Warfarin was not more effective than aspirin and increased adverse events in symptomatic intracranial arterial stenosis


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

Q In patients with symptomatic intracranial arterial stenosis, how does aspirin compare with warfarin?

### METHODS

- **Design:** randomised controlled trial (Warfarin-Aspirin Symptomatic Intracranial Disease [WASID] Trial).
- **Allocation:** concealed.
- **Blinding:** blinded (patients and outcome assessors).
- **Follow up period:** mean 1.8 years.
- **Setting:** 59 sites in North America.
- **Patients:** 569 patients 40 years of age (mean age 64 y, 61.5% men) with transient ischaemic attack or non-disabling stroke in the previous 90 days caused by 50–99% stenosis of a major intracranial artery and a modified Rankin score <3. Exclusion criteria included tandem 50–99% stenosis of the extracranial carotid artery, non-atherosclerotic stenosis of an intracranial artery, and a cardiac source of embolism.
- **Intervention:** aspirin, 1300 mg/day (n = 280), or warfarin, 5 mg/day initial dose, which was adjusted to achieve an international normalised ratio (INR) of 2.0–3.0 (n = 289).
- **Outcomes:** primary composite endpoint of ischaemic stroke, brain haemorrhage, and death from vascular causes other than stroke; and adverse events.
- **Patient follow up:** 98% (intention to treat analysis).

*See glossary.

### MAIN RESULTS

Aspirin and warfarin did not differ for the primary composite endpoint or for death from vascular or non-vascular causes (table). Warfarin was associated with higher rates of all cause death, major haemorrhage, and myocardial infarction or sudden death than aspirin (table).

### CONCLUSION

In patients with symptomatic intracranial arterial stenosis, warfarin was not more effective than aspirin and increased the rates of all cause death, major haemorrhage, and myocardial infarction or sudden death.

Abstract and commentary also appear in ACP Journal Club.

### Commentary

Uncertainty has existed on whether aspirin or warfarin should be the preferred antithrombotic in selected patients at high risk for non-cardioembolic stroke, and whether aspirin is effective and safe for primary prevention of cardiovascular disease (CVD) in women.

The WASID trial did not show any difference in efficacy between warfarin (target INR 2.0–3.0) and aspirin for preventing stroke or non-stroke vascular death in patients with symptomatic major intracranial artery stenosis. However, the study had to be stopped early because of evidence of harm with warfarin.

The high incidence of bleeding in patients treated with warfarin (5/100 patient y) is surprising. This may be due to the broad definition of major bleeding. The high dose of aspirin used in this study (1300 mg/d) may have selectively increased bleeding in patients treated with aspirin,1 reducing the difference between the 2 treatments. Nevertheless, a clear excess of bleeding with warfarin remained evident. The increased all cause mortality with warfarin compared with aspirin is unexplained. Previous randomised trials suggest that moderate intensity warfarin (INR 2.0–3.0) is at least as effective as aspirin for preventing major vascular events.2 Yet, warfarin in the WASID trial was associated with a consistent pattern of excess deaths from both vascular and non-vascular causes, including myocardial infarction (MI), sudden death, and cancer. This is unlikely to be explained by the efficacy of high dose aspirin because, unlike safety, no convincing evidence exists to suggest that aspirin’s efficacy is dose related.1 3 The optimal dose of aspirin is less clear from these data but, when considered in the context of what we already know about aspirin, a strong argument can be made to use the lowest proven effective dose (75–150 mg/d), thereby minimising the risk of bleeding complications.

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### Aspirin v warfarin for symptomatic intracranial arterial stenosis at mean 1.8 years*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Aspirin</th>
<th>Warfarin</th>
<th>RRI (CI)</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint†</td>
<td>22.1%</td>
<td>21.8%</td>
<td>4% (-25 to 40)</td>
<td>Not significant</td>
</tr>
<tr>
<td>All cause death</td>
<td>4.3%</td>
<td>9.7%</td>
<td>53% (10 to 76)</td>
<td>20 (14 to 108)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>3.2%</td>
<td>5.9%</td>
<td>43% (-25 to 74)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Non-vascular death</td>
<td>1.1%</td>
<td>3.8%</td>
<td>70% (-7 to 92)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Major haemorrhage</td>
<td>3.2%</td>
<td>8.3%</td>
<td>60% (15 to 81)</td>
<td>18 (13 to 67)</td>
</tr>
<tr>
<td>MI or sudden death</td>
<td>2.9%</td>
<td>7.3%</td>
<td>59% (9 to 81)</td>
<td>24 (17 to 158)</td>
</tr>
</tbody>
</table>

*MI = myocardial infarction. Other abbreviations defined in glossary; NNT and CI calculated from data in article.

†Primary composite outcome = ischaemic stroke, brain haemorrhage, and death from vascular causes other than stroke.