Early Dual Versus Mono Antiplatelet Therapy for Acute Non-Cardioembolic Ischemic Stroke or Transient Ischemic Attack

An Updated Systematic Review and Meta-Analysis

Ka Sing Lawrence Wong, FRCP; Yilong Wang, MD; Xinyi Leng, PhD; Chen Mao, PhD; Jinling Tang, FFPH; Philip M.W. Bath, FRCP; Hugh S. Markus, FRCP; Philip B. Gorelick, FACP; Liping Liu, MD; Wenhua Lin, PhD; Yongjun Wang, MD

Background—Emerging studies suggest that early administration of dual antiplatelet therapy may be better than monotherapy for prevention of early recurrent stroke and cardiovascular outcomes in acute ischemic stroke and transient ischemic attack (TIA). We performed a meta-analysis of randomized, controlled trials evaluating dual versus mono antiplatelet therapy for acute noncardioembolic ischemic stroke or TIA.

Methods and Results—We assessed randomized, controlled trials investigating dual versus mono antiplatelet therapy published up to November 2012 and the CHANCE trial (Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events), for efficacy and safety outcomes in adult patients with acute noncardioembolic ischemic stroke or TIA with treatment initiated within 3 days of ictus. In total, 14 studies of 9012 patients were included in the systematic review and meta-analysis. Dual antiplatelet therapy significantly reduced risk of stroke recurrence (risk ratio, 0.69; 95% confidence interval, 0.60–0.80; \( P < 0.001 \)) and the composite outcome of stroke, TIA, acute coronary syndrome, and all death (risk ratio, 0.71; 95% confidence interval, 0.63–0.81; \( P < 0.001 \)) when compared with monotherapy, and nonsignificantly increased risk of major bleeding (risk ratio, 1.35; 95% confidence interval, 0.70–2.59, \( P = 0.37 \)). Analyses restricted to the CHANCE Trial or the 7 double-blind randomized, controlled trials showed similar results.

Conclusions—For patients with acute noncardioembolic ischemic stroke or TIA, dual therapy was more effective than monotherapy in reducing risks of early recurrent stroke. The results of the CHANCE study are consistent with previous studies done in other parts of the world. (Circulation. 2013;128:1656-1666.)

Key Words: antiplatelet agents • meta-analysis • review, systematic • stroke • transient ischemic attack

Patients with ischemic stroke (IS) or transient ischemic attack (TIA) are at high risk of recurrent stroke, and a considerable proportion of these recurrent events occur during the first few days after the index stroke or TIA. Antiplatelet therapy reduces the risk of vascular events in high-risk patients by ≈22% on average, as shown by a meta-analysis of 195 trials with different treatment durations. Therefore, current guidelines recommend antiplatelet therapy, including aspirin, clopidogrel, or aspirin plus dipyridamole, for prevention of stroke recurrence and other vascular events in these patients. For example, the 2008 National Institute for Health and Clinical Excellence (NICE) guideline recommends the use of aspirin alone for the treatment of acute IS and TIA. Aspirin plus dipyridamole is the only dual antiplatelet therapy recommended by current guidelines.

