Effect of clopidogrel plus ASA vs. ASA early after TIA and ischaemic stroke: a substudy of the CHARISMA trial

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Background The Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance (CHARISMA) trial reported no statistically significant benefit of adding clopidogrel to acetylsalicylic acid in the long-term management of a broad population of patients with stable vascular disease. However, a subanalysis raised the hypothesis that dual antiplatelet therapy with clopidogrel plus acetylsalicylic acid may be more effective than aspirin in patients with prior ischaemic stroke, myocardial infarction of symptomatic peripheral arterial disease. We aimed to determine whether the possible benefits of clopidogrel plus acetylsalicylic acid in patients with transient ischaemic attack and ischaemic stroke may be ‘front-loaded’, and maximal within the first 30-days of randomisation, without being unduly hazardous.

Methods This was a subanalysis of a randomised, double-blind, placebo-controlled trial of clopidogrel vs. placebo, in addition to background therapy with low-dose acetylsalicylic acid (CHARISMA trial), restricted to all patients with transient ischaemic attack or ischaemic stroke. The primary efficacy outcome was stroke, and safety outcome severe bleeding, during the follow-up period.

Results Among all transient ischaemic attack and ischaemic stroke patients randomised to placebo (n = 2163), 131 (6.1%) experienced a stroke during follow-up compared with 105 (4.9%) of 2157 patients assigned clopidogrel (hazard ratio: 0.80, 95% confidence intervals: 0.62–1.03). There was no significant difference in severe bleeding (1.7% placebo vs. 1.9% clopidogrel, hazard ratio: 1.11, 95% confidence intervals: 0.71–1.73). Among all patients randomised within 30-days of their qualifying transient ischaemic attack or ischaemic stroke to placebo (n = 667), 46 (6.9%) experienced a stroke compared with 34 (5.1%) of 664 patients assigned clopidogrel (hazard ratio: 0.74, 0.46–1.16). There was no significant difference in severe bleeding (1.6% placebo vs. 1.4% clopidogrel, hazard ratio: 0.83, 95% confidence intervals: 0.34–2.01).

Conclusion The data are consistent with, but do not prove the hypothesis that early addition of clopidogrel to acetylsalicylic acid in patients with transient ischaemic attack and ischaemic stroke of arterial origin may be more effective and acceptably safe compared with acetylsalicylic acid alone. Adequately powered clinical trials that are dedicated to exploring this hypothesis are needed.

Key words: antiplatelet therapy, aspirin, atherothrombotic, CHARISMA, clinical trial, clopidogrel, ischaemic stroke

Conflicts of interest:
Graeme J. Hankey: I declare that I participated in the design and execution of the study, analysis of the data and reviewing of the manuscript. I have seen and approved the final version. I have the following conflicts of interest: consulting fees from Sanofi-Aventis; Bristol-Myers Squibb, Bayer and Boehringer Ingelheim; and the following:(S. Claiborne Johnston): I declare that I participated in the design and execution of the study, analysis of the data and reviewing of the manuscript. I have seen and approved the final version. I have the following conflicts of interest: None; J. Donald Easton: I declare that I participated in the design and execution of the study, analysis of the data and reviewing of the manuscript. I have seen and approved the final version. I have the following conflicts of interest: consulting fees from Sanofi-Aventis, Bristol-Myers Squibb; Werner Hacke: I declare that I participated in the design and execution of the study, analysis of the data and reviewing of the manuscript. I have seen and approved the final version. I have the following conflicts of interest: consulting fees from Sanofi-Aventis and Bristol-Myers Squibb; Jean-Louis Mas: I declare that I participated in the design and execution of the study, analysis of the data.

