2. Cardiogenic Cerebral Embolism Associated with Atrial Fibrillation

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Key words: nonvalvular atrial fibrillation (NVAF), cerebral embolism, warfarin, aspirin

Nonvalvular atrial fibrillation (NVAF) as an important cause of embolism

Cardiogenic embolism is recognized to account for about 15% to 20% of all ischemic strokes in clinical studies. As cardiac sources of embolic strokes, atrial fibrillation, especially nonvalvular atrial fibrillation (NVAF) is the most common cardiac source, accounting for approximately 50% of embolic strokes (Table 1) (1). From an autopsy study in the elderly, 28% of the cerebral infarctions were embolic strokes of cardiac origin, 56% of which were caused by NVAF (2).

Atrial fibrillation (AF) increases in incidence with increasing age. Kuramoto et al reported that 10% of all autopsied patients had chronic AF, 7% had paroxysmal AF, most of which were non-rheumatic AF or NVAF (3). Approximately 35% of patients with AF will experience an ischemic stroke during their lifetime. Åberg indicated that 42% of autopsied AF patients without valvular or congenital heart diseases had systemic embolism, half of which were brain embolism (4). Twenty-two percent of the AF patients had large cerebral infarctions, and 15% had medium-sized cortical infarctions at the autopsy (3). NVAF is an important cause of fatal massive cerebral infarctions in the elderly. Approximately half of the patients with fatal massive cerebral infarctions who died within 2 weeks after the strokes had embolic infarctions due to NVAF (5).

Prophylactic therapy for the prevention of recurrent embolic stroke

Cardiogenic embolic brain infarctions recur frequently. Sage and Uitert reported the high risk of recurrent cerebral infarctions over the long-term in NVAF stroke patients who had no anti-coagulant therapy (6). From an autopsy study, we indicated frequent recurrences in embolic strokes over the long-term with NVAF (7). Although the risk of early recurrences is well known in cerebral embolism of cardiac origin, these data show that the

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References

Table 1. Cardiac Sources of Embolic Stroke: Aggregate Clinical Data [Cerebral Embolism Task Force (1)]

<table>
<thead>
<tr>
<th>Source</th>
<th>Fraction of all embolic stroke</th>
<th>Stroke risk in population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonvalvular atrial fibrillation</td>
<td>45%</td>
<td>5% per year</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>15%</td>
<td>3% within 4 wk</td>
</tr>
<tr>
<td>Ventricular aneurysm</td>
<td>10%</td>
<td>5% prevalence</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>10%</td>
<td>20% prevalence</td>
</tr>
<tr>
<td>Prosthetic cardiac valves</td>
<td>10%</td>
<td>1-4% per year</td>
</tr>
<tr>
<td>Other heart diseases*</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

*mitral valve prolapse, mitral annulus calcification, nonbacterial thrombotic endocarditis, calcific aortic stenosis, cardiac myxoma, etc.

Late recurrences are also important and suggest that long-term prophylactic therapy should be considered for the prevention of recurrent embolic strokes in patients with NVAF.

The optimal time to initiate anticoagulation following a cardioembolic stroke continues to be controversial. Immediate anticoagulation starting within 24-hour or a few days after the embolic stroke reduces the early recurrence of embolism, but can sometimes induce brain hemorrhage or conversion of ischemic to hemorrhagic infarction. The Cerebral Embolism Task Force stated that "withholding anticoagulation for several weeks in all patients or in those with nonrheumatic AF is a more conservative, but acceptable alternative approach (8)."

Our study indicated that long-term anticoagulant therapy (warfarin) prevented the recurrent embolic brain infarction without major hemorrhagic complications even in the elderly patients with NVAF (9). Although hypertension is the most important predisposing condition for cerebral hemorrhage and the risk of hemorrhagic complications rises with increasing intensity of anticoagulation, major hemorrhagic complications can be reduced if blood pressure is kept within the normal range and the adequate therapeutic anticoagulation is maintained. The European AF Trial Study Group showed that the optimal intensity of anticoagulation was between an international normalized ratio (INR) of 2.0 and an INR of 3.9 (10).