Editorial see p 1598
Clinical Perspective on p 1666

In the coronary circulation, the use of dual or triple antiplatelet agents is the standard practice for acute coronary syndrome (ACS). However, dual antiplatelet therapies, expect for the combination of aspirin and dipyridamole,
Table 1. Design and Baseline Characteristics of Included Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Country and Centers</th>
<th>Sample Size*</th>
<th>Blinding</th>
<th>Treatment Groups and Dosages</th>
<th>Severity of Stroke</th>
<th>Onset-to-Treatment Interval, D</th>
<th>Treatment Duration for Dual Therapy, Mo</th>
<th>Overall Treatment Duration, Mo</th>
<th>Mean Age, Y</th>
<th>Male %</th>
<th>Duration of Follow-Up, %</th>
<th>Lost to Follow-Up, %</th>
<th>ITT Analysis</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matias-Guiu 1987</td>
<td>Spain, single center</td>
<td>109</td>
<td>Open</td>
<td>Asp (50 mg od) + Dip (100 mg qid)</td>
<td>NA</td>
<td>&lt;3</td>
<td>21.4 (mean)</td>
<td>21 (mean)</td>
<td>55</td>
<td>77</td>
<td>21 (mean)</td>
<td>4.5</td>
<td>UNK</td>
<td>B</td>
</tr>
<tr>
<td>Kaye 1989</td>
<td>UNK</td>
<td>178</td>
<td>UNK</td>
<td>Asp (900 mg od) + Dip</td>
<td>IS, TIA</td>
<td>mRS 0–5</td>
<td>24</td>
<td>24 (mean)</td>
<td>67</td>
<td>58</td>
<td>24 (mean)</td>
<td>0.64</td>
<td>ITT</td>
<td>A</td>
</tr>
<tr>
<td>ESPS 2 1996</td>
<td>Europe, 59 centers</td>
<td>221</td>
<td>Double-blind</td>
<td>Asp (25 mg bd) + Dip (200 mg bd)</td>
<td>IS, TIA</td>
<td>mRS 0–5</td>
<td>18</td>
<td>18 (mean)</td>
<td>66</td>
<td>63</td>
<td>18 (mean)</td>
<td>4</td>
<td>ITT</td>
<td>A</td>
</tr>
<tr>
<td>MATCH 2004</td>
<td>Worldwide, 507 centers</td>
<td>491</td>
<td>Double-blind</td>
<td>Asp (75 mg od) + Clop (75 mg od)</td>
<td>IS, TIA</td>
<td>mRS 0–5</td>
<td>7d</td>
<td>7d (mean)</td>
<td>65</td>
<td>69</td>
<td>7d (mean)</td>
<td>0</td>
<td>ITT</td>
<td>A</td>
</tr>
<tr>
<td>CARESS 2005</td>
<td>Europe, 11 centers</td>
<td>25</td>
<td>Double-blind</td>
<td>Asp (75 mg od) + Clop (300 mg load then 75 mg od)</td>
<td>IS, TIA</td>
<td>NIHSS≤22</td>
<td>&lt;3</td>
<td>3 (mean)</td>
<td>68</td>
<td>53</td>
<td>3 (mean)</td>
<td>1.8</td>
<td>ITT</td>
<td>A</td>
</tr>
<tr>
<td>Chairangsait 2005</td>
<td>Thailand, Single center</td>
<td>38</td>
<td>Open</td>
<td>Asp (300 mg od) + Dip (225 mg od)</td>
<td>UNK</td>
<td>&lt;2</td>
<td>6 (mean)</td>
<td>6 (mean)</td>
<td>64</td>
<td>53</td>
<td>6 (mean)</td>
<td>UNK</td>
<td>UNK</td>
<td>A</td>
</tr>
<tr>
<td>CHARISMA 2006</td>
<td>Worldwide, 786 centers</td>
<td>216</td>
<td>Double-blind</td>
<td>Asp (75–162 mg od) + Clop (75 mg od)</td>
<td>IS, TIA</td>
<td>UNK</td>
<td>28 (median)</td>
<td>28 (median)</td>
<td>64</td>
<td>70</td>
<td>28 (median)</td>
<td>≤0.5</td>
<td>ITT</td>
<td>A</td>
</tr>
<tr>
<td>ESPRIT 2006</td>
<td>Worldwide, 86 centers</td>
<td>95</td>
<td>Open</td>
<td>Asp (30–325 mg od) + Dip (200 mg bd)</td>
<td>Minor IS, TIA</td>
<td>mRS≤3</td>
<td>42</td>
<td>42 (mean)</td>
<td>63</td>
<td>66</td>
<td>42 (mean)</td>
<td>3.8</td>
<td>ITT</td>
<td>A</td>
</tr>
<tr>
<td>FASTER 2007</td>
<td>North America, 18 centers</td>
<td>392</td>
<td>Double-blind</td>
<td>Asp (162 mg load then 81 mg od) + Clop (300 mg load then 75 mg od)</td>
<td>Minor IS, TIA</td>
<td>NIHSS≤3</td>
<td>&lt;1</td>
<td>3 (mean)</td>
<td>68</td>
<td>53</td>
<td>3 (mean)</td>
<td>1.8</td>
<td>ITT</td>
<td>A</td>
</tr>
<tr>
<td>EARLY 2009</td>
<td>Germany, 46 centers</td>
<td>543</td>
<td>Blinded outcomes</td>
<td>Asp (25 mg bd) + Dip (200 mg bd) for 3 m</td>
<td>IS, TIA</td>
<td>NIHSS≤20</td>
<td>&lt;1</td>
<td>3 (mean)</td>
<td>69</td>
<td>62</td>
<td>3 (mean)</td>
<td>2.9</td>
<td>Analyzed as treated</td>
<td>A</td>
</tr>
<tr>
<td>PROFESS 2009</td>
<td>Worldwide, 695 centers</td>
<td>1,360</td>
<td>Double-blind</td>
<td>Asp (25 mg bd) + Dip (200 mg bd) for up to 90d</td>
<td>IS, TIA</td>
<td>NIHSS≤20</td>
<td>&lt;1</td>
<td>3 (mean)</td>
<td>69</td>
<td>62</td>
<td>3 (mean)</td>
<td>2.9</td>
<td>Analyzed as treated</td>
<td>A</td>
</tr>
<tr>
<td>CLAIR 2010</td>
<td>Asia, Multi-centers</td>
<td>98</td>
<td>Double-blind</td>
<td>Asp (75–160 mg od) + Clop (300 mg load then 75 mg od)</td>
<td>Minor IS, TIA</td>
<td>NIHSS≤8</td>
<td>≤3</td>
<td>7d (mean)</td>
<td>58</td>
<td>78</td>
<td>7d (mean)</td>
<td>1.0</td>
<td>ITT</td>
<td>A</td>
</tr>
<tr>
<td>Nakamura 2012</td>
<td>Japan, single center</td>
<td>76</td>
<td>UNK</td>
<td>Cil (100 mg bd) + Asp (500 mg then 100 mg od)</td>
<td>IS</td>
<td>mRS 1–4</td>
<td>&lt;2</td>
<td>6 (mean)</td>
<td>67</td>
<td>74</td>
<td>6 (mean)</td>
<td>16.7</td>
<td>Analyzed per protocol</td>
<td>B</td>
</tr>
<tr>
<td>CHANCE 2012</td>
<td>China, 114 centers</td>
<td>5,170</td>
<td>Double-blind</td>
<td>Asp (300 mg load then 75 mg od) + Clop (75–300 mg load then 75 mg od) for 21 days; then Clop alone (75 mg od) afterward</td>
<td>Minor IS, TIA</td>
<td>NIHSS≤3</td>
<td>&lt;1</td>
<td>21d (mean)</td>
<td>62</td>
<td>66</td>
<td>3 (mean)</td>
<td>0.7</td>
<td>ITT</td>
<td>A</td>
</tr>
</tbody>
</table>

ITT indicates intention-to-treat; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; and UNK, unknown.

