>Pince 1981</td>
<td>Asp + Dip v Placebo</td>
<td>80</td>
<td>Dual vs. no antiplatelets</td>
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<td>Guiraud- Chaumeil 1982</td>
<td>Asp + Dip v Asp</td>
<td>440</td>
<td>Time from stroke onset not clear</td>
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<td>ALICA 1983</td>
<td>Asp + Dip vs Asp</td>
<td>604</td>
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<tr>
<td>ACCSG 1985</td>
<td>Asp + Dip v Asp</td>
<td>890</td>
<td>Time from stroke onset not clear</td>
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<td>Caneschi 1985</td>
<td>Asp + Dip v Asp v Dip</td>
<td>50</td>
<td>Data not available</td>
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<tr>
<td>Caneschi 1985</td>
<td>Asp + Dip v Asp v Dip v Ditazol v</td>
<td>80</td>
<td>Observational study</td>
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<td></td>
<td>Isosuprine</td>
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<tr>
<td>ESPS 1987</td>
<td>Asp + Dip v Placebo</td>
<td>243</td>
<td>Dual vs. no antiplatelets</td>
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<td>Akyuz 1999</td>
<td>Asp + Tic v Asp v Tic</td>
<td>100</td>
<td>Platelet function study with no clinical outcomes</td>
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<tr>
<td>PLUTO stroke 2005</td>
<td>Asp + Clop v Clop</td>
<td>70</td>
<td>Patients enrolled 1-3 months after event onset</td>
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<tr>
<td>Zaidi 2006</td>
<td>Asp + Dip</td>
<td>356</td>
<td>Observational study</td>
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<tr>
<td>LOAD 2008</td>
<td>Asp + Clop</td>
<td>40</td>
<td>Observational study</td>
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<tr>
<td>Lee 2010</td>
<td>Asp + Clop v Asp</td>
<td>244</td>
<td>Patients enrolled &gt;2 weeks from after event</td>
</tr>
</tbody>
</table>
onset

Takigawa 2010  Asp + Clop v Tic v Cil  97  Observational study

Asp: aspirin; Cil: cilostazol; Clop: clopidogrel; Dip: dipyridamole; Sul: sulfinpyrazone; Tic: ticlopidine; v: versus
REFERENCES


急性虚血性脳卒中または一過性脳虚血発作患者に対する2剤併用または単剤の抗血小板療法
——無作為比較試験の系統的レビューおよびメタ解析

Dual or Mono Antiplatelet Therapy for Patients With Acute Ischemic Stroke or Transient Ischemic Attack — Systematic Review and Meta-Analysis of Randomized Controlled Trials

Chamila M. Geeganage, PhD1; Hans-Christoph Diener, MD, PhD2; Ale Algra, MD3; Christopher Chen, FRCP4; Eric J. Topol, MD5; Reinhard Dengler, MD6; Hugh S. Markus, FRCP7; Matthew W. Bath1; Philip M. W. Bath, MD, FRCP1; for the Acute Ischemic Stroke Trialsists Collaboration

1 Stroke Trials Unit, University of Nottingham, Nottingham, UK; 2 Department of Neurology, University Duisburg-Essen, Essen, Germany; 3 Department of Neurology and Neurosurgery and Julius Center, University Medical Center Utrecht, Utrecht, Netherlands; 4 Department of Pharmacology, National University of Singapore, Singapore; 5 The Scripps Research Institute and Scripps Clinic, La Jolla, CA; 6 Department of Neurology and Clinical Neurophysiology, Hannover Medical School, Hannover, Germany; 7 the Stroke and Dementia Research Centre, St George’s University of London, London, UK

背景および目的：急性非心原性脳塞栓症の患者または一過性脳虚血発作患者に対しては、抗血小板薬が推奨されている。我々は、急性虚血性脳卒中または一過性脳虚血発作患者において、2剤併用と単剤による抗血小板療法の安全性および有効性を比較検討した。

方法：急性(≤3日)虚血性脳卒中または一過性脳虚血発作の患者において2剤併用および単剤の抗血小板療法を評価した完済済の無作為比較試験を、電子的文献検索を用いて同定した。主な要因は脳卒中(虚血性、出血性、不明、致死的、非致死的)の再発とした。

