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;43:1058-1066.)

Key Words: acute ischemic stroke ▪ antiplatelet therapy ▪ cardiovascular prevention ▪ transient ischemic attack

The risk of recurrent stroke is highest immediately after a transient ischemic attack (TIA) or ischemic stroke, especially during the subsequent hours and days,1–4 and patients who substantially recover from their initial deficit are at the greatest risk of deterioration.5,6 Additionally, patients who do not receive thrombolysis are at a high subsequent risk of death or dependency.7,8 As a result, clinical guidelines recommend antiplatelet therapy for patients with noncardioembolic stroke or TIA.9–11 Treatment options include aspirin (Asp), clopidogrel (Clop), extended-release dipyridamole (Dip), and Asp plus Dip. For the secondary prevention of stroke after the acute phase, the combination of Asp+Dip has been shown to be more effective than Asp or Dip monotherapy.12,13 In patients at risk of stroke recurrence, Clop was nonsignificantly more effective than Asp in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death.14 However, rates of recurrent stroke were similar when Asp+Dip versus Clop monotherapy were compared in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial.15

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In acute ischemic stroke, 2 megatrials established the efficacy of Asp.16,17 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.18 Although this trial was stopped early because of slow recruitment, a trend to less stroke recurrence was present with dual therapy. A similar pattern of findings was seen for Asp+Dip versus 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.19 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.15,20 Although not reported separately, some secondary prevention trials such as Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA),21 European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT),13 and Management of ATherothrombosis with Clopidogrel in High-risk patients (MATCH)22 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 mono therapy 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.

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 (&lt;=3 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESPS 2 199512</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 A</td>
<td>221</td>
<td></td>
</tr>
<tr>
<td>ESPRIT 200613</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 A</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>FASTER 200714</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>&lt;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 A</td>
<td>392</td>
<td></td>
</tr>
<tr>
<td>EARLY 200915</td>
<td>Asp (25 mg) + Dip (200 mg bd) vs Asp (100 mg od)</td>
<td>IS, TIA</td>
<td>&lt;1</td>
<td>7 d</td>
<td>69</td>
<td>62</td>
<td>Blinded outcomes</td>
<td>Not given</td>
<td>Analyzed as treated A</td>
<td>543</td>
<td></td>
</tr>
<tr>
<td>PRoFESS 200916</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 A</td>
<td>1360</td>
<td></td>
</tr>
<tr>
<td>CHARISMA 200617</td>
<td>Asp (75–162 mg od) + Clop (75 mg od) vs Asp</td>
<td>IS, TIA</td>
<td>&lt;1</td>
<td>28</td>
<td>64</td>
<td>70</td>
<td>Loss of follow-up ≤0.5%</td>
<td>Intention-to-treat A</td>
<td>216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MATCH 200418</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 A</td>
<td>491</td>
<td></td>
</tr>
<tr>
<td>CARESS 200519</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 d</td>
<td>65</td>
<td>69</td>
<td>Double-blind</td>
<td>None</td>
<td>Intention-to-treat A</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>CLAIR 201020</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 d</td>
<td>58</td>
<td>78</td>
<td>Blinded outcomes</td>
<td>1 lost to follow-up</td>
<td>Intention-to-treat A</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Geeganage et al 200721</td>
<td>Asp (50 mg od) + Dip (100 mg qds) vs Dip</td>
<td>TIA</td>
<td>&lt;3</td>
<td>21</td>
<td>55</td>
<td>77</td>
<td>Open</td>
<td>11 lost to follow-up</td>
<td>Not described B</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>Kaye 199822</td>
<td>Asp (900 mg od) + Dip vs Asp</td>
<td>IS</td>
<td>&lt;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>Chaiangsarit 200523</td>
<td>Asp (300 mg od) + Dip (225 mg od) vs Asp</td>
<td>IS</td>
<td>&lt;2</td>
<td>6</td>
<td>64</td>
<td>53</td>
<td>Open</td>
<td>Unclear</td>
<td>Not described A</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