*Sample size for patients randomized and treated within 3 days.

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

‡Mean follow-up of the study was 30 m, but outcomes assessed in this meta-analysis was at 3 m.
have not been established in treatment of acute noncardioembolic IS and TIA. Large randomized, controlled trials (RCTs) have failed to show the efficacy and safety of dual versus mono antiplatelet therapies in long-term secondary stroke prevention.\textsuperscript{10–13} However, these large trials involved many different study populations, and treatment was often started after the initial high-risk phase and was given for several years, increasing the risk of potential side effects, particularly bleeding. Uncertainties remain concerning the efficacy and safety of dual therapy for IS or TIA in the acute phase; the higher recurrent stroke risk during this period might merit a more intensive antiplatelet regimen. This hypothesis was supported by surrogate markers RCT [the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial\textsuperscript{16} and the Clopidogrel plus Aspirin for Infarction Reduction in Acute Stroke or Transient Ischemic Attack Patients with Large Artery Stenosis and Microembolic Signals (CLAIR) trial],\textsuperscript{17} which showed that dual antiplatelet therapy was more effective at reducing cerebral embolization than monotherapy.

A previous meta-analysis synthesizing only acute data (patients randomized within 3 days of ictus) from all these large trials and other RCTs up to April 2011 found reduced risks of stroke recurrence (risk ratio [RR], 0.67; 95% confidence interval [CI], 0.49–0.93; \(P=0.02\)) and composite end points including stroke, TIA, ACS, and all death (RR, 0.71; 95% CI, 0.56–0.91; \(P=0.007\)) for dual antiplatelet therapy versus mono therapy. The risk of major bleeding tended to be increased with dual therapy, although this was not statistically significant (RR, 2.09; 95% CI, 0.86–5.06, \(P=0.10\)).\textsuperscript{16} Benefit was only seen across all trials and not for any particular comparison of dual versus mono antiplatelet therapy. However, this added evidence favoring the use of dual antiplatelet therapy in treatment of acute IS or TIA.

The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial\textsuperscript{17,18} (Clinicaltrials.gov identifier NCT00979589) is a randomized, double-blind, multicenter, placebo-controlled trial designed to test efficacy and safety for clopidogrel plus aspirin against aspirin alone in the prevention of recurrent stroke in Chinese patients with acute minor stroke or TIA. All subjects were randomized within 24 hours of symptom onset. For the first 21 days after recruitment, patients were randomized to Group 1 with treatment of clopidogrel (300 mg loading dose once then 75 mg od) plus aspirin (75–300 mg loading dose then 75 mg od), or Group 2 with treatment of aspirin alone (75–300 mg loading dose then 75 mg od). Between 21 days and 3 months, patients in Groups 1 and 2 were respectively treated with clopidogrel (75 mg od) alone or aspirin (75 mg od) alone. Overall, 5170 patients were recruited (median age 62 years, and 66% males), 2584 and 2586 in the study and control groups, respectively, and only 0.7% of patients were lost to follow-up at 3 months. Based on an intention-to-treat analysis, the CHANCE study found that dual therapy was more effective in reducing stroke risk (hazard ratio [HR], 0.68; 95% CI, 0.57–0.81; \(P<0.001\)) without increasing risks of severe or moderate bleeding (\(P=0.73\)) at 3 months.\textsuperscript{18}

With the recent completion of CHANCE, we performed an updated systematic review and meta-analysis of dual versus mono antiplatelet therapy for acute noncardioembolic IS or TIA patients within 3 days of symptom onset, to further explore the efficacy and safety of dual antiplatelet therapy initiated in the acute phase of IS and TIA. The analyses were limited to noncardioembolic IS or TIA, because effective risk-reducing treatments are fundamentally different between cardioembolic and noncardioembolic strokes.

**Methods**

**Data Sources and Searches**

We updated the previous systematic review published in Stroke in 2011,\textsuperscript{19} with the new review including the eligible studies up to November 2012 plus CHANCE.\textsuperscript{17,18} The 12 eligible studies up to April 2011 in the previous meta-analysis\textsuperscript{19} were also included in this current meta-analysis. For other potentially eligible studies published after 2011, we searched PubMed for relevant articles from January 2011 to November 2012, with search words of “antipla¬lete therapy,” “aspirin,” “dipyridamole,” “clopidogrel,” “ticlopidine,” “prasugrel,” “cilostazol,” “trifusal,” “glycoprotein IIb/IIIa receptor antagonists,” “stroke,” “cerebral ischemia,” “cerebral infarction,” “transient ischemic attack,” and “randomized controlled trial,” and we also performed manual search of references from original articles and pertinent reviews. Searches were restricted to completed trials in human beings with abstracts or full texts published in English. The search strategy in the current meta-analysis was similar to what was used in the previous one.\textsuperscript{16}

**Study Selection**

One author (X.L.) screened the search results, excluded irrelevant publications based on title and abstract, obtained full-texts of potentially relevant articles for detailed review, and selected eligible studies under supervision of other authors (K.S.L.W., C.M., and J.T.).

RCTs meeting the following criteria were included: (1) Dual versus mono antiplatelet therapy was assessed in adult patients (≥18 years) with noncardioembolic IS or TIA; (2) Enrollment and randomization of all or at least a portion of the patients was within 3 days of the index event. TIA and ischemic stroke in the primary studies were mostly defined as neurological deficit attributed to focal brain ischemia lasting less or more than 24 hours, respectively. The definition of ischemic stroke was usually supported by brain imaging results in the primary studies. Retinal events were not specifically stated in the definition of TIA in most primary studies recruiting TIA patients. Definitions of noncardioembolic IS or TIA were in compliance with what were used in the primary studies, which were similar between the CHANCE trial and the other primary studies. Cardioembolic stroke was defined in most of the primary studies as stroke with presumed cardiac source of embolus, such as atrial fibrillation, valvular heart disease, endocarditis, and recent myocardial infarction.

