Antiplatelet Therapy for Preventing Stroke and Other Vascular Events After Carotid Endarterectomy

Stefan Engelter, MD; Philippe Lyrer, MD

Antiplatelet drugs are effective and safe in a wide variety of patients at high risk for vascular ischemic events. Among patients undergoing vascular surgical procedures, these agents significantly reduce the risk of graft or native vessel occlusion. In this context, we examined their effects in patients after carotid endarterectomy (CEA).

Objectives
The objective of this review was to evaluate whether antiplatelet agents are safe and beneficial after endarterectomy of the internal carotid artery.

Search Strategy
We searched the Cochrane Stroke Group Trials Register (last search October 1, 2002). In addition, we performed comprehensive searches of the Cochrane Controlled Trials Register (Cochrane Library Issue 3, 2002), MEDLINE (January 1966 to September 2002), and EMBASE (January 1980 to September 2002), and we checked all relevant articles for additional eligible studies.

Selection Criteria
We selected randomized, controlled, unconfounded trials (RCTs) comparing antiplatelet agents with control after carotid endarterectomy in symptomatic or asymptomatic carotid stenosis of different degrees. Treatment duration had to be at least 30 days after CEA. Follow-up should be at least 3 months.

Data Collection and Analysis
Two reviewers selected trials for inclusion, assessed trial quality, and extracted data independently from each other. From each trial, we extracted the number of patients originally allocated to each treatment group and the number of patients who met the criteria for each outcome (intention-to-treat analysis). We calculated a weighted estimate of the odds for each outcome event across studies using the Peto OR (OR) method.

Main Results
Six trials involving 907 patients were identified. For death (all causes), the Peto OR of 0.77 with a 95% confidence interval (CI) of 0.48 to 1.24 did not show a statistically significant difference between both treatment groups. For stroke (any), the Peto OR of 0.58 (95% CI: 0.34 to 0.98) indicated a statistically significant benefit in favor of antiplatelet drugs ($P=0.04$; Figure). Concerning the secondary outcome events, vascular death, stroke or vascular death, serious vascular events, death or dependency, myocardial infarction, local hemorrhage requiring surgery, restenosis, and TIA or amaurosis fugax, no benefit or hazard of antiplatelet drugs could be shown. For the outcome events intracranial hemorrhage, ischemic stroke, and occurrence or progression of contralateral stenosis, data were either too sparse for meaningful analyses or not available at all.

For the event known as major extracranial hemorrhage, a Peto OR of 1.71 (95% CI: 0.73 to 4.03) showed no significant difference between both treatment groups. However, a statistically significant hazardous effect of antiplatelets might simply be missed because of a relatively small sample size.

Implications for Practice
There is some suggestion, that antiplatelet drugs reduce the odds of death after carotid endarterectomy, although the results are inconclusive. Antiplatelet drugs reduce the odds of stroke after carotid endarterectomy. The risk of serious bleeding seems to be low. Therefore, from a clinical point of view, there is no reason to withhold antiplatelet drugs from patients undergoing CEA. Our data do not allow the recommendation for a precise dose, because most trials used high doses of acetylsalicylic acid (ASA) alone or in combination with other antiplatelet drugs.

Implications for Research
The results of this systematic review indicated that antiplatelet therapy appears superior to placebo after CEA; hazardous effects of antiplatelets were not shown so far. Thus, testing antiplatelet drugs against placebo in a future RCT appears not to be an issue. Because antiplatelet drugs so far predominantly meant ASA, and because the protective effect (regarding stroke, myocardial infarction, vascular death) seems to be low, a future RCT in CEA patients should test ASA against a...
Comparison of antiplatelet drugs versus control for preventing death (A) or stroke

(B) after carotid endarterectomy.

A: Outcome event 'death (all causes)'

<table>
<thead>
<tr>
<th>Study</th>
<th>Antplatelets n/</th>
<th>Control n/</th>
<th>Peto OR (95% CI/95% Freq)</th>
<th>Weight %</th>
<th>Peto OR (95% CI/95% Freq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATLAS-6 1979</td>
<td>6 / 63</td>
<td>3 / 60</td>
<td></td>
<td>12.2</td>
<td>1.01[0.46, 2.24]</td>
</tr>
<tr>
<td>Deyo 1990</td>
<td>16 / 150</td>
<td>11 / 150</td>
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<td>35.9</td>
<td>1.01[0.46, 2.30]</td>
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<tr>
<td>Heister 1992</td>
<td>3 / 60</td>
<td>0 / 60</td>
<td></td>
<td>12.4</td>
<td>0.88[0.27, 2.92]</td>
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<tr>
<td>Komatsu 1992</td>
<td>6 / 32</td>
<td>14 / 34</td>
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<td>20.6</td>
<td>0.30[0.12, 0.77]</td>
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<tr>
<td>Lindblad_Juengel 1992</td>
<td>4 / 117</td>
<td>10 / 116</td>
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<td>0.48[0.13, 1.65]</td>
</tr>
<tr>
<td>x Proctor 1991</td>
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<td>0 / 10</td>
<td></td>
<td>0.0</td>
<td>Not Estimable</td>
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<tr>
<td>Total(95% CI)</td>
<td>26 / 447</td>
<td>44 / 485</td>
<td></td>
<td>100.0</td>
<td>0.77[0.48, 1.24]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: chi-square = 0.59 df/4 = 0.62
Test for overall effect: z = 1.05 p = 0.3

B: Outcome event 'stroke (any)'

<table>
<thead>
<tr>
<th>Study</th>
<th>Antplatelets n/</th>
<th>Control n/</th>
<th>Peto OR (95% CI/95% Freq)</th>
<th>Weight %</th>
<th>Peto OR (95% CI/95% Freq)</th>
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</thead>
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<td>0.49[0.11, 1.87]</td>
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<td>Komatsu 1992</td>
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<td>4 / 34</td>
<td></td>
<td>9.0</td>
<td>0.52[0.16, 1.67]</td>
</tr>
<tr>
<td>Lindblad_Juengel 1992</td>
<td>6 / 117</td>
<td>12 / 116</td>
<td></td>
<td>25.4</td>
<td>0.99[0.27, 1.50]</td>
</tr>
<tr>
<td>x Proctor 1991</td>
<td>0 / 10</td>
<td>0 / 10</td>
<td></td>
<td>0.0</td>
<td>Not Estimable</td>
</tr>
<tr>
<td>Total(95% CI)</td>
<td>25 / 417</td>
<td>38 / 485</td>
<td></td>
<td>100.0</td>
<td>0.72[0.47, 1.12]</td>
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</tbody>
</table>

Test for heterogeneity: chi-square = 2.26 df/4 = 0.09
Test for overall effect: z = 2.05 p = 0.04

**Conclusions**

Our results may indicate that antiplatelet drugs did not significantly change the odds of death but reduce the outcome stroke of any cause in patients undergoing CEA. However, it cannot be excluded that the beneficial effect in reducing stroke is caused by chance. It is possible that antiplatelets may increase the odds of hemorrhage, but there are currently too few data to quantify this effect.

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