Quality scale: A, true randomization and allocation concealed; B, process of randomization not given and concealment of allocation unclear.
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; 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 kappa 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 \( \chi^2 \) and \( I^2 \) statistics.\(^3\) Egger test and Begg funnel plot were performed to assess any publication bias in the included trials.\(^3\) The methodological quality of trials was assessed in relation to randomization and concealment of allocation as recommended by the Cochrane collaboration.\(^3\) 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+Clop versus Asp (4 trials, 731 patients); Asp+Clop versus Clop (1 trial, 491 patients); Asp+Dip versus Asp (5 trials, 964 patients); Asp+Dip versus Dip (2 trials, 220 patients); and Asp+Dip versus Clop (1 trial, 1360 patients). No studies of dual versus monotherapy involving cilostazol, prasugrel, ticlopidine, 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).
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.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Asp+Clo vs Asp</th>
<th>Asp+Clo 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></td>
<td>N = 4 (515)</td>
<td>N = 1 (491)</td>
<td>N = 2 (638)</td>
<td>...</td>
<td>N = 1 (1360)</td>
<td>N = 8–n = 3004–E = 236</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></td>
<td>N = 1 (96)</td>
<td>N = 1 (491)</td>
<td>N = 1 (527)</td>
<td>...</td>
<td>N = 1 (1310)</td>
<td>N = 4–n = 2424–E = 885</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></td>
<td>N = 4 (731)</td>
<td>N = 1 (491)</td>
<td>N = 2 (638)</td>
<td>...</td>
<td>N = 1 (1360)</td>
<td>N = 8–n = 3220–E = 21</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, dipyridamole; 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).
(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/H11001Clop and Asp/H11001Dip—with 3 different single antiplatelets—Asp, Clop, and Dip. Importantly, there was no heterogeneity (assessed as 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 predict 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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Dual therapy</th>
<th>Monotherapy</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARESS 2005</td>
<td>1</td>
<td>11</td>
<td>14 1.2% 0.64 [0.07, 6.14]</td>
</tr>
<tr>
<td>CLAIR 2010</td>
<td>2</td>
<td>46</td>
<td>3 52 2.0% 0.75 [0.13, 4.31]</td>
</tr>
<tr>
<td>FASTER (no statin) 2007</td>
<td>12 98 48</td>
<td>21 95 14.1%</td>
<td>0.55 [0.29, 1.06]</td>
</tr>
<tr>
<td>FASTER (statin) 2007</td>
<td>17 100 121</td>
<td>21 99 18.0%</td>
<td>0.80 [0.45, 1.43]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>255</td>
<td>260</td>
<td>35.2% 0.68 [0.45, 1.03]</td>
</tr>
<tr>
<td>Total events</td>
<td>32</td>
<td>47</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)

| 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)

| 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)

| PReFESS 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)

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 versus dipyridamole versus aspirin versus 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 intracranial hemorrhage needs to be considered. The question of whether dual therapy is better than mono therapy for reducing embolization is not definitively answered by this review.
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.

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35. Bloch MJ, Basile JN. Largest meta-analysis to date suggests that patients at risk for cardiovascular disease events derive benefit from antihypertensive therapy regardless of baseline blood pressure and to reduce vascular events, lowering blood pressure is more important than choice of antihypertensive drug class. J Clin Hypertens (Greenwich). 2009;11:743–745.


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, Hans-Christoph Diener, Ale Algra, Christopher Chen, Eric J. Topol, Reinhard Dengler, Hugh S. Markus, Matthew W. Bath, Philip M.W. Bath and for the Acute Antiplatelet Stroke Trialists Collaboration

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ONLINE SUPPLEMENT

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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NG5 1PB UK

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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>
</tr>
<tr>
<td>1978</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pince 1981</td>
<td>Asp + Dip v Placebo</td>
<td>80</td>
<td>Dual vs. no antiplatelets</td>
</tr>
<tr>
<td>Guiraud-Chaumeil 1982</td>
<td>Asp + Dip v Asp</td>
<td>440</td>
<td>Time from stroke onset not clear</td>
</tr>
<tr>
<td>ALICA 1983</td>
<td>Asp + Dip vs Asp</td>
<td>604</td>
<td>Time from stroke onset not clear</td>
</tr>
<tr>
<td>ACCSG 1985</td>
<td>Asp + Dip v Asp</td>
<td>890</td>
<td>Time from stroke onset not clear</td>
</tr>
<tr>
<td>Caneschi 1985</td>
<td>Asp + Dip v Asp v Dip</td>
<td>50</td>
<td>Data not available</td>
</tr>
<tr>
<td>Caneschi 1985</td>
<td>Asp + Dip v Asp v Dip</td>
<td>80</td>
<td>Observational study</td>
</tr>
<tr>
<td></td>
<td>v Ditazol v Isosuprime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPS 1987</td>
<td>Asp + Dip v Placebo</td>
<td>243</td>
<td>Dual vs. no antiplatelets</td>
</tr>
<tr>
<td>Akyuz 1999</td>
<td>Asp + Tic v Asp v Tic</td>
<td>100</td>
<td>Platelet function study with no clinical outcomes</td>
</tr>
<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>
</tr>
<tr>
<td>Zaidi 2006</td>
<td>Asp + Dip</td>
<td>356</td>
<td>Observational study</td>
</tr>
<tr>
<td>LOAD 2008</td>
<td>Asp + Clop</td>
<td>40</td>
<td>Observational study</td>
</tr>
<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