**Data Extraction and Quality Assessment**

For the present meta-analysis, we independently repeated data extraction from the 12 studies included in the previous systematic review and cross checked our results with those published previously. However, unpublished subgroup data from these 12 studies were used directly from the previous systematic review in the present meta-analysis. Further, for studies published from April 2011 to November 2012, study quality was independently assessed and data were independently extracted by two authors (X.L. and W.L.) using a standardized form with the help and supervision from other authors (K.S.L.W., C.M., and J.T.). Disagreements were resolved by consensus. Besides, data from CHANCE were provided by the principal investigator of the trial.

The following data were extracted: Publication characteristics, countries or regions of the study, study centers (single or multicenter),...
blinding, patient characteristics, sample size of patients enrolled and randomized within 3 days of ictus, treatment groups (medications and dosages), onset-to-treatment interval, treatment duration for dual therapy and overall treatment duration, duration of follow-up, completeness of follow-up, and efficacy and safety outcomes. The efficacy outcomes evaluated were stroke recurrence and the composite of stroke, TIA, ACS, and all death. The safety outcome was major bleeding. All the 3 efficacy and safety outcomes were defined in accordance with what were used in the primary studies included. ACS in the present meta-analysis was defined as including the outcomes of myocardial infarction and unstable angina pectoris in the primary studies. Major bleeding in the primary studies was mostly defined in accordance with moderate-to-severe bleeding by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.29

Data Synthesis and Analysis
All data were analyzed using Cochrane Review Manager (version 5.2). Primary analyses were performed for each outcome, with trials subdivided by the different medications assessed. The overall estimates from all previous trials were compared with the CHANCE study, and with the updated overall results across all trials included in the current meta-analysis. For each outcome, we performed a sensitivity analysis by restricting the analysis to double-blind studies, to test whether the results of the present meta-analysis were sensitive to certain restrictions on the data included. For all outcomes, RR and 95% CIs were calculated using the DerSimonian and Laird random-effects model.20 Between-study and between-subgroup heterogeneities, which were variations in treatment effects of dual versus mono antiplatelet therapies across studies or subgroups regarding the 3 efficacy and safety outcomes, were evaluated by calculating the I² statistic and the Cochrane Q (χ²) statistic. Publication bias of studies with different sample sizes was assessed by performing funnel plots.21 Two-sided probability values of <0.05 were considered statistically significant, except for the heterogeneity test in which probability values of <0.10 were used.

Results
Study Selection and Characteristics
All the 12 studies in the previous meta-analysis were included. For other updated relevant studies from January 2011 to November 2012 (as shown in the flow chart for study selection in Figure 1 in the online-only Data Supplement), an electronic search of PubMed and manual search of references from original articles and pertinent reviews identified 219 publications. By reviewing title and abstract, 209 articles were excluded. Ten articles were reviewed by full-text for details, and 9 of them were excluded: not a RCT (n=2), no acute data present (n=1), duplicate publications (n=2), or other reasons (n=4). Therefore, besides CHANCE, only 1 other eligible RCT published after January 2011 was identified, which compared cilostazol (100 mg bd) plus aspirin (300 mg loading dose then 100 mg od) versus aspirin alone (300 mg loading dose then 100 mg od) in 76 adult patients (mean age 67 years, and 74% males) with acute noncardioembolic IS, though whether treatment was blinded is unknown.29 Therefore, in total, there were 14 studies with 9012 patients in the present systematic review and meta-analysis (study characteristics are listed in Table 1), among which 7 were double-blind, 9 were intention-to-treat, and 11 had concealed allocation. Four trials enrolled IS patients only,12,23,25,29 1 trial enrolled TIA patients only,22 and the others enrolled both IS and TIA patients. For trials enrolling IS (with or without TIA) patients, stroke severities varied: 4 focused on minor stroke,15,17,26,27 others recruited IS patients regardless of stroke severities or stroke severity was not specified. Onset-to-treatment intervals were ≤1 day in 4 trials,11,17,22,28 ≤2 days in 2 trials,25,28 and ≤3 days in the other trials. For those trials that had a recruitment window extending beyond three days after the index event, we only used data from those patients recruited and randomized within the 3-day time window.10,11,14,24,26

The following antiplatelet medications were assessed in the trials: aspirin + clopidogrel versus aspirin (5 trials with 5901 patients);11,14,15,17,27, asprin + clopidogrel versus clopidogrel (1 trial with 491 patients);16 aspirin + dipyridamole versus aspirin (5 trials with 964 patients);23–26 aspirin + dipyridamole versus dipyridamole (2 trials with 220 patients);22,24 aspirin + dipyridamole versus clopidogrel (1 trial with 1360 patients);22 and cilostazol + aspirin versus aspirin (1 trial with 76 patients).20 The European Stroke Prevention Study 2 (ESPS 2) investigated the combination of aspirin and dipyridamole against aspirin alone and dipyridamole alone, and the other studies each investigated one antiplatelet in the monotherapy group. No studies involving prasugrel, ticlopidine, or triflusal were identified. Follow-up durations were 7 days in 2 trials,14,15 3 months in 4 trials,10,17,27,28 6 months in 2 trials,25,29 ≥18 months in 5 trials,10,11,22,24,26 and unknown in 1 trial.

