Atrial Fibrillation and Stroke: New Ideas, Persisting Dilemmas

Jonathan L. Halperin, MD, and Robert G. Hart, MD

The risk of systemic embolism associated with atrial fibrillation (AF) in patients with rheumatic mitral valve disease has long been appreciated. In only the past decade has it become clear that nonrheumatic (nonvalvulopathic) AF is a marker of increased risk for ischemic stroke.1-3 Several recent clinical and epidemiologic surveys have confirmed this association (Table 1) and suggest a fivefold increased risk of stroke. At least 15% of all ischemic strokes and more than a third of ischemic strokes in the elderly are associated with AF.4-14 About one in three people with AF will experience a stroke during their lifetime.1-4 An estimated 75,000 strokes occur each year among the 1-1.5 million North Americans with AF.

In addition to these clinical strokes, AF has been associated with an undue risk of subclinical, “silent” strokes.15-19 Silent infarcts detected by computed tomography (CT) have been found in 35-37% of nonrheumatic AF patients with no history of stroke.16,17 In a preliminary report including patients with rheumatic and nonrheumatic AF but without previous stroke, CT evidence of previous stroke was 2.9-4.5 times as frequent as in non-AF patients.17 Kempster and colleagues18 found CT evidence of remote infarct in 13% of patients with AF-related stroke compared with 4% of non-AF controls. While these CT-defined infarcts are labeled asymptomatic or “silent,” it is likely that they take a subtle, but cumulative, toll on cognition in elderly people.19 Considering the combined risk of clinical and subclinical stroke, AF becomes a substantial threat to the brain.

While the importance of AF-associated stroke is not in doubt, preventive strategies and management have remained empiric and controversial. Despite vigorous ongoing work by several groups of investigators, major unanswered questions remain in three related areas: the mechanism(s) of AF-associated stroke, the identification of clinical subgroups at particularly high or low risk, and the optimal antithrombotic prophylaxis.

**Mechanism(s) of Stroke**

Not all strokes in AF patients are cardioembolic; other causes also exist in elderly AF patients, and vary in likelihood with other risk factors such as age and hypertension. The fraction of AF-associated strokes due to cardiogenic embolism versus coexistent cerebrovascular disease is uncertain. Clinical estimates of the cardioembolic fraction vary widely, from 19% to 75%.12,13,20 A recent arteriographic study of 12 consecutive patients with AF and stroke supported a cardioembolic etiology in as many as 75%.3 Preliminary studies of ultrasonic duplex imaging of carotid arteries in AF patients with stroke have revealed a low prevalence of ipsilateral carotid stenosis.21,22 Two autopsy studies, presumably with a high proportion of large infarcts, reported that 50-71% of AF-associated strokes were cardioembolic.12,23 An inability to diagnose cardioembolic mechanisms with certainty, even at autopsy, clouds this issue, but it is likely that a substantial fraction of strokes associated with AF is cardioembolic in origin. Nonvisualization of atrial thrombi does not argue strongly against a cardioembolic mechanism (Figure 1) because left atrial thrombi are poorly detected by conventional transthoracic echocardiography.24,25 Transesophageal echocardiography detects atrial thrombi, particularly appendage thrombi, with much greater sensitivity.24,25 Other imaging techniques, including CT, ultrastaf CT, and magnetic resonance imaging of the heart, may improve detection of atrial thrombi, thereby supporting a cardioembolic mechanism.20,26

The intermittency of ischemic events associated with chronic, sustained AF has hypothetical implications regarding mechanism. Embolic episodes are sometimes separated by minutes, in other instances by years. If the primary substrate is the formation of stasis-related thrombi in a constantly fibrillating and enlarged atrium, what accounts for the intermittency of embolism? This intermittent pattern also occurs in young people with rheumatic AF in whom the ischemic events are more certainly cardioembolic. Alterations in atrial blood flow patterns...
Autopsy Epidemiologic event rates over observation period. Risk ratio, atrial fibrillation:

**TABLE 1. Stroke Risk and Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Study, year of publication</th>
<th>Stroke incidence (%/yr)</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Framingham, 1978†</td>
<td>4.2</td>
<td>5.6:1</td>
</tr>
<tr>
<td>Whitehall, 1987†</td>
<td>1.8†</td>
<td>6.9:1</td>
</tr>
<tr>
<td>Shibata, 1985*†</td>
<td>5.0</td>
<td>5.6:1</td>
</tr>
<tr>
<td>Reykjavik, 1987*</td>
<td>—</td>
<td>7.5:1</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher, 1979*†</td>
<td>8.8</td>
<td>—</td>
</tr>
<tr>
<td>Roy et al, 1986†</td>
<td>5.1</td>
<td>—</td>
</tr>
<tr>
<td>Treseder et al, 1986*</td>
<td>—</td>
<td>1.8:1</td>
</tr>
<tr>
<td>Fairfax et al, 1976*</td>
<td>—</td>
<td>6.1:1</td>
</tr>
<tr>
<td><strong>Autopsy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al, 1977†</td>
<td>—</td>
<td>3.5:1</td>
</tr>
<tr>
<td>Aberg, 1969†</td>
<td>—</td>
<td>3.0:1</td>
</tr>
</tbody>
</table>

Approximate stroke incidence estimated by linearization of event rates over observation period. Risk ratio, atrial fibrillation: control.

*A minority had valvular atrial fibrillation.
†Mean age at observation approximately 55 years, confidence interval of risk ratio 3.0–13.5.

could result from intermittent sinus rhythm or from transient mitral regurgitation associated with ventricular dilatation or ventricular premature systoles. Intermittent formation and/or embolism of atrial thrombi could theoretically be influenced by such changes in blood flow patterns or conceivably by subtle changes in blood viscosity/coagulability. Identification of the stroke mechanism in AF patients, as well as factors precipitating stroke, has important implications for management and prevention.

**Subgroups of Atrial Fibrillation Patients With High or Low Risk for Stroke**

Within the broad spectrum of patients with nonrheumatic AF, it is likely that high- or low-risk subgroups exist. Identification and risk stratification of these subgroups would clearly influence preventive efforts (Table 2). For example, if low-risk subgroups are given anticoagulants, the treatment could be worse than the disease. With few exceptions, however, these subgroups have not been convincingly identified.

Recent studies suggest that in younger patients (mean age 45 years), AF not associated with other cardiopulmonary disease carries a very low risk of embolism.3,6,30,33 These studies contrast with the findings of the Framingham Heart Study in which older, hypertensive patients were included. In thyrotoxic AF, embolism risk is highest in older patients with cardiac dilatation and congestive heart failure.33,34 It is thus reasonable to hypothesize that other cardiac factors or associated cerebrovascular disease contribute importantly to the risk of AF-associated stroke.

Cardiologic subgroups of AF patients at high risk of embolism are presently ill-defined. Although AF associated with congestive heart failure appears to carry a higher risk,1,3,6-31 uncertainty about the basis for diagnosis, the severity, and the degree of compensation of heart failure limit practical application of this observation. Embolic risk may also be great during the initial months following the onset of AF,36,37 and embolism is a well-known complication of electrical cardioversion of AF, suggesting that intermittency may signal high risk. However, intermittent (paroxysmal) AF in younger patients is associated with an embolic risk of only approximately 2.5%/yr,28,29,39 and most patients with stroke have AF that is chronic and apparently sustained.8,12,15,20,35

Echocardiographically-defined subsets of AF patients at high stroke risk are also not yet well-defined. Left ventricular dysfunction and segmental wall motion abnormalities have been associated with thromboembolic risk.40 However, studies relating left atrial diameter to stroke risk have yielded conflicting results.35,40-42 These studies have usually used single-dimension measurements from M-mode echocardiography. As the left atrium is a complex geometric structure, three-dimensional measurements of volume and transmural diastolic blood flow evaluated by Doppler techniques may more accurately predict thrombus development and embolic potential.

Nonrheumatic AF patients with a previous clinical stroke have a substantial risk of subsequent stroke, with a recurrence rate of 15–20% in the first year alone.3,15,43-45 It is unclear whether this high risk is limited to the initial months44 or persists

**TABLE 2. Risk Stratification: Atrial Fibrillation and Stroke**

<table>
<thead>
<tr>
<th>High risk (&gt;6%/yr)</th>
<th>Low risk (&lt;3%/yr)</th>
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<tbody>
<tr>
<td>Mitral stenosis</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Previous stroke</td>
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<tr>
<td>Prosthetic mitral cardiac valve</td>
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<tr>
<td><strong>Low risk (&lt;3%/yr)</strong></td>
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<tr>
<td>&quot;Lone&quot; atrial fibrillation, age &lt;60 yrs</td>
<td></td>
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<tr>
<td>Paroxysmal atrial fibrillation, age &lt;60 yrs</td>
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<tr>
<td><strong>Uncertain risk</strong></td>
<td></td>
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<tr>
<td>Recent-onset vs. chronic atrial fibrillation</td>
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</tr>
<tr>
<td>Intermittent vs. sustained atrial fibrillation, age &gt;60 yrs</td>
<td></td>
</tr>
<tr>
<td>Previous &quot;silent&quot;/asymptomatic stroke on computed tomography</td>
<td></td>
</tr>
<tr>
<td>Associated carotid artery disease</td>
<td></td>
</tr>
<tr>
<td>Underlying etiology of atrial fibrillation</td>
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<tr>
<td><strong>Echocardiographic features</strong></td>
<td></td>
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<tr>
<td>Mitral regurgitation</td>
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<tr>
<td>Left atrial size/volume</td>
<td></td>
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<tr>
<td>Ventricular function</td>
<td></td>
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<tr>
<td>Left atrial blood flow patterns</td>
<td></td>
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<tr>
<td>Left atrial thrombi (transesophageal echocardiography)</td>
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</tbody>
</table>