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Patients with transient ischaemic attack (TIA) and ischaemic stroke of presumed arterial origin are at higher risk of a recurrent stroke within the first 30-days (about 15%) than in the longer term (about 3–5% per annum) (1–3). This may reflect temporary instability of the symptomatic arterial lesion, predisposing it to cause further thromboembolism to the brain. Recurrent stroke risk can be reduced by approximately 13% [95% confidence interval (CI): 6–19%], compared with control, by means of early (and sustained) administration of acetylsalicylic acid (ASA), beginning within 48 h of onset (4, 5). However, the effectiveness and safety of other antiplatelet regimens in acute TIA or ischaemic stroke are unknown because they have not been evaluated in large randomised controlled trials (RCTs); a recent small trial comparing the combination of aspirin plus extended-release dipyridamole with aspirin within 24 h of ischaemic stroke or TIA was inconclusive (6). The combination of ASA and clopidogrel has been shown to be significantly more effective than ASA alone in large RCTs involving patients with acute coronary syndromes, reducing the risk of recurrent vascular events by about one-fifth (7, 8). There is indirect, hypothesis-generating evidence from three RCTs supporting the efficacy and safety of the combination of ASA and clopidogrel, compared with ASA in patients with acute TIA or ischaemic stroke (9–11).

The results of these three RCTs can be summarised briefly as follows:

- the Clopidogrel and ASA for Reduction of Emboli in Symptomatic carotid Stenosis trial showed that in patients with recently symptomatic ≥50% carotid stenosis, combination treatment with ASA and clopidogrel was more effective than ASA alone in reducing asymptomatic embolisation to the brain, as detected by transcranial Doppler ultrasound (9)
- a post hoc, hypothesis-generating, subgroup analysis of the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke trial showed a nonsignificant trend towards greater effectiveness of the combination of clopidogrel plus ASA, compared with clopidogrel alone, among the subgroup of patients with TIA and ischaemic stroke who were randomised within the first week of the qualifying neurovascular event (10), and
- the Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence (FASTER) pilot trial showed that of 392 patients with TIA or nondisabling ischaemic stroke who were treated with ASA and randomised within 24 h of symptom onset to placebo (n = 194) or clopidogrel (n = 198), the primary outcome event of stroke was 10.8% among patients assigned placebo and 7.1% among patients assigned clopidogrel (RR 0.7, 95% CI: 0.3–1.2) at 90-days (11).

The Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance (CHARISMA) trial was designed to explore the hypothesis that long-term treatment with a combination of ASA and clopidogrel may be more effective than ASA alone in preventing the composite outcome of stroke, myocardial infarction (MI), or death due to vascular causes among a broad population of patients with multiple cardiovascular risk factors or with established atherothrombotic disease (12). The primary result of CHARISMA indicated that clopidogrel plus ASA was not significantly more effective than ASA alone in the long-term (RRR: 7%, hazard ratio (HR) 0.98, 95% CI: 0.94–1.03) (13). Any benefits in reducing ischaemic events were offset by haemorrhagic complications, but this adverse effect was maximal in patients who had no prior history of an ischaemic event (13). Among the subgroup of 3245 patients enrolled in the CHARISMA trial with prior ischaemic stroke, the rate of stroke, MI, or cardiovascular death was significantly lower among patients assigned clopidogrel (plus aspirin) compared with placebo (plus aspirin): 8.4% vs. 10.7%, hazard ratio (HR) 0.78, 95% CI: 0.62–0.98 (14).

We aimed to determine whether the benefits of adding clopidogrel to ASA in preventing major vascular events among...
patients with ischaemic stroke in the CHARISMA trial may have been ‘front-loaded’ and maximal among patients randomised within 30-days of an acute ischaemic event of the brain, and maximal in preventing recurrent stroke.

Methods

Design

The methods of the CHARISMA trial have been described in detail elsewhere (11, 12). CHARISMA was a multicentre, multinational, randomised, parallel group, double-blind trial of clopidogrel vs. placebo in a mix of high-risk patients at risk of atherothrombotic events, and who were receiving low-dose ASA at the time of randomisation. A total of 15 603 patients with either clinically established atherothrombotic disease or multiple cardiovascular risk factors were randomly assigned to receive clopidogrel (75 mg/day) plus low-dose ASA (75–162 mg/day) or placebo plus low-dose ASA. The primary efficacy endpoint for the CHARISMA trial was a composite of stroke, MI, or death from cardiovascular causes.