Synthesis of Results
For analyses of efficacy and safety outcomes, no evidence existed for between-study or between-subgroup heterogeneities by the Cochrane Q statistic and the I² statistic. No significant publication bias was identified by visual inspection of asymmetry of the funnel plots.

Twelve studies had data regarding the efficacy outcome of stroke recurrence. In these 12 studies with different follow-up durations, dual antiplatelet therapy reduced risk of stroke recurrence by ≈30% in patients with acute IS or TIA, as compared with monotherapy (RR, 0.69; 95% CI, 0.60–0.80; P<0.001; Figure 1). The overall effect (RR, 0.69) was consistent with the overall estimate from all trials before CHANCE (RR, 0.66), but the 95% CI became narrower with the addition of CHANCE (0.60–0.80 versus 0.48–0.91; Figure 2).

Eight studies had data regarding the composite outcome of stroke, TIA, ACS, and all death. Among these 8 studies, dual antiplatelet therapy significantly reduced risk of the composite efficacy outcome by ≈30% in patients with IS or TIA randomized within 3 days of ictus, when compared with monotherapy (RR, 0.71; 95% CI, 0.63–0.81; P<0.001; Figure 3). The results were consistent between CHANCE and all other trials; as with the outcome of stroke recurrence, the 95% CI of the overall effect for the composite efficacy outcome became much narrower after adding data from CHANCE (Figure 4).

Ten studies had data regarding the safety outcome of major bleeding, which were analyzed in the current meta-analysis for this outcome. It occurred in ≈0.5% and 0.4% of patients in the dual and monotherapy groups, respectively, when all trial data...
were combined. As compared with mono antiplatelet therapy, dual therapy for acute IS or TIA patients was not associated with a significant increase in the risk of major bleeding (RR, 1.35; 95% CI, 0.70–2.59; P = 0.37; Figures 5 and 6).

Sensitivity analyses restricted to the 7 double-blind trials10–12,14–17,24,27 showed similar results for each outcome (Table 2) when compared with the full analyses.

In the subgroup of the 5 RCTs comparing clopidogrel plus aspirin versus aspirin alone, 4 trials14–15,17,27 had dual therapy of ≤3 months (7 days to 3 months), whereas the other 11 had a median treatment duration of 28 months for dual therapy (Table 1). Except for CHANCE, in which trial clopidogrel was used alone after 21 days of clopidogrel plus aspirin in the dual therapy group, all the other 4 RCTs11,14,15,27 had clopidogrel plus aspirin in the dual therapy group throughout the entire treatment duration. When compared with aspirin alone, the combination of clopidogrel and aspirin was associated with a significant reduction in stroke recurrence (RR, 0.70; 95% CI, 0.59–0.82; P < 0.001; Figure 1) as well as the composite of vascular events and all death (RR, 0.71; 95% CI, 0.62–0.82; P < 0.001; Figure 3), and there was no significant increase in major bleeding (RR, 1.24; 95% CI, 0.51–3.00; P = 0.63; Figure 5). The other combinations of dual antiplatelets analyzed did not significantly reduce risks of stroke recurrence or the composite efficacy outcome, as compared with monotherapies (Figures 1 and 3), though...

**Table 2.** Risk Ratio for Major Complications Across Subgroups Related to Dual Antiplatelet Therapy for Patients with Acute Ischemic Stroke or Transient Ischemic Attack

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Dual therapy</th>
<th>Monotherapy</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.1.1 AC vs A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARESS 2005</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>CHANCE 2012</td>
<td>212</td>
<td>2564</td>
<td>303</td>
<td>2566</td>
</tr>
<tr>
<td>CHARISMA 2006</td>
<td>2</td>
<td>98</td>
<td>1</td>
<td>118</td>
</tr>
<tr>
<td>CLAIR 2010</td>
<td>0</td>
<td>46</td>
<td>2</td>
<td>52</td>
</tr>
<tr>
<td>FASTER (no statin) 2007</td>
<td>5</td>
<td>98</td>
<td>9</td>
<td>95</td>
</tr>
<tr>
<td>FASTER (statin) 2007</td>
<td>100</td>
<td>12</td>
<td>99</td>
<td>3.3%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2937</td>
<td>2964</td>
<td>84.4%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>228</td>
<td>328</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 5 (P = 0.66); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.39 (P = 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.1.2 AC vs C
MATCH 2004
10 256 11 235 3.1% 0.83 [0.36, 1.93] |
Subtotal (95% CI) 256 235 3.1% 0.83 [0.36, 1.93] |
Total events 10 11 |
Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.67)

1.1.3 AD vs A
EARLY 2009
16 283 26 260 6.1% 0.57 [0.31, 1.03] |
ESPRIT 2006
1 43 1 52 0.3% 1.21 [0.08, 18.77] |
ESPS2 1996 (AD vs A)
2 32 4 78 0.8% 1.22 [0.23, 6.33] |
Subtotal (95% CI) 358 390 7.2% 0.64 [0.37, 1.10] |
Total events 19 31 |
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 2 (P = 0.62); I² = 0% |
Test for overall effect: Z = 1.61 (P = 0.11)

1.1.4 AD vs D
ESPS2 1996 (AD vs D)
2 32 4 79 0.8% 1.29 [0.24, 6.41] |
Mattias Guli 1987
0 69 0 40 |
Subtotal (95% CI) 101 119 8.3% 1.23 [0.24, 6.41] |
Total events 2 4 |
Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)