All atrial fibrillation does not carry identical stroke risk. This preliminary risk stratification is based on available data summarized in the text; application to clinical practice awaits further confirmation in most instances.
indefinitely. Whether CT-detected silent/asymptomatic strokes also define a population at high risk for future clinical stroke is unknown.

Optimal Preventive Therapy

Optimal therapy to prevent stroke and/or systemic embolism in AF has not been determined, with controversy linked to the uncertainties surrounding stroke mechanism and risk stratification as described. The conventional practice of many physicians is to withhold antithrombotic therapy until there is evidence of embolism, but the possibility of a devastating stroke as the initial manifestation of embolism makes this approach unsatisfactory. Prophylactic anticoagulation has been advocated, based on its efficacy in embolism reduction in patients with rheumatic AF and with prosthetic cardiac valves. The dangers of chronic anticoagulation in elderly, often hypertensive AF patients may be considerable. In patients given conventional anticoagulation therapy, brain hemorrhage may occur in 1%/yr (eightfold increased risk) and major non-central nervous system hemorrhage in 3%/yr. Less intensive anticoagulation (prolongation of the rabbit brain prothrombin time to 1.5 times control) may be associated with fewer bleeding complications, but efficacy in stroke prevention in this setting is not established.

In a recent retrospective study of 134 inpatients with nonrheumatic AF followed for a mean of 3.3 years, emboli occurred in 5.9%/yr among patients who were not given conventional levels of anticoagulants compared with 0.7%/yr among those treated with anticoagulants (the latter group experienced major hemorrhage at a rate of 2.1%/yr). However, potential selection bias in determining which patients were treated with anticoagulants seriously limits the extrapolation of these observations to patient care.

The use of platelet antiaggregation agents for stroke prophylaxis in AF patients has not been evaluated, so drug selection, dose, and efficacy are unknown. A recent clinical trial of aspirin in patients with primary cerebrovascular disease (not AF) suggests that 325 mg/day is as effective as higher doses for stroke prevention and is associated with fewer side effects. However, if most strokes are the result of stasis-induced atrial thrombi (similar to venous thrombi), aspirin might not be beneficial.

In summary, although the presence of AF identifies patients at increased risk of ischemic stroke, there are no clinical data determining how to prevent these strokes effectively and safely. In younger patients with "lone" or paroxysmal AF who appear to have a relatively low stroke risk, chronic anticoagulation is not warranted. For the remaining majority of AF patients, preventive therapy is entirely empiric. Low-intensity anticoagulation or platelet antiaggregation agents are sometimes advocated, although their safety and efficacy are not established at present. If reversion from AF to sinus rhythm is a high-risk period for some AF patients (suggested by studies of electrical cardioversion)
but unconfirmed by observations of spontaneous cardioversion in younger patients, attempts to restore sinus rhythm in the hope of minimizing the long-term risk of embolism should be undertaken with caution and with an appreciation of the likelihood of recurrent AF. In AF patients with initial stroke, evaluation of stroke mechanism will influence secondary preventive strategies. Anticoagulation is recommended only if a cardioembolic source is deemed probable and only if such therapy can be safely administered to the individual patient.

It is our hypothesis that emboli arising from the left atrium and its appendage underlie many of the more devastating and unheralded strokes in people with AF. We speculate that thromboembolism requires the presence of AF plus contributing, as yet ill-defined, cardiac factors. Stroke prevention in people with AF is an important problem affecting millions of people. Five ongoing treatment-efficacy trials are now underway to determine optimal antithrombotic prophylaxis and to define high-risk subgroups. We should have some much-needed answers soon.

References


KEY WORDS: atrial fibrillation • cerebral infarction • embolism
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Stroke. 1988;19:937-941
doi: 10.1161/01.STR.19.8.937

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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