Potential Value of Triple Antiplatelet Therapy for Secondary Stroke Prevention

To the Editor:

We present (see the Table) our meta-analyses of the effects of antiplatelet regimens on the endpoint of stroke in long-term secondary stroke prevention trials (CAPRIE\(^1\) and AAASPS\(^2\); references for all other trials are in antiplatelet trialist articles\(^3,4\)). Statistically significant results are indicated by their 95% confidence intervals (CI). That aspirin (ASA) is better than placebo is well demonstrated statistically \((P<0.001)\), but the benefit is modest: a relative risk reduction (RRR) of 16%. The benefit from dipyridamole (DP) monotherapy appears to be similar to that of ASA. The ADP receptor antagonists (ADPRAs) clopidogrel and ticlopidine are perhaps somewhat more effective than ASA (estimate, 8%), but the differences are not statistically significant. Furthermore, there are serious safety concerns with ticlopidine.

In contrast, the combination of DP and ASA is much superior to placebo: \(\text{RR}=0.652\ (95\%\ CI, 0.562\ to\ 0.756)\) for an RRR of 35%. This combination is also clearly superior to ASA alone: \(\text{RR}=0.796\ (95\%\ CI, 0.676\ to\ 0.939)\) for an RRR of 20%. Therefore, in the absence of specific contraindications, for long-term secondary prevention of noncardiac stroke, monotherapy is scientifically and ethically unacceptable; dual therapy with DP plus ASA must be the standard treatment for individuals and the control regimen in clinical trials.

What about triple rather than dual therapy? Zhao et al\(^5\) have explored in vitro the effects on platelet and leukocyte function of ASA, DP, and AR-C69931 used singly, in pairs, and in triple combination (AR-C69931 has effects similar to those of clopidogrel but, unlike clopidogrel, which must be transformed in the liver, is active in vitro). They conclude, "In summary, the overall message of our work is that combinations of three antiplatelet drugs which work through different mechanisms are superior to any single agent alone, or pairs of agents, in modifying platelet activity and heterotypic cell adhesion and leukocyte activation. Combining three different antiplatelet agents may be a new mechanistic strategy for antiplatelet therapy, specifically in the secondary prevention of vascular disease.”

Based on the observed mean RR for DP plus ASA versus ASA \((0.796;\ 95\%\ CI, 0.676\ to\ 0.939)\), on the assumption that ADPRA effects and DP+ASA effects are independent, and on the conservative estimate that ADPRA and ASA effects are equal, ie, they each reduce risk by 16% \((\text{RRR}=0.838)\) versus placebo, the projection of RR for the combination DP+ASA+ADPRA versus ASA is \(0.796\times0.838=0.656\), for an RRR of 33%. The projection of RR for the combination DP+ASA+ADPRA versus placebo is \(0.652\times0.838=0.546\), for an RRR of 45%.

Thus, triple therapy might improve the best current RRR for stroke from 35% against placebo to (an estimated mean value of) 45% versus placebo. This potential for improvement in prophylaxis warrants a clinical trial.

In conclusion, dual therapy with DP and ASA (not monotherapy with any antiplatelet agent) should be the standard regimen for the individual patient who has had transient ischemic attack or ischemic stroke of noncardiac origin and is the only currently acceptable control regimen in clinical trials. Triple therapy with DP+ASA+ADPRA projects as superior to DP+ASA dual therapy; a trial of triple versus dual therapy is warranted.

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Meta-Analyses of Stroke* as Endpoint in Secondary Stroke Prevention Trials† of Antiplatelet Regimens Against Placebo or Aspirin

<table>
<thead>
<tr>
<th>Regimens: Treatment vs Control</th>
<th>(No. of Endpoint Strokes)/(No. of Subjects)</th>
<th>Control</th>
<th>Treatment</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin vs placebo‡</td>
<td>606/4824</td>
<td>605/4023</td>
<td>0.838</td>
<td>0.754–0.932</td>
<td>0.001</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>DP vs placebo§</td>
<td>223/1739</td>
<td>261/1733</td>
<td>0.851</td>
<td>0.721–1.005</td>
<td>0.058</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>DP vs ASA</td>
<td>211/1654</td>
<td>206/1649</td>
<td>1.021</td>
<td>0.853–1.222</td>
<td>0.819</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>DP+ASA vs placebo¶</td>
<td>259/3102</td>
<td>397/3103</td>
<td>0.652</td>
<td>0.562–0.756</td>
<td>0.000</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>DP+ASA vs ASA#</td>
<td>228/2300</td>
<td>265/2289</td>
<td>0.796</td>
<td>0.676–0.939</td>
<td>0.007</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel vs ASA**</td>
<td>315/3233</td>
<td>338/3198</td>
<td>0.922</td>
<td>0.797–1.066</td>
<td>0.273</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Ticlopidine vs ASA††</td>
<td>286/2601</td>
<td>311/2617</td>
<td>0.925</td>
<td>0.795–1.077</td>
<td>0.317</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel or ticlopidine vs ASA</td>
<td>601/5834</td>
<td>649/5815</td>
<td>0.924</td>
<td>0.831–1.026</td>
<td>0.138</td>
<td>8%</td>
<td></td>
</tr>
</tbody>
</table>

RR indicates relative risk; RRR, relative risk reduction (RR and RRR values in bold are statistically significant); CI, confidence interval; ASA, aspirin; DP, dipyridamole. Doses listed below are total daily.

*For all but 2 trials the endpoint is Any Stroke: any ischemic stroke, intracranial hemorrhage, or stroke of uncertain mechanism.
†The studies selected were long-term prophylactic trials (not 2- to 4-week studies after acute stroke) in which antiplatelet regimens were tested against other antiplatelet regimens or against placebo in people who had had TIA or ischemic stroke not of cardiac origin.
‡Aspirin 50 –1500 mg. The studies were AICLA, AITIA, Canadian cooperative, Danish cooperative, ESPS2, Reuther, SALT, Britton (Swedish cooperative study), and UK-TIA.
§Dipyridamole 400 –800 mg vs placebo; data from ESPS2, Stoke.
# Dipyridamole 225–400 mg plus aspirin 50 –1300 mg vs placebo; data from AICLA, ESPS1 and 2.
**Clopidogrel 75 mg vs ASA 325 mg; data from CAPRIE.
††Ticlopidine 200–500 mg vs ASA 500–1300 mg; data from AAASPS, Japanese B, TASS.
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*Stroke*. 2003;34:e182-e183; originally published online September 25, 2003;
doi: 10.1161/01.STR.0000092896.70446.87

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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World Wide Web at:
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