1.1.5 AD vs C
PROFESS acute 2009
11 672 20 688 4.1% 0.56 [0.27, 1.17] |
Subtotal (95% CI) 672 688 4.1% 0.56 [0.27, 1.17] |
Total events 11 20 |
Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)

1.1.6 Clopidogrel vs A
Nakamura 2012
1 38 3 38 0.4% 0.33 [0.04, 3.06] |
Subtotal (95% CI) 38 38 0.4% 0.33 [0.04, 3.06] |
Total events 1 3 |
Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

Total (95% CI) 4362 4434 100.0% 0.69 [0.60, 0.80] |
Total events 271 397 |
Heterogeneity: Tau² = 0.00; Chi² = 4.36, df = 12 (P = 0.98); I² = 0% |
Test for overall effect: Z = 4.88 (P < 0.00001)

**Figure 1.** Risk of stroke recurrence in dual vs mono antiplatelet therapy for patients with acute ischemic stroke or transient ischemic attack, across primary studies included in the present meta-analysis, including CHANCE. A indicates aspirin; AC, aspirin plus clopidogrel; AD, aspirin plus dipyridamole; C, clopidogrel; CI, confidence interval; D, dipyridamole; and M-H, Mantel-Haenszel method.
there were no significant between-subgroup heterogenei-

ties throughout the analyses. For trials comparing aspirin
plus dipyridamole versus aspirin alone, there were no sig-
nificant differences between dual antiplatelet therapy and

monotherapy in the efficacy outcome of stroke recurrence
(RR, 0.64; 95% CI, 0.37–1.10; P=0.11; Figure 1) and in the
safety outcome of major bleeding (RR, 0.92; 95% CI, 0.06–
14.61; P=0.95; Figure 5).

Figure 3. Risk of the composite outcome of stroke, transient ischemic attack, acute coronary syndrome, and all death, in dual vs mono antiplatelet therapy for patients with acute ischemic stroke or transient ischemic attack, across primary studies included in the present meta-analysis, including CHANCE. A indicates aspirin; AD, aspirin plus dipyridamole; AC, aspirin plus clopidogrel; CI, confidence interval; D, dipyridamole; and M-H, Mantel-Haenszel method.

Figure 2. Comparison of the separate CHANCE results and the overall estimates of dual vs mono antiplatelet therapy from all other trials included in the present meta-analysis, for the outcome of stroke recurrence. A indicates aspirin; AD, aspirin plus dipyridamole; AC, aspirin plus clopidogrel; CI, confidence interval; D, dipyridamole; and M-H, Mantel-Haenszel method.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Dual therapy</th>
<th>Monotherapy</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random. 95% CI</td>
</tr>
<tr>
<td>1.2.1 All trials before CHANCE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARESS 2005</td>
<td>0</td>
<td>11</td>
<td>14</td>
<td>0.2%</td>
</tr>
<tr>
<td>CHARISMA 2006</td>
<td>2</td>
<td>98</td>
<td>118</td>
<td>0.4%</td>
</tr>
<tr>
<td>CLAIR 2010</td>
<td>0</td>
<td>46</td>
<td>52</td>
<td>0.2%</td>
</tr>
<tr>
<td>EARLY 2009</td>
<td>16</td>
<td>283</td>
<td>260</td>
<td>6.1%</td>
</tr>
<tr>
<td>ESPRIT 2006</td>
<td>1</td>
<td>43</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>ESPS2 1999 (AD vs A)</td>
<td>2</td>
<td>32</td>
<td>4</td>
<td>78</td>
</tr>
<tr>
<td>ESPS2 1996 (AD vs D)</td>
<td>2</td>
<td>32</td>
<td>4</td>
<td>79</td>
</tr>
<tr>
<td>FASTER (no statin) 2007</td>
<td>5</td>
<td>98</td>
<td>9</td>
<td>95</td>
</tr>
<tr>
<td>FASTER (statin) 2007</td>
<td>9</td>
<td>100</td>
<td>12</td>
<td>99</td>
</tr>
<tr>
<td>MATCH 2004</td>
<td>10</td>
<td>256</td>
<td>11</td>
<td>235</td>
</tr>
<tr>
<td>Matias-Guiu 1987</td>
<td>0</td>
<td>69</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Nakamura 2012</td>
<td>1</td>
<td>38</td>
<td>3</td>
<td>38</td>
</tr>
<tr>
<td>PRoFESS acute 2009</td>
<td>11</td>
<td>572</td>
<td>20</td>
<td>668</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1778</td>
<td>1648</td>
<td>21.7%</td>
<td>0.66 [0.48, 0.91]</td>
</tr>
</tbody>
</table>

Total events: 59

Heterogeneity: Tau² = 0.00; CHI² = 4.31, df = 11 (P = 0.96); I² = 0%

Test for overall effect: Z = 2.53 (P = 0.01)

1.2.2 CHANCE

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Dual therapy</th>
<th>Monotherapy</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random. 95% CI</td>
</tr>
<tr>
<td>CHANCE 2012</td>
<td>212</td>
<td>2584</td>
<td>303</td>
<td>2586</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2584</td>
<td>2586</td>
<td>78.3%</td>
<td>0.70 [0.59, 0.83]</td>
</tr>
</tbody>
</table>

Total events: 212

Heterogeneity: Not applicable

Test for overall effect: Z = 4.19 (P < 0.0001)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Dual therapy</th>
<th>Monotherapy</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random. 95% CI</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>4362</td>
<td>4434</td>
<td>100.0%</td>
<td>0.69 [0.60, 0.80]</td>
</tr>
</tbody>
</table>