結果：脳卒中の主な合併症は、急性虚血性脳卒中または一過性脳虚血発作の患者において、2剤併用群で4例(4.4%)に対して単剤群で106例(6%)、リスク比=0.75、95%CI:0.56～0.91であった。2剤併用療法には大出血の有無が増加傾向を認められ、2剤併用群で15例(0.9%)に対し単剤群で6例(0.4%)、リスク比=2.09、95%CI:0.86～5.06であった。

結論：2剤併用による抗血小板療法は単剤療法と比べた場合、急性虚血性脳卒中または一過性脳虚血発作の患者における脳卒中再発と複合行動イベントの抑制のために、安全かつ有効と思われる。これらの結果は前向き試験で検証する必要がある。
Dual or Mono Antiplatelet Therapy for Patients With Acute Ischemic Stroke or Transient Ischemic Attack
Systematic Review and Meta-Analysis of Randomized Controlled Trials

Chamila M. Geeganage, PhD; Hans-Christoph Diener, MD, PhD; Ale Algra, MD; Christopher Chen, FRCP; Eric J. Topol, MD; Reinhard Dengler, MD; Hugh S. Markus, FRCP; Matthew W. Bath; Philip M.W. Bath, MD, FRCP;
for the Acute Antiplatelet Stroke Trialists Collaboration
(Stroke. 2012;43:1058-1066.)

Key Words: acute ischemic stroke ■ antiplatelet therapy ■ cardiovascular prevention ■ transient ischemic attack
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Dual therapy</th>
<th>Monotherapy</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.1.1 AC v A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARESS 2005</td>
<td>1</td>
<td>11</td>
<td>2</td>
<td>14</td>
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<tr>
<td>CLAIR 2010</td>
<td>2</td>
<td>46</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>FASTER (no statin) 2007</td>
<td>12</td>
<td>98</td>
<td>21</td>
<td>95</td>
</tr>
<tr>
<td>FASTER (statin) 2007</td>
<td>17</td>
<td>100</td>
<td>21</td>
<td>99</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>255</td>
<td>260</td>
<td>35.2%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>32</td>
<td>47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.00 \); \( \chi^2 = 0.71 \), df = 3 (\( P = 0.87 \)); \( I^2 = 0% \)

Test for overall effect: \( Z = 1.81 \) (\( P = 0.07 \))

1.1.2 AC v C

| MATCH 2004 | 15 | 256 | 17 | 235 | 13.2% | 0.81 [0.41, 1.59] |
| Subtotal (95% CI) | 256 | 235 | 13.2% | 0.81 [0.41, 1.59] |
| Total events | 15 | 17 |        |       |        |                  |                  |

Heterogeneity: Not applicable

Test for overall effect: \( Z = 0.62 \) (\( P = 0.54 \))

1.1.3 AD v A

| EARLY 2009 | 27 | 283 | 37 | 260 | 27.4% | 0.67 [0.42, 1.07] |
| Subtotal (95% CI) | 326 | 312 | 27.4% | 0.67 [0.42, 1.07] |
| Total events | 27 | 37 |        |       |        |                  |                  |

Heterogeneity: Not applicable

Test for overall effect: \( Z = 1.68 \) (\( P = 0.09 \))

1.1.4 AD v D

| Subtotal (95% CI) | 0 | 0 | Not estimable |
| Total events | 0 | 0 |                  |

Heterogeneity: Not applicable

Test for overall effect: Not applicable

1.1.5 AD v C

| PROFESS acute 2009 | 26 | 672 | 35 | 688 | 24.2% | 0.76 [0.46, 1.25] |
| Subtotal (95% CI) | 672 | 688 | 24.2% | 0.76 [0.46, 1.25] |
| Total events | 26 | 35 |        |       |        |                  |                  |

Heterogeneity: Not applicable

Test for overall effect: \( Z = 1.08 \) (\( P = 0.28 \))

| Total (95% CI) | 1509 | 1495 | 100.0% | 0.71 [0.56, 0.91] |
| Total events | 100 | 136 |        |       |                  |                  |

Heterogeneity: \( \tau^2 = 0.00 \); \( \chi^2 = 1.02 \), df = 6 (\( P = 0.98 \)); \( I^2 = 0% \)

Test for overall effect: \( Z = 2.71 \) (\( P = 0.007 \))

Test for subgroup differences: \( \chi^2 = 0.31 \), df = 3 (\( P = 0.96 \)); \( I^2 = 0% \)

Figure 3. Comparison of dual versus mono antiplatelet therapy in acute ischemic stroke/TIA on stroke, TIA, ACS, and all death. TIA indicates transient ischemic attack; ACS, acute coronary syndrome.