Subjects

The CHARISMA trial enrolled 4320 patients with previous symptomatic cerebrovascular disease within the previous five-years (2163 assigned ASA + placebo, 2157 assigned ASA + clopidogrel). The qualifying diagnosis was a previous TIA in 1233 patients and a previous ischaemic stroke in 3245 patients; 158 patients had a previous TIA and ischaemic stroke.

Outcome evaluation

The primary outcome measure of efficacy for this substudy was any stroke during follow-up. Secondary outcome measures of efficacy were any MI, vascular death, or the composite of stroke, MI, or vascular death during follow-up.

The primary outcome measure of safety for this substudy was severe bleeding as defined by bleeding that was fatal, intracranial, or causing haemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention. Secondary outcome measures of safety were any bleeding, moderate bleeding (bleeding that led to transfusion but did not meet the criteria for severe bleeding) and primary intracranial haemorrhage.

Follow-up

Patients were followed up at one-, three-, and six-months after randomisation, and every six-months thereafter, until the trial ended.

The median follow-up period was 25-months for patients with confirmed cerebrovascular disease.

Statistical methods

Data were analysed on an intention-to-treat basis. A patient was considered randomised as soon as a treatment number was assigned by the Interactive Voice Response System.

Only observed values were used in the analysis and presentations, i.e. no attempt was made to impute missing values.

The effect of clopidogrel (on a background of ASA) vs. placebo (on a background of ASA) on the primary outcome of stroke was assessed using a two-sided log-rank test. Treatment effect and safety event rates as measured by the HR (relative risk) and their associated 95% CI were estimated using Cox’s proportional hazards model. Cumulative Kaplan–Meier estimates of the event rates were also calculated. No adjustments for multiple comparisons were made. All analyses were performed using SAS version 8.0 (SAS Institute Inc., Cary, NC, USA).

Results

Subjects

Among the 4320 patients with a history of TIA or ischaemic stroke within the previous five-years, 1331 patients (30.8%) were randomised within 30-days after the qualifying TIA or ischaemic stroke (664 were assigned to clopidogrel and 667 assigned to placebo) and 2989 (69.2%) were randomised more than 30-days after the qualifying TIA or ischaemic stroke (1493 were assigned to clopidogrel and 1496 assigned to placebo).

Baseline demographic and prognostic data

Table 1 shows the baseline demographic and prognostic data of all 4320 patients who were enrolled into CHARISMA with a qualifying TIA or ischaemic stroke in the previous five-years, and the subset of 1331 patients enrolled within 30-days of their qualifying TIA or ischaemic stroke.

There were no significant differences in the prevalence and level of baseline demographic and prognostic data among patients assigned placebo plus ASA and clopidogrel plus ASA.

Outcomes during long-term follow-up of all patients randomised after a qualifying TIA or ischaemic stroke

Efficacy

Table 2 shows that 236 of the 4320 (5.5%, 95% CI: 4.8–6.1%) patients with TIA or ischaemic stroke experienced a stroke outcome event during the 25-month follow-up period.

Among patients randomised to placebo on a background of ASA, 131 (6.1%) experienced a stroke compared with 105 (4.9%) patients randomised to clopidogrel on a background of ASA (HR: 0.80, 95% CI: 0.62–1.03). Haemorrhagic stroke was
Table 1 Baseline demographic and prognostic data for all patients randomised with the qualifying condition of TIA or ischaemic stroke, and all patients randomised within 30-days of TIA or ischaemic stroke in the CHARISMA trial