Total events: 271

Heterogeneity: Tau² = 0.00; CHI² = 4.30, df = 12 (P = 0.98); I² = 0%

Test for overall effect: Z = 4.68 (P < 0.00001)

Test for subgroups differences: CHI² = 0.06, df = 1 (P = 0.77), I² = 0%

Figure 3. Risk of the composite outcome of stroke, transient ischemic attack, acute coronary syndrome, and all death, in dual vs mono antiplatelet therapy for patients with acute ischemic stroke or transient ischemic attack, across primary studies included in the present meta-analysis, including CHANCE. A indicates aspirin; AD, aspirin plus dipyridamole; AC, aspirin plus clopidogrel; CI, confidence interval; D, dipyridamole; and M-H, Mantel-Haenszel method.
Discussion

In this systematic review and meta-analysis, we included 14 RCTs (9012 patients) comparing dual versus mono antiplatelet therapy for acute noncardioembolic IS or TIA within 3 days of ictus. We found that when compared with mono antiplatelet therapy, dual therapy was associated with a reduction in stroke recurrence, and composite vascular events, but without a significant increase in the risk of major bleeding. A sensitivity analysis restricted to the 7 double-blind RCTs showed similar results, which indicated that results of the present meta-analysis were generalizable. For each outcome, no significant between-study or between-subgroup heterogeneity in treatment effects of dual versus mono antiplatelet therapies was found. The overall results of the updated meta-analysis were consistent with the overall estimate of all previous trials before CHANCE, which further suggest the efficacy and safety of administering dual antiplatelet therapy in the acute phase of IS or TIA.

In subgroup analyses of clopidogrel plus aspirin versus aspirin alone in the current meta-analysis, significant reductions were found in risks of stroke recurrence and the composite of vascular events and all death (Figures 1 and 3). This was different from results of the previous meta-analysis, in which the effects of clopidogrel plus aspirin versus aspirin alone on both of the two efficacy outcomes were not statistically significant. But results on the safety outcome of major bleeding in this subgroup were similar between the current review and the previous one, both of which indicated a nonsignificant increase in major bleeding with dual versus monotherapy. Therefore, the CHANCE study added evidence for the superiority of clopidogrel plus aspirin over aspirin alone for the prevention of stroke recurrence and other vascular events in acute IS or TIA patients, but meanwhile did not alter the nonsignificant increase of major bleeding in patients treated with the dual therapy. Other subgroup analyses showed no significant reduction in stroke recurrence and the composite efficacy outcome in patients treated with dual therapy, which were consistent with the previous meta-analysis. Specifically, aspirin plus dipyridamole was found to be not significantly different from aspirin alone on the efficacy and safety outcomes in the present meta-analysis. However, this did not challenge recommendations of aspirin plus dipyridamole for management of IS and TIA in current guidelines, because only patients recruited and randomized within 3 days of ictus, which was a small portion of subjects recruited in the RCTs assessing treatment effects of aspirin plus dipyridamole versus aspirin alone in IS or TIA patients, were analyzed in the present meta-analysis. Future large RCTs may verify the efficacy and safety of dual antiplatelet therapies other than clopidogrel plus aspirin versus monotherapy for treatment of acute IS and TIA.

The recently published Secondary Prevention of Small Subcortical Strokes (SPS3) trial, a large trial involving 3020 patients (mean age 63 years, 63% males) with symptomatic lacunar stroke within the preceding 180 days, was not included in the present systematic review, because SPS3 excluded patients within 2 weeks of ictus. In SPS3, long-term dual antiplatelet therapy with combined clopidogrel plus aspirin did not significantly reduce the risk of recurrent stroke (HR, 0.92; 95% CI, 0.72–1.16; \( P = 0.48 \)) but did significantly increase major bleeding (HR, 1.97; 95% CI, 1.41–2.71; \( P = 0.001 \)), as compared with aspirin alone. Differences between results from the current meta-analysis and the SPS3 study might be partly explained by different onset-to-treatment intervals, which were within 3 days for this meta-analysis and between 14 to 180 days in SPS3. The benefits of dual antiplatelet therapy probably overweigh harms if started early, because risk of stroke recurrence could be high during...
the first a few hours or days after an IS or TIA. In addition, SPS3 was exclusively in patients with lacunar stroke, and this group may have a higher bleeding risk especially if there is associated leukoaraiosis.

Two other relevant multicenter RCTs are ongoing. The double-blind POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke, ClinicalTrials.gov Identifier: NCT00991029) trial is assessing the safety and efficacy of clopidogrel (75 mg od after a loading dose of 600 mg) plus aspirin (50–325 mg od) versus aspirin alone (50–325 mg od) for reducing risk of major ischemic vascular events at 90 days, in TIA or minor stroke patients within 12 hours of symptom onset. It was initiated in May 2010 and aims to enroll 4150 patients over a 5-year period. Meanwhile, the open-label, blinded-end point TARDIS (Triple Antiplatelet for Reducing Dependency after Ischemic Stroke, ISRCTN47823388) trial is comparing the safety of triple antiplatelet therapy (combined aspirin, clopidogrel and dipyridamole) versus guideline therapy (aspirin and dipyridamole, or clopidogrel alone) in 4100 patients with acute stroke/TIA. Both may shed new light on the treatment of acute ischemic stroke and TIA. The study design of the POINT study is very similar to the CHANCE study and will be included in an updated meta-analysis when finished.

In contrast, the TARDIS study compares triple antiplatelet agents with current guideline-based therapy, which may include dual antiplatelet agents and thus will not be covered in an updated meta-analysis like this one.

