Atrial Fibrillation and Stroke
Concepts and Controversies

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

In 1985, patients with nonvalvular atrial fibrillation (AF) first entered randomized clinical trials that tested antithrombotic therapies for stroke prevention.1-3 Since then, >12,000 AF patients have been included in 25 trials that involved >40 randomized treatment comparisons (Table 1). During this interval, we reviewed the pathogenesis and prevention of stroke in AF patients in 2 previous editorials in Stroke.4,5 Here, we offer commentary on selected concepts and controversies.

The prevalence of AF increases with age, affecting ∼5% of people at age 70 years. Although AF-associated stroke can occur at any age, it is predominantly a problem of the elderly. The median age of AF patients with stroke in population-based studies is ∼75 years; more than half are women. In people over age 75, AF is the most important single cause of ischemic stroke. This epidemiology is relevant when considering stroke prevention, because the risks of and ability to sustain preventive therapies are special problems for the very elderly.

Left Atrial Appendage Thrombi

The left atrial appendage is a unique substrate for stroke. It is an elongated cul-de-sac lined with endothelium, a remnant of the embryonic atrium, trabeculated by pectinate muscles (Figure 1). The contractility of the appendage is reduced in AF, but the degree varies widely and is an important determinant of stasis and thrombus formation. In AF patients, atrial thrombi almost always originate in the appendage, rather than in the smooth-walled atrium proper, and are not reliably detected with transthoracic echocardiography. Transesophageal echocardiography is much more sensitive for the detection of appendage thrombi in AF patients, but the complex structure is usually multilobed, projecting in unpredictable planes. This, coupled with the minute size of clinically important thrombi (2 to 3 mm), makes the exclusion of small thrombi problematic.6 Transesophageal echocardiography reveals left atrial appendage thrombi in ∼10% of patients with nonvalvular AF and in 20% to 40% of AF patients with recent thromboembolism.

Stasis is fundamental to the formation of atrial appendage thrombi in AF.7 Endothelial lesions in the appendage have not been found, and systemic prothrombotic diatheses that contribute to thrombus formation have been suggested but not convincingly identified.8 Hormone replacement therapy was an independent predictor of stroke risk in AF patients in 1 study, supporting a potential role for a prothrombotic state.9 Appendage thrombi resemble those formed in the venous system; it is unclear whether they usually begin as free-floating clots in the appendage cavities and then attach to the walls or originate on the endothelial surface. It seems likely that some emboli from the appendage never adhere, and the lack of visualization of appendage thrombi on transesophageal echocardiography after stroke does not exclude the appendage as the embolic source.

Thrombi in AF patients have been strongly and consistently linked to reduced blood flow velocities in the left atrial appendage, confirming the role of stasis in their genesis.7 Appendix flow velocities range over a wide continuum in AF and are determined by the strength of the uncoordinated appendage contractions, passive emptying during left ventricular diastole (influenced by ventricular relaxation/diastolic properties), and atrial pressure. Flow velocities are only 1 component and hence an incomplete gauge of stasis, to which duration and volume of flow also contribute; the presence of spontaneous echodensities in the appendage may be a better overall indicator of stasis. Clinical risk factors for cardioembolic stroke in AF patients can generally be related to increased stasis in the left atrial appendage. Advancing age is associated with decreased appendage contractility and reduced flow velocity. Hypertension, the most prevalent stroke risk factor in AF patients, leads to atrial enlargement and appendage stasis,10 probably mediated by ventricular diastolic dysfunction.

Many questions remain about the formation and embolism of left atrial appendage thrombi and, consequently, about the pathogenesis of AF-associated stroke. Aortic arch plaque, widened pulse pressure, and elevated systolic blood pressure are associated with reduced appendage flow velocity; this surprising association of aortic disease and its manifestations with appendage stasis has not been adequately explained and is a crucial missing link in the understanding of stroke mechanisms in AF. Elderly women with AF appear to have
more strokes than elderly men, when matched for other risk factors, and this is not accounted for by transesophageal echocardiographic markers of stasis. It is unclear whether sustained control of hypertension reverses the left atrial appendage stasis that leads to thrombus formation; in the elderly, ventricular diastolic abnormalities from hypertension do not always resolve with antihypertensive treatment. Embolism even in patients with chronic, sustained AF is intermittent, separated by days or years, suggesting that the formation of appendage thrombi occurs intermittently. In short, the formation of left atrial appendage thrombi in AF is influenced by several hemodynamic factors that promote stasis, each of which can fluctuate over time, and perhaps also by mild prothrombotic hematological perturbations that favor thrombosis, as yet incompletely defined.

Although embolism of left atrial appendage thrombi accounts for most strokes in AF patients, and particularly the larger and more disabling strokes, some brain infarcts in these typically elderly, hypertensive patients are due to other mechanisms. Based on the best available clinical estimates, about two thirds of strokes in AF patients are due to atrial thrombi. This fraction varies according to the distribution of additional risk factors and antithrombotic therapy; high-risk AF patients have a particularly high proportion of cardioembolic strokes. Overall, ≈10% of all ischemic strokes in population-based cohorts are due to embolism of left atrial appendage thrombi in AF patients (Figure 2).