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Placebo (+ ASA) all TIA/stroke patients (n = 2163)</th>
<th>Clopidogrel (+ ASA) all TIA/stroke patients (n = 2157)</th>
<th>Placebo (+ ASA) TIA/stroke &lt;30-days (n = 667)</th>
<th>Clopidogrel (+ ASA) TIA/stroke &lt;30-days (n = 664)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean (SD)</td>
<td>64.9 (9.8)</td>
<td>64.8 (9.8)</td>
<td>66.3 (9.8)</td>
<td>66.1 (10.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>Age ≥60-years (%)</td>
<td>67.4</td>
<td>68.1</td>
<td>72.0</td>
<td>71.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>36.2</td>
<td>37.4</td>
<td>37.9</td>
<td>40.8</td>
<td>0.28</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>88.5</td>
<td>87.8</td>
<td>92.2</td>
<td>89.9</td>
<td>0.42</td>
</tr>
<tr>
<td>Black (%)</td>
<td>3.2</td>
<td>3.2</td>
<td>1.6</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Asian/Oriental (%)</td>
<td>7.3</td>
<td>7.7</td>
<td>5.5</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>1.0</td>
<td>1.3</td>
<td>0.6</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Systolic BP: mean (SD)</td>
<td>140.2 (19-2)</td>
<td>140.3 (19-1)</td>
<td>141.0 (19-6)</td>
<td>140.9 (19-0)</td>
<td>0.016</td>
</tr>
<tr>
<td>Systolic BP &gt;140 mmHg</td>
<td>54.1</td>
<td>54.1</td>
<td>56.5</td>
<td>55.3</td>
<td>0.65</td>
</tr>
<tr>
<td>Diastolic BP: mean (SD)</td>
<td>80.1 (10-9)</td>
<td>80.3 (10-6)</td>
<td>79.9 (10-6)</td>
<td>79.7 (10-5)</td>
<td>0.81</td>
</tr>
<tr>
<td>Diastolic BP &gt;90 mmHg</td>
<td>23.0</td>
<td>23.0</td>
<td>23.4</td>
<td>21.5</td>
<td>0.41</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>29.7</td>
<td>28.3</td>
<td>26.1</td>
<td>28.8</td>
<td>0.27</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>20.1</td>
<td>18.6</td>
<td>21.4</td>
<td>19.8</td>
<td>0.45</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>76.4</td>
<td>76.2</td>
<td>73.3</td>
<td>71.8</td>
<td>0.55</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>76.9</td>
<td>77.4</td>
<td>79.0</td>
<td>77.7</td>
<td>0.56</td>
</tr>
<tr>
<td>TIA (%)</td>
<td>32.8</td>
<td>32.5</td>
<td>30.6</td>
<td>31.6</td>
<td>0.68</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2.3</td>
<td>2.2</td>
<td>1.9</td>
<td>1.7</td>
<td>0.69</td>
</tr>
<tr>
<td>PAD (%)</td>
<td>6.2</td>
<td>5.8</td>
<td>3.7</td>
<td>3.8</td>
<td>0.99</td>
</tr>
<tr>
<td>PCI (%)</td>
<td>3.8</td>
<td>3.7</td>
<td>2.1</td>
<td>2.6</td>
<td>0.58</td>
</tr>
<tr>
<td>CABG surgery (%)</td>
<td>5.7</td>
<td>4.3</td>
<td>2.5</td>
<td>2.7</td>
<td>0.85</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>7.3</td>
<td>6.7</td>
<td>2.5</td>
<td>2.4</td>
<td>0.87</td>
</tr>
</tbody>
</table>

ASA, acetylsalicylic acid; BP, blood pressure; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance; TIA, transient ischaemic attack.

Outcomes during long-term follow-up of patients randomised within 30-days of qualifying TIA and ischaemic stroke

Efficacy

Table 2 shows that 80 of the 1331 patients (6.0%) with a recent (<30-days) TIA or ischaemic stroke experienced a recurrent stroke outcome during the 25-month follow-up period.

Among patients assigned to placebo plus ASA, 46 (6.9%) experienced a stroke compared with 34 (5.1%) patients assigned clopidogrel plus ASA (HR: 0.74, 0.48–1.16). The actuarial rate of survival free of stroke among patients with a qualifying TIA or ischaemic stroke within 30-days of randomisation into CHARISMA is shown in Fig. 1. Haemorrhagic stroke was uncommon in both treatment groups (HR: 0.67, 0.11–4.02). The composite outcome of stroke, MI, or vascular death occurred in 74 (11.1%) patients assigned placebo and 56 (8.4%) patients assigned clopidogrel (HR: 0.76, 0.54–1.07) (Table 2).