Can antiplatelet therapy (aspirin) prevent the recurrent embolic infarction in NVAF patients? The European AF Trial Study Group indicated that anticoagulant therapy was effective in reducing the risk of recurrent vascular events in nonrheumatic AF patients with a recent TIA or minor ischemic stroke, but aspirin was less effective (Table 2) (11).

**Primary prevention for embolic stroke in NVAF**

All prospective studies revealed a reduction in the stroke rate for patients treated with warfarin and a small incidence of major hemorrhagic complications. The Copenhagen AFASAK Study (12) indicated that the thromboembolic events and vascular mortality were significantly lower in the warfarin group than in the aspirin and placebo groups, which did not differ significantly (Table 3). In this study, aspirin (75 mg per day) did not reduce the risk of thromboembolic complications in patients with nonrheumatic AF. The SPAF Study (13) showed the reduction of stroke in aspirin therapy (325 mg per day), but it was less effective than the warfarin therapy.

Adjusted-dose warfarin is highly efficacious for the prevention of ischemic stroke in patients with AF. However, this treatment carries a risk of bleeding and the need for frequent medical monitoring. The SPAF Study Group (14) compared a combination of low-intensity, fixed-dose warfarin plus aspirin with conventional adjusted-dose warfarin in patients with AF at a high risk of stroke. The results showed that low-intensity, fixed-dose warfarin plus aspirin was insufficient for stroke prevention; adjusted-dose warfarin (target INR 2.0–3.0) obviously reduced stroke.

Older ages, a history of hypertension, recent congestive

Table 2. Secondary Prevention in Non-Rheumatic Atrial Fibrillation after TIA or Minor Stroke
[European Atrial Fibrillation Trial Study Group (11)]

<table>
<thead>
<tr>
<th></th>
<th>Anticoagulants (INR 2.5–4.0)</th>
<th>Placebo</th>
<th>Aspirin (300 mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n=225</td>
<td>n=214</td>
<td>n=404</td>
<td>n=378</td>
</tr>
<tr>
<td>Primary outcome event*</td>
<td>8%/yr</td>
<td>17%/yr</td>
<td>15%/yr</td>
<td>19%/yr</td>
</tr>
<tr>
<td>All strokes</td>
<td>4%/yr</td>
<td>12%/yr</td>
<td>10%/yr</td>
<td>12%/yr</td>
</tr>
<tr>
<td>All deaths</td>
<td>8%/yr</td>
<td>9%/yr</td>
<td>11%/yr</td>
<td>12%/yr</td>
</tr>
<tr>
<td>Major bleeding events</td>
<td>2.8%/yr</td>
<td></td>
<td>0.9%/yr</td>
<td></td>
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</tbody>
</table>

*strokes, myocardial infarctions, systemic embolism, vascular death.
heart failure, previous arterial thromboembolism, thrombus in the left atrium, enlarged left atrium and left ventricular dysfunction on the echocardiograms can be predictors of thromboembolism in non-rheumatic AF or in NVAF.

The reduction of embolic events associated with chronic anticoagulant therapy (warfarin) appears to outweigh the risks of hemorrhagic complication for patients with NVAF. Aspirin may offer an alternative for patients who are not good candidates for anticoagulation, but may be less effective.

References


3. Anti-Neutrophil Cytoplasmic Autoantibodies Associated Renal Diseases and Thrombotic Microangiopathy

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Key words: anti-platelet agent, crescent, thrombomodulin, plasminogen activator inhibitor-1 (PAI-1), glomerular endothelial cell

Introduction

Patients with many renal diseases, including renal arterial stenosis, renal vein thrombosis, and primary glomerular diseases, had been clinically treated with anti-platelet agents. In

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