Dipyridamole plus Aspirin: The Best Regimen for Stroke Prevention after Noncardioembolic Focal Cerebral Ischemia

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In this issue of Cerebrovascular Diseases, Sacco et al. [1] report subgroup analyses for the previously reported Warfarin-Aspirin Recurrent Stroke Study (WARSS) [2]. They conclude that antiplatelet therapy rather than warfarin 'should be the mainstay of secondary stroke prevention after noncardioembolic stroke'. They go on to agree with the Antithrombotic Trialists’ Collaboration’s recommendation [3] of 'the use of aspirin, extended-release dipyridamole plus aspirin, and clopidogrel as acceptable options for secondary stroke prevention after noncardioembolic TIA or stroke'.

Our meta-analysis of the WARSS, WASID [4] and the warfarin vs. aspirin study of Garde et al. [5] (table 1) leads us to agree fully that antiplatelet treatment should be the mainstay of secondary stroke prevention. However our meta-analyses of antiplatelet treatments lead us to conclude that the three antiplatelet options are not equally efficacious; rather, the combination of dipyridamole and aspirin is clearly superior to antiplatelet monotherapy, and should be the default recommendation for secondary stroke prevention after prior noncardioembolic TIA or stroke.

We note (table 1) that extended-release dipyridamole plus aspirin is clearly superior (relative risk of stroke, RR = 0.762; p = 0.006) to aspirin alone (ESPS2 [6]), but that clopidogrel was shown not statistically significantly better than aspirin (CAPRIE study [7]). Thus, the available indirect evidence favors dipyridamole plus aspirin over clopidogrel, until and unless the ongoing PROFESS study [8–10] proves otherwise. Therefore, based on a combination of currently available direct and indirect evidence, dipyridamole plus aspirin is the proper recommendation: it is not statistically in the best interests of the patient to prescribe monotherapy with either aspirin or clopidogrel. The only issue we see here is: which formulation of dipyridamole should be employed? We shall present evidence for conventional dipyridamole 225 mg daily rather than extended-release dipyridamole 400 mg daily. We raise this issue for the following reasons:

- We find that the proprietary formulation of 200 mg of extended-release dipyridamole produces objectionable headache in many patients, even when treatment is begun with one dose rather than two daily.
- In contrast, it is relatively easy to avoid objectionable headache in most patients by building toward 225 mg daily of conventional dipyridamole through the use of 25 or 75 mg tablets.
Table 1. Randomized secondary stroke prevention trials in patients with previous noncardioembolic stroke: endpoint stroke rates