**Clinical Trials of Antithrombotic Therapies**

The results of 18 randomized trials have revolutionized the management of AF patients. These trials have focused on comparisons of oral vitamin K antagonists and aspirin in various doses with placebo, with each other, and with their combination (Table 1). Some trials were restricted to high-risk AF patients, others involved those at a low inherent risk, and still others were limited to participants aged 75 or older. Results from 10 146 participants tell a reasonably consistent story: adjusted-dose warfarin is highly

<table>
<thead>
<tr>
<th>Year Published</th>
<th>n</th>
<th>Interventions</th>
</tr>
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<tbody>
<tr>
<td>Large published trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copenhagen AF, Aspirin, Anticoagulation I (AFASAK I)</td>
<td>1989</td>
<td>1007</td>
</tr>
<tr>
<td>Copenhagen AF, Aspirin, Anticoagulation II (AFASAK II)</td>
<td>1998</td>
<td>677</td>
</tr>
<tr>
<td>Stroke Prevention in AF I (SPAF I)</td>
<td>1991</td>
<td>1330</td>
</tr>
<tr>
<td>Stroke Prevention in AF II (SPAF II)</td>
<td>1994</td>
<td>1100</td>
</tr>
<tr>
<td>Stroke Prevention in AF III (SPAF III)</td>
<td>1996</td>
<td>1044</td>
</tr>
<tr>
<td>Boston Area Anticoagulation Trial for AF (BAATAF)</td>
<td>1990</td>
<td>420</td>
</tr>
<tr>
<td>Canadian AF Anticoagulation (CAFA)</td>
<td>1991</td>
<td>378</td>
</tr>
<tr>
<td>Stroke Prevention In Nonrheumatic AF (SPINAF)</td>
<td>1992</td>
<td>571</td>
</tr>
<tr>
<td>European AF Trial (EAF)</td>
<td>1993</td>
<td>1007</td>
</tr>
<tr>
<td>Studio Italiano Fibrillazione Atriale (SIFA)</td>
<td>1997</td>
<td>916</td>
</tr>
<tr>
<td>Minidose Warfarin in Nonrheumatic AF</td>
<td>1998</td>
<td>303</td>
</tr>
<tr>
<td>Prevention of Arterial Thromboembolism in AF (PATAF)</td>
<td>1999</td>
<td>729</td>
</tr>
</tbody>
</table>

Small or pilot trials

Harenberg et al. | 1993 | 75 | LMW-heparin, no Rx |
Low-dose Aspirin, Stroke, AF (LASAF) | 1999 | 285 | ASA (2 doses), PLA |
Japanese Nonvalvular AF Embolism Secondary Prevention | 2000 | 115 | AC (2 levels) |
Fluindione Fibrillation Auriculaire Aspirin Contraste Spontané (FFACS) | 2000 | 157 | AC, AC+ASA |

Subgroups with AF in other trials

European Stroke Prevention Study II (ESPS II) | 1997 | 429 | ASA+dipyridamole, PLA |
United Kingdom TIA (UK-TIA) | 1999 | 49 | ASA (2 doses), PLA |

Ongoing or unpublished trials

Swedish AF Trial (SAFT) | ... | ~500 | AC+ASA, PLA |
Birmingham AF Treatment in the Aged (BAFTA) | ... | (1240) | AC, ASA |
Athens | ... | 45 | AC (2 levels), PLA |
Stroke Prevention Using Oral Thrombin Inhibition in AF (SPORTIF) II | ... | 257 | AC, thrombin inhibitor |
Stroke Prevention Using Oral Thrombin Inhibition in AF (SPORTIF) III/V | ... | (6000) | AC, thrombin inhibitor |
Japan AF Stroke Prevention Trial (JAST) | ... | (1000) | ASA, no Rx |
Stroke Prevention in Atrial Fibrillation among Chinese | ... | (200) | AC, clopidogrel |

AF indicates atrial fibrillation; n, number of participants; AC, oral vitamin K inhibitor anticoagulant; ASA, aspirin; LMW, low-molecular-weight; PLA, placebo; Rx, antithrombotic therapy; parentheses, anticipated recruitment in ongoing trials.

**TABLE 1. Randomized Trials of Antithrombotic Therapy in Atrial Fibrillation**

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efficacious (60% stroke reduction), aspirin is modestly efficacious (20% reduction), warfarin is much more efficacious than aspirin (40% reduction), and low-intensity warfarin (INRs <1.5) alone or combined with aspirin offers minimal protection (Table 2). Other randomized comparisons of antithrombotic agents (including dipyridamole) have involved too few patients to be conclusive. Recent surveys of warfarin use in AF patients from clinical practice reveal that the striking efficacy and the modest increases in bleeding are comparable to those observed in the clinical trials. Nevertheless, antithrombotic regimens that are more efficacious than aspirin and easier to administer than adjusted-dose warfarin are needed.