Safety

Table 2 shows that severe bleeding occurred during the 25-month follow-up period in 20 of the 1331 (1.5%, 95% CI: 0.9–2.3%) patients with TIA or ischaemic stroke who were...
randomised within 30-days of onset of focal neurovascular symptoms. Among patients randomised to placebo plus ASA, 11 (1.6%) experienced a severe bleed compared with nine (1.4%) patients randomised to clopidogrel plus ASA (HR: 0.83, 95% CI: 0.34–2.01). Intracerebral haemorrhage was equally uncommon in both treatment groups [0.4% (placebo plus ASA) vs. 0.5% (clopidogrel plus ASA), HR: 1.01, 0.20–5.0], and there was no significant difference in the rates of moderate bleeding (1.2% placebo plus ASA, 1.7% clopidogrel plus ASA, HR: 1.41, 95% CI: 0.57–3.50). However, there was a significant excess of any bleeding (21.7% placebo plus ASA, 34.8% clopidogrel plus ASA, HR: 1.81, 95% CI: 1.47–2.23) among patients assigned clopidogrel compared with placebo (Table 2).

Stroke outcomes during long-term follow-up of patients randomised more than 30 days after qualifying TIA and ischaemic stroke

Among the 2989 patients with a TIA or ischaemic stroke more than 30-days before enrolment in CHARISMA, 156 (5.2%, 4.4–6.2%) experienced a stroke outcome during the 25-month follow-up period.

Among patients assigned to placebo plus ASA, 85 (5.7%) experienced a stroke compared with 71 (4.8%) patients assigned to clopidogrel plus ASA (HR: 0.83, 0.60–1.14). Haemorrhagic stroke was uncommon in both treatment groups [0.4% (placebo) vs. 0.7% (clopidogrel), HR: 1.32, 0.46–3.79]. The composite outcome of stroke, MI, or vascular death occurred in 133 (8.9%) patients assigned placebo and 118 (7.9%) patients assigned clopidogrel (HR: 0.88, 0.69–1.13).

Figure 2 is a forest plot showing the HR and its 95% CI for each outcome event among the 1331 patients enrolled in the CHARISMA trial within 30-days of their qualifying TIA and ischaemic stroke, the 2989 patients enrolled in the CHARISMA trial beyond 30-days of their qualifying TIA and ischaemic stroke, and all 4320 patients enrolled with a qualifying TIA and ischaemic stroke.

Fig 1. Kaplan–Meier curve showing the actuarial rate of survival free of stroke during at least two-years follow-up among patients enrolled into the Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance trial with a qualifying transient ischaemic attack (TIA) or ischaemic stroke within the previous 30-days.

Fig 2. Forest plot showing the hazard ratio and its 95% confidence interval for each outcome event among (a) the 1331 patients enrolled in the CHARISMA trial within 30-days of their qualifying TIA and ischaemic stroke (< 30 days); (b) the 2989 patients enrolled in the CHARISMA trial beyond 30-days of their qualifying TIA and ischaemic stroke (> 30 days); (c) all 4320 patients enrolled in the CHARISMA trial with a qualifying TIA and ischaemic stroke (All TIA/Stroke). CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance; TIA, transient ischaemic attack; MI, myocardial infarction.
The principal findings of this substudy of the CHARISMA trial were that the absolute rates of stroke and the composite of stroke, MI, or vascular death were higher among patients randomised earlier (within 30-days) after their qualifying TIA or ischaemic stroke compared with patients enrolled later, and there was a nonsignificant trend towards a more favourable effect of combination clopidogrel and ASA therapy, compared with ASA alone, in the prevention of stroke and other serious vascular events among patients treated earlier (about a 25% relative risk reduction) than later (about a 15% relative risk reduction) at the expense of an excess of mild, but not severe, bleeding.