There are several limitations of the present systematic review and meta-analysis. First, included studies varied in relation to the study population, stroke severity, antiplatelet medications, onset-to-treatment interval, treatment and...
follow-up durations, and other aspects. All of these factors could be potential confounders. Secondly, for some of the studies included, IS or TIA patients within 3 days of symptom onset were not the primary target population and were usually a small portion of the primary study populations. Confounders might not be well balanced between dual and monotherapy groups for such patients. Thirdly, CHANCE, as a large trial, accounted for ≈50% of participants in the meta-analysis, and therefore its results drove much of the findings. Beside, CHANCE investigated dual versus monotherapy and then different monotherapies in acute IS and TIA, the study design of which was different in this point as compared with most of other RCTs included in the present meta-analysis. We cannot determine the extent to which clopidogrel alone from day 21 to the end of the 3rd month post ictus (after 21 days of dual clopidogrel and aspirin therapy) in the CHANCE Trial drove the difference in recurrent event rates compared to 3 months of aspirin monotherapy.

Conclusions

Early use of dual antiplatelet therapy was effective in reducing the risk of early stroke recurrence and other vascular events, when compared with mono antiplatelet therapy in patients with acute noncardioembolic ischemic stroke or TIA. No significant excess in major bleeding was observed. Results of ongoing large trials will provide more evidence to assist health care providers in the selection between dual and mono antiplatelet therapies for acute IS or TIA. Based on the current data, early use of dual antiplatelet therapy after acute noncardioembolic IS or TIA for a limited time period appears to be efficacious and safe.

Sources of Funding

This research was supported by the Ministry of Science and Technology of the People’s Republic of China (grant Nos. 2008ZX09312-008, 2011BAI08B02, 2012ZX09303, and 200902004), and the S. H. Ho Cardiovascular Disease and Stroke Center, Institute of Vascular Medicine, the Chinese University of Hong Kong.

Disclosures

Dr Wong is the principal investigator (PI) of the CLAIR study and received honorarium from Bayer, Boehringer Ingelheim, Otsuka and Sanofi. Dr Wang (Yongjun) is the PI of the CHANCE study. Drs Wang (Yilong), Liu and Wang (Yongjun) are members of the steering committee for CHANCE. Dr Bath was a member of PROFESS trial steering committee and chief investigator of the ongoing TARDIS trial; he is a Stroke Association Professor of Stroke Medicine. Dr Markus was co-PI for the CARESS study and received a consultancy fee from Sanofi for this work; he has received honorarium and consultancy fees for advisory board work and talks for Sanofi and Boehringer Ingelheim. Dr Gorelick

Table 2. Sensitivity Analyses for Efficacy and Safety Outcomes (Dual Versus Mono Antiplatelet Therapy)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies, n</th>
<th>Patients, n</th>
<th>Risk ratio (95% CI)</th>
<th>P Value</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke recurrence</td>
<td>7</td>
<td>7875</td>
<td>0.70 (0.60–0.82)</td>
<td>&lt;0.001</td>
<td>0</td>
</tr>
<tr>
<td>Stroke, TIA, ACS, all death</td>
<td>5</td>
<td>7438</td>
<td>0.72 (0.63–0.82)</td>
<td>&lt;0.001</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>6</td>
<td>7654</td>
<td>1.47 (0.74–2.93)</td>
<td>0.27</td>
<td>0</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CI, confidence interval; and TIA, transient ischemic attack.
serves on a steering committee for the ARRIVE trial sponsored by Bayer, as a speaker’s bureau member for dabigatran sponsored by Boehringer Ingelheim, and as Co-Director of the US DIAS 4 Coordinating Center sponsored by H. Lundbeck. The other authors report no conflicts.

References
Ischemic stroke and transient ischemic attack are common problems in clinical practice and, typically, treated with aspirin. However, the results of the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) study (5170 patients, comparison of aspirin/clopidogrel versus aspirin alone) showed that the combination of antiplatelet therapies is superior for stroke prevention without a significant increase in bleeding. Building on these single-country findings, this updated systematic review and meta-analysis suggests that the results of the CHANCE study are consistent with previous studies done in other parts of the world. These findings, although suggestive of dual antiplatelet treatment for ischemic stroke and transient ischemic attack, need to be repeated in prospective/randomized trials to confirm their utility in a broader population.
Early Dual Versus Mono Antiplatelet Therapy for Acute Non-Cardioembolic Ischemic Stroke or Transient Ischemic Attack: An Updated Systematic Review and Meta-Analysis

Ka Sing Lawrence Wong, Yilong Wang, Xinyi Leng, Chen Mao, Jinling Tang, Philip M.W. Bath, Hugh S. Markus, Philip B. Gorelick, Liping Liu, Wenhua Lin and Yongjun Wang

_Circulation_. 2013;128:1656-1666; originally published online September 12, 2013;
doi: 10.1161/CIRCULATIONAHA.113.003187
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/128/15/1656

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2013/09/11/CIRCULATIONAHA.113.003187.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/
SUPPLEMENTAL MATERIAL

Legend

Supplemental Figure 1. Flow chart for selection of published eligible studies from January 2011 to November 2012.
Supplemental Figure 1.

219 records identified through database searching

2 additional records identified through other sources

219 records after duplicates removed

209 records excluded by title and abstract

7 full-text articles excluded
Not RCT: 2;
No acute data: 1;
Duplication: 2;
Others: 4.

10 full-text articles assessed for eligibility

1 updated study (from Jan 2011 to Nov 2012) included in qualitative synthesis

1 updated study (from Jan 2011 to Nov 2012) included in quantitative synthesis (meta-analysis)