Clopidogrel plus aspirin did not differ from aspirin alone for reducing MI, stroke, and CV death in high risk atherothrombosis

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THERAPEUTICS

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Clinical impact ratings GP/FP/Primary care ★★★★★★ IM/Ambulatory care ★★★★★★ Internal medicine ★★★★★★ Neurology ★★★★★★ Cardiology ★★★★★★

Q In patients with high risk atherothrombosis, is long term treatment with clopidogrel plus aspirin more effective than aspirin alone for reducing cardiovascular (CV) events?

METHODS

Design: randomised placebo controlled trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management, and Avoidance [CHARISMA]).

Allocation: concealed.*

Blinding: blinded (clinicians, patients, data collectors, outcome assessors, data analysts, and data safety and monitoring committee).†

Follow up period: median 28 months.

Setting: 768 sites in 32 countries.

Patients: 15 603 patients (median age 64 y, 70% men, 80% white) who had multiple atherothrombotic risk factors (type 1 or 2 diabetes, diabetic nephropathy, ankle brachial index <0.9, asymptomatic carotid stenosis >70% of luminal diameter, >1 carotid plaque, systolic blood pressure >150 mm Hg, primary hypercholesterolaemia, smoking >15 cigarettes/d, or men >65 y or women >70 y of age), coronary disease, cerebrovascular disease, or symptomatic peripheral arterial disease. Exclusion criteria were long term use of antithrombotic or non-steroidal anti-inflammatory drugs, indications for clopidogrel therapy, or revascularisation.

Intervention: clopidogrel, 75 mg/day, plus aspirin, 75–162 mg/day (n = 7802), or matching placebo plus aspirin (n = 7801).

Outcomes: composite end point of myocardial infarction (MI), stroke, or CV death; and severe bleeding. Secondary outcomes included the primary composite end point or hospital admission for unstable angina, revascularisation, or transient ischaemic attack (secondary composite end point); individual outcomes of the composite end points; all cause and CV mortality; and moderate bleeding. The study had 90% power to detect a 20% relative risk reduction in the primary composite end point.

Patient follow up: 99.5% (intention to treat analysis).

*See glossary. †Information provided by author.

MAIN RESULTS

The table shows the results. Groups did not differ for all cause mortality, CV death, or non-fatal MI.

CONCLUSION

In patients with high risk atherothrombosis, long term treatment with clopidogrel plus aspirin did not differ from aspirin alone for reducing the composite end point of myocardial infarction, stroke, and cardiovascular death.

Abstract and commentary also appear in ACP Journal Club

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Clop + Asp</th>
<th>Asp alone</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite end point</td>
<td>6.8%</td>
<td>7.3%</td>
<td>7.0% (5.0 to 17)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Secondary composite end point</td>
<td>16.7%</td>
<td>17.9%</td>
<td>8.0% (5.0 to 14)</td>
<td>70 (40 to 1119)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.9%</td>
<td>2.4%</td>
<td>21% (2.0 to 36)</td>
<td>197 (115 to 2064)</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>1.7%</td>
<td>1.3%</td>
<td>25% (3.0 to 61)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Moderate bleeding</td>
<td>2.1%</td>
<td>1.3%</td>
<td>62% (27 to 108)</td>
<td>125 (72 to 287)</td>
</tr>
</tbody>
</table>

*Abbreviations defined in glossary: RRR, RRI, NNT, NNH, and CI calculated from relative risks in article. †Cardiovascular death, myocardial infarction, or stroke. Primary composite end point, or hospital admission for unstable angina, transient ischaemic attack, or revascularisation.

Commentary

A

Aspirin, which blocks the platelet cyclo-oxygenase pathway, is effective for preventing vascular events. Recent short term studies combining aspirin with clopidogrel, another antiplatelet drug that blocks the adenosine diphosphate P2Y1 receptor, have shown significant benefit in patients with acute coronary syndromes and those undergoing percutaneous revascularisation.

The CHARISMA trial by Bhatt et al was designed to determine if long term therapy with aspirin plus clopidogrel was better than aspirin alone in patients with high risk atherothrombosis. Overall, there was no benefit in using dual therapy over aspirin alone for the primary outcome and only a small benefit for the secondary outcome. However, it is logical that if dual therapy is effective for short term therapy in acute coronary syndromes, there may be some patients for whom long term therapy might also be beneficial. To address this possibility, the authors did a prespecified subgroup analysis, including patients with multiple risk factors alone and those with a history of vascular events. Dual therapy provided no benefit for patients with multiple risk factors alone but a small risk reduction in the primary end point for patients who had established vascular disease (6.9% vs 7.9%). The usual cautions about subgroup analysis apply, and further research is needed to show benefit for long term dual therapy. Dual therapy is more expensive than aspirin alone, and this trial showed an increased risk of moderate bleeding. For now, clinicians should use aspirin alone for long term antiplatelet therapy.

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