Abstract

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 Antiplatelet Stroke Trialists Collaboration

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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、抗血小板療法が推奨されている。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了済みの無作為比較試験を電子的文献検索で得た。主な転帰は脳卒中（虚血性、出血性、不明、致死的、非致死的）の再発として、電子的文献検索で得た。

結果：3,666例を評価した12の完了済みの無作為比較試験を解析に含めた。単剤による抗血小板療法と比較すると、2剤併用による抗血小板療法（アスピリン+ジピリダモールおよびアスピリン+クロビドグレル）は脳卒中再発のリスクを有意に抑制した。再発例は2剤併用群が58例（3.3%）であったのに対し、単剤群では91例であった（5.0%、リスク比=0.67, 95% CI: 0.49～0.93）。複合血管イベント（脳卒中、心筋梗塞、血管死）は、2剤併用群で74例（4.4%）に対して単剤群で106例（6.0%）、リスク比=0.75, 95% CI: 0.56～0.99）であった。脳卒中、一過性脳虚血発作、急性冠動脈症候群および全死亡の組み合わせでは、2剤併用群100例（1.7%）に対し単剤群136例（9.1%）、リスク比=0.71, 95% CI: 0.56～0.91）であった。2剤併用療法は大出血の有無以外の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血管イベントの抑制のために、安全かつ有効とされる。これらの結果は前向き試験で検討する必要がある。

Stroke 2012; 43: 1058-1066

Stroke 誌の図を一部省略して記載
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

배경과 목적
항혈소관계는 비심인성 뇌졸중 및 일가성혈관척 환자치료에 추천된다. 본 연구에서는 단독 항혈소관계 치료의 안전성과 효능을 단독 항혈소관계 치료와 비교하고자 한다.

방법
3일 이내 입원한 급성기 뇌졸중 환자군에서 단독 또는 복합 항혈소관계를 사용한 무작위 배정 임상연구를 전자서지목록을 이용하여 검색하였다. 재발성 뇌졸중(혈전성, 출혈성 및 분류되지 않는 뇌졸중: 치명적 및 비치명적 뇌졸중)을 일차 결과로 하고 자유효과 모형(random effect model)을 이용, 분석하여, 위험비로 표기하였다.

결과
열두 개의 종료된 무작위 배정 임상연구를 통해 3,766명 환자 가 포함되었다. 단독 항혈소관계와 비교하여, 복합 항혈소관계 (아스피린과 디피리다졸, 아스피린과 클로피드로그릴) 사용은 뇌졸중 재발률을 유의하게 감소시킨다(복합치료군 58명[3.3%] 대 단독치료군 91명[5.0%; RR, 0.67; 95% CI, 0.49~0.93]). 또한, 뇌경색, 심근경색증 발생 및 심혈관질환으로 인한 사망률(복합치료군 74명[4.4%] 대 단독치료군 106명[6%; RR, 0.75; 95% CI, 0.55~0.99]), 뇌졸중, 일가성혈관척, 급성 관상동맥질환 및 전체 사망률(복합치료군 100명[1.7%] 대 단독치료군 136명[9.1%; RR, 0.71; 95% CI, 0.56~0.91])을 각각 분석했을 때 역시 유의한 감소효과를 보였다. 복합 항혈소관계 사용이 주요한 출혈부작용 증가에 미치는 영향에 대해서는 통계적으로 유의하지 않았다(복합치료군 15명[0.9%] 대 단독치료군 6명[0.4%; RR, 2.09; 95% CI, 0.86~5.06]).

결론
복합 항혈소관계 치료는 단독 항혈소관계 치료와 비교하여 급성기 뇌졸중 혹은 일가성혈관척 환자에서 뇌졸중 재발과 심혈관질환 발생을 줄이는 데 효과적이고 안전하다. 이 결과는 전형적 연구에서 확인할 필요가 있다.
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.