Warfarin reduced major stroke more than aspirin in elderly patients with atrial fibrillation in primary care


Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Cardiology ★★★★★★☆ Geriatrics ★★★★★☆ Hematol/Thrombo ★★★★★☆ Neurorology ★★★☆☆☆

Question
In elderly primary care patients with atrial fibrillation (AF), is warfarin more effective than aspirin for preventing major stroke, arterial embolism, and intracranial hemorrhage?

Methods
Design: Randomized controlled trial (Birmingham Atrial Fibrillation Treatment of the Aged [BAFTA] study).
Allocation: Concealed.*
Blinding: Blinded (outcome assessors).*
Follow-up period: Mean 2.7 years.
Setting: 234 general practices in England and Wales.

Patients: 973 patients ≥75 years of age (mean age 81 y; 55% men) with AF or fluctuating within the past 2 years (confirmed by electrocardiography). Exclusion criteria included terminal illness, rheumatic heart disease, major nontraumatic hemorrhage within 5 years, intracranial hemorrhage, peptic ulcer in the previous year, esophageal varices, warfarin or aspirin allergy, surgery in the previous 3 months, BP >180/110 mm Hg, or belief of the primary care physician that 1 of the study medications was more appropriate for the patient.

Intervention: Warfarin, with a target international normalized ratio (INR) of 2.5 (acceptable range 2 to 3) evaluated according to individual general practice routine (n = 488), or aspirin 75 mg/d (n = 485). Current treatment with warfarin or aspirin was stopped if patients were randomized to the opposite treatment group.

Outcomes: Fatal or nonfatal disabling stroke, intracranial hemorrhage (confirmed by brain imaging), or significant arterial embolism (confirmed by vascular imaging, scintigraphy, surgery, or autopsy). Secondary outcomes included other major hemorrhage, other vascular events requiring hospitalization or resulting in death, and all-cause mortality.

Patient follow-up: 965 patients (99%) (intention-to-treat analysis).

Main results
At a mean follow-up of 2.7 years, the incidence of major stroke, other intracranial hemorrhage, or systemic embolism was lower in the warfarin group than the aspirin group (Table). All-cause mortality (8.0% vs 8.4% per year, respectively) and major hemorrhage (1.9% vs 2.0% per year, respectively) were similar for both groups, although the trial was not powered to detect group differences in those outcomes.

Conclusion
In primary care patients ≥75 years of age with atrial fibrillation, warfarin was more effective than aspirin for reducing major stroke.

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*See Glossary.

<table>
<thead>
<tr>
<th>Outcome at mean 2.7 y</th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
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<tbody>
<tr>
<td>Major stroke, intracranial hemorrhage, or systemic embolism†</td>
<td>4.9% (24/488)</td>
<td>9.9% (48/485)</td>
<td>50% (21 to 69)</td>
<td>21 (12 to 58)</td>
</tr>
</tbody>
</table>

†Abbreviations defined in Glossary. RRR, NNT, and CI calculated from data in article.
‡Major stroke (4.3% vs 9.1%), other intracranial hemorrhage (0.4% vs 0.2%), and systemic embolism (0.2% vs 0.6%).

Commentary
AF is the most common arrhythmia in the elderly and is a strong independent risk factor for stroke. Warfarin remains underutilized in the elderly despite the fact that age independently predicts stroke risk in AF (1). A recent meta-analysis of adjusted-dose warfarin compared with placebo in AF showed a relative risk reduction (RRR) of 64% and absolute risk reduction (ARR) of 2.7%/y for stroke with warfarin (2). In the same meta-analysis, adjusted-dose warfarin compared with antplatelet therapy had an RRR of 37% and an ARR of 0.9%/y. Absolute increases in major extracranial hemorrhage with warfarin were small (about 0.3%/y). A limitation of prior randomized trials has been underrepresentation of the elderly. The BAFTA study is a step forward in helping to convince clinicians that warfarin dosed to a target INR of 2.5 in the elderly is more effective in preventing stroke and systemic embolism than aspirin. Although the study was not powered to detect a difference in major bleeding, a low rate of such bleeding in both groups is somewhat reassuring.

Study features that make the results more generalizable to the elderly include enrollment from primary care practices, mean age of 81 y, CHADS2 score of 1 or 2 (3) in more than 70% of patients, blinded outcome assessment, and a fair amount of crossover between groups. The aspect that makes this study less generalizable is that >50% of the patients were managed by hospital-run anticoagulation clinics, which are better than individual doctors in managing INR and, therefore, may be a reason for the high rate of therapeutic INRs and the low rate of bleeding.

The BAFTA study results would support adjusted-dose warfarin with a target INR of 2.5 (range 2 to 3) for all patients ≥75 years with AF in the absence of contraindications. This recommendation is more liberal than the current referenced guidelines (1, 3, 4).

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References