<table>
<thead>
<tr>
<th>Studies and (1st vs. 2nd) regimens (doses are total mg/day)</th>
<th>Strokes/subjects randomized</th>
<th>RR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>W vs. A (3 trials)</td>
<td></td>
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<tr>
<td>Garde: W vs. A1000</td>
<td>4/114</td>
<td>0.891</td>
<td>0.245</td>
<td>3.238</td>
</tr>
<tr>
<td>WARSS: W vs. A325</td>
<td>149/1,103</td>
<td>1.211</td>
<td>0.969</td>
<td>1.515</td>
</tr>
<tr>
<td>WASID: W vs. A1300</td>
<td>51/289</td>
<td>0.852</td>
<td>0.607</td>
<td>1.195</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>204/1,506</td>
<td>1.084</td>
<td>0.901</td>
<td>1.304</td>
</tr>
<tr>
<td>D(ER)+A vs. A (1 trial)</td>
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</tr>
<tr>
<td>ESPS2: D400(ER)+A50 vs. A50</td>
<td>157/1,650</td>
<td>0.762</td>
<td>0.626</td>
<td>0.927</td>
</tr>
<tr>
<td>Clopidogrel vs. A (1 trial)</td>
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</tr>
<tr>
<td>CAPRIE: clopidogrel 75 vs. A325</td>
<td>334/3,333</td>
<td>0.913</td>
<td>0.793</td>
<td>1.050</td>
</tr>
<tr>
<td>D(conventional)+A vs. A (2 trials)</td>
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<tr>
<td>AICLA: D225+A900 vs. A990</td>
<td>19/202</td>
<td>0.980</td>
<td>0.795</td>
<td>1.795</td>
</tr>
<tr>
<td>Caneschl: D225+A150 vs. A300</td>
<td>3/22</td>
<td>0.636</td>
<td>0.149</td>
<td>2.722</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>22/224</td>
<td>0.920</td>
<td>0.526</td>
<td>1.608</td>
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<tr>
<td>D(ER)+A vs. placebo (1 trial)</td>
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<td></td>
<td></td>
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<tr>
<td>ESPS2: D400+50 vs. placebo</td>
<td>157/1,650</td>
<td>0.628</td>
<td>0.520</td>
<td>0.757</td>
</tr>
<tr>
<td>D(conventional)+A vs. placebo (2 trials)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AICLA: D225+A990 vs. placebo</td>
<td>19/202</td>
<td>0.581</td>
<td>0.342</td>
<td>0.988</td>
</tr>
<tr>
<td>ESPS2: D225+A975 vs. placebo</td>
<td>114/1,250</td>
<td>0.620</td>
<td>0.497</td>
<td>0.772</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>133/1,452</td>
<td>0.614</td>
<td>0.501</td>
<td>0.752</td>
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<tr>
<td>A vs. A (2 trials)</td>
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<tr>
<td>Dutch TIA: A30 vs. A283</td>
<td>122/1,555</td>
<td>0.824</td>
<td>0.656</td>
<td>1.036</td>
</tr>
<tr>
<td>UK-TIA: A300 vs. A1200</td>
<td>100/806</td>
<td>1.001</td>
<td>0.773</td>
<td>1.297</td>
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<tr>
<td>A vs. A secondary stroke prevention combined with postcarotid endarterectomy/stroke trial data</td>
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<td>30–81 vs. 283–1,300 mg (2 trials)</td>
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<tr>
<td>ACE: A 81 vs. A 325–1,300</td>
<td>40/698</td>
<td>1.107</td>
<td>0.779</td>
<td>1.574</td>
</tr>
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<td>0.824</td>
<td>0.656</td>
<td>1.036</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>162/2,253</td>
<td>0.900</td>
<td>0.743</td>
<td>1.090</td>
</tr>
<tr>
<td>300–325 vs. 1,200–1,300 mg (2 trials)</td>
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<td></td>
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</tr>
<tr>
<td>ACE: A 325 vs. A 1300</td>
<td>24/697</td>
<td>0.608</td>
<td>0.370</td>
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<td>1.297</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>124/1,503</td>
<td>0.808</td>
<td>0.461</td>
<td>1.415</td>
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</tbody>
</table>

In addition to the citations in the text, data from and references for most of these studies may also be found in the antiplatelet trialists’ papers [3, 15]. Values in bold signify p < 0.05. Stroke = Any stroke (ischemic or hemorrhagic, fatal or nonfatal); A = aspirin; D = dipyridamole; ER = extended release; RR = relative risk of stroke among patients randomized to the 1st vs. the 2nd regimen; W = warfarin.

a WARSS: nonfatal ischemic stroke.

b The CAPRIE paper gives ischemic, but not hemorrhagic, stroke as an endpoint for the 6,431 patients who were randomized because of prior ischemic stroke. We obtained the any-stroke outcome data in a personal communication from Dr. Robin Roberts.

Table 1 shows the direct comparison (two trials and meta-analysis) of conventional dipyridamole 225 mg plus aspirin vs. aspirin monotherapy. There is no significant difference. However, the studies were grossly underpowered. While the ESPS2 with a sample size of 1,650 had 78% power (two-tailed α = 0.05) to show an RR of 0.762 for combination therapy given a stroke rate of 12.49% (206/1,649) for aspirin, AICLA [11] had only 16% power to show the same benefit with a sample size of only 200. On the other hand, the conventional dipyridamole
225 mg plus aspirin vs. placebo trial comparisons, with a combined sample size of 1,450, demonstrated almost identical results (RR = 0.614; p = 0.000) to the ESPS2 regimen of extended-release dipyridamole 400 mg plus aspirin vs. placebo (RR = 0.628; p = 0.000). Thus by indirect comparison 225 mg/day of conventional dipyridamole is as effective as 400 mg/day of extended-release dipyridamole, in combination with aspirin.

Is it necessary to use 975–990 mg of aspirin daily with conventional dipyridamole? We think not. Based on the Dutch [12] and UK TIA results [13] it appears that medium or high aspirin doses offer no advantage over very low doses. The stroke outcome results of the ACE study [14] comparing four doses of aspirin in carotid endarterectomy patients (most of whom had had a prior TIA or nondisabling stroke) provide additional evidence for the conclusion that very low doses of aspirin are as efficacious as higher doses.

In conclusion, antiplatelet therapy with dipyridamole plus aspirin is the best treatment yet studied for secondary stroke prevention after noncardioembolic stroke. The best available evidence is that conventional generic dipyridamole (total of 225 mg/day) plus low-dose aspirin is as effective as a substantially more expensive preparation of proprietary extended-release dipyridamole (total of 400 mg/day) plus low-dose aspirin.

References