The strengths of this study are that it was a randomised double-blind, placebo-controlled trial in which a large number of patients were randomised soon after the onset of TIA and ischaemic stroke, and followed up prospectively for early recurrent stroke and other serious vascular events, which were assessed and recorded by observers who were blind to treatment allocation. The results are therefore unlikely to be affected by systematic bias in treatment allocation (the groups are comparable at baseline), performance bias (the groups were treated equally during the study apart from exposure to the study drug), attrition bias (inequality in duration and losses to follow-up between the treatment groups), or detection bias associated with awareness by outcome assessors of the study hypothesis.

However, the results of this study are prone to random error and therefore not statistically reliable because this substudy was not powered to reliably identify or exclude a statistically significant effect of clopidogrel combined with ASA among stroke patients only (11–13), let alone those enrolled early vs. late after their qualifying TIA and ischaemic stroke. Also, because randomisation was not stratified according to time since the qualifying TIA and ischaemic stroke, it is possible that there was some imbalance in the prevalence or level of unmeasured prognostic factors between the treatment groups.

The implications of these results for clinicians are that they are hypothesis generating, and not sufficiently robust to influence clinical practice guidelines.

The implications of these results for researchers are that they endorse the hypothesis of a potentially augmented favourable treatment effect of potent dual antiplatelet therapy immediately after TIA and ischaemic stroke without undue risk of severe bleeding and intracranial bleeding. These results reinforce the need for at least one large, adequately powered randomised trial comparing the effectiveness and safety of immediate clopidogrel combined with ASA, compared with ASA alone, in patients with TIA and ischaemic stroke of arterial origin who are at high risk of patients were randomised soon after the onset of TIA and ischaemic stroke of arterial origin who are at high risk of recurrent stroke and other serious vascular events, which ischaemic stroke, and followed up prospectively for early recurrent stroke and other serious vascular events, which were assessed and recorded by observers who were blind to treatment allocation. The results are therefore unlikely to be affected by systematic bias in treatment allocation (the groups are comparable at baseline), performance bias (the groups were treated equally during the study apart from exposure to the study drug), attrition bias (inequality in duration and losses to follow-up between the treatment groups), or detection bias associated with awareness by outcome assessors of the study hypothesis.

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The implications of these results for researchers are that they endorse the hypothesis of a potentially augmented favourable treatment effect of potent dual antiplatelet therapy immediately after TIA and ischaemic stroke without undue risk of severe bleeding and intracranial bleeding. These results reinforce the need for at least one large, adequately powered randomised trial comparing the effectiveness and safety of immediate clopidogrel combined with ASA, compared with ASA alone, in patients with TIA and ischaemic stroke of arterial origin who are at high risk of
Table 3  Sample size required to detect a difference in response rates between two groups, given power (1-β) = 80% and significance level (α) = 5% in a two-sided test

<table>
<thead>
<tr>
<th>Event rate in control group (%)</th>
<th>Event rate in intervention group (%)</th>
<th>Sample size required per group (n)</th>
<th>Sample size required total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-8</td>
<td>7-1</td>
<td>934</td>
<td>1868</td>
</tr>
<tr>
<td>10-0</td>
<td>7-0</td>
<td>1356</td>
<td>2712</td>
</tr>
<tr>
<td>10-0</td>
<td>7-5</td>
<td>2005</td>
<td>4010</td>
</tr>
<tr>
<td>10-0</td>
<td>8-0</td>
<td>3213</td>
<td>6426</td>
</tr>
<tr>
<td>10-0</td>
<td>8-5</td>
<td>5856</td>
<td>1172</td>
</tr>
</tbody>
</table>

In conclusion, our data support the hypothesis that early administration of the combination of ASA and clopidogrel to patients with TIA and ischaemic stroke of arterial origin may be more effective and acceptably safe compared with ASA alone. Adequately powered clinical trials that are dedicated to exploring this hypothesis are needed.

Acknowledgements

Tingfei Hu, Statistician, Cleveland Clinic, OH, USA conducted the statistical analysis.

References


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