The effect of antithrombotic therapy varies according to the ischemic stroke mechanism in AF patients. Aspirin reduces noncardioembolic strokes more than cardioembolic strokes in AF patients, whereas adjusted-dose warfarin is much more efficacious than aspirin for the prevention of cardioembolic strokes.21,22 Cardioembolic strokes in AF patients are particularly disabling and frequent among AF patients at high risk for stroke. Warfarin reduces cardioembolic stroke in AF patients by ≈85% during therapeutic anticoagulation, whereas the effect of aspirin on this stroke subtype is probably closer to 15%.21 Not surprisingly, then, the reduction in disabling stroke (most cardioembolic) with aspirin in a meta-analysis of 3 clinical trials was only 13%.11

The differential effect of antithrombotic therapies according to stroke mechanism in AF explains discrepant results from clinical trials and is important to consider when choosing antithrombotic prophylaxis for individual patients. For example, lower-risk AF patients have a lesser proportion of cardioembolic stroke, and the reduction in stroke with warfarin compared with aspirin is smaller, in both relative and absolute terms (Figure 3). Hence, although warfarin is clearly more efficacious than aspirin for the prevention of stroke in all AF patients, the magnitude of benefit varies according to the inherent stroke risk, explained by differing proportions of stroke subtypes. AF patients with the highest risk of stroke have the largest proportion of cardioembolic strokes and the
largest relative and absolute reductions in stroke by warfarin compared with aspirin.

Intracerebral hemorrhage is the most devastating complication of anticoagulation. Regarding intracerebral bleeding, AF patients appear to tolerate anticoagulation better than do patients with intrinsic cerebrovascular disease.\(^{23}\) In the 6 most recent clinical trials that tested the use of warfarin in AF patients, 1486 warfarin-treated participants had a mean age of 72 years, a mean achieved INR estimated as 2.5 during an average follow-up of 1.4 years, and an observed rate of intracerebral hemorrhage of 0.5%/y.\(^{13–16,19,20}\) The only clinical trial that involved AF patients and reported a substantially higher rate of intracerebral bleeding associated with warfarin (1.8%/y) included participants with a mean age of 80 years and an upper limit of anticoagulation intensity equivalent to an INR of 4.5, monitored with prothrombin time ratios rather than the more accurate INRs.\(^{17}\)

**Optimal Intensity of Anticoagulation in AF**

Optimal protection against ischemic stroke for AF patients is probably achieved with INRs between 2 and 3,\(^{24}\) with minimal protection when INRs fall below 1.6 (Figure 4). The use of lower-intensity anticoagulation makes warfarin safer and better tolerated, particularly for the elderly, who are at special risk of both major bleeding and the minor bleeding that leads to the discontinuation of anticoagulation. The optimal intensity that balances risk with benefit remains controversial and probably is not the same for all AF patients but rather depends on the estimated risks of cardioembolic stroke and of major bleeding during anticoagulation.\(^{20,24,25}\) There is no “safe” INR prolongation that does not increase intracerebral bleeding to some degree; most warfarin-associated intracerebral hemorrhages in recent reports occurred when the INR was within the therapeutic range.\(^{26,27}\) A target of 2.5 (target range 2 to 3) seems appropriate for younger AF patients and for secondary prevention at any age, whereas an INR of 2.0 (target range 1.6 to 2.5) may be sensible for primary prevention in AF patients over age 75. There may be ethnic influences.\(^{20,28}\) Additional trials that focus on AF patients over age 75 are warranted to better define the risks and benefits of antithrombotic therapies and

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**TABLE 2. Antithrombotic Therapies for Stroke Prevention in Atrial Fibrillation: Meta-Analysis of Randomized Trials**

<table>
<thead>
<tr>
<th></th>
<th>No. of Trials</th>
<th>No. of Participants</th>
<th>Risk Reduction (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted-dose warfarin vs placebo</td>
<td>6</td>
<td>2900</td>
<td>62% (48–72%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin vs placebo</td>
<td>6</td>
<td>3119</td>
<td>22% (2–38%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Antiplatelet vs placebo*</td>
<td>6</td>
<td>3337</td>
<td>24% (7–39%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted-dose warfarin vs aspirin</td>
<td>5</td>
<td>2837</td>
<td>36% (14–52%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Adjusted-dose warfarin vs low-dose warfarin†</td>
<td>3</td>
<td>893</td>
<td>38% (–20–68%)</td>
<td>NS</td>
</tr>
<tr>
<td>Aspirin vs low-dose warfarin</td>
<td>2</td>
<td>934</td>
<td>15% (–42–49%)</td>
<td>NS</td>
</tr>
<tr>
<td>Adjusted-dose warfarin vs low-dose warfarin aspirin†</td>
<td>2</td>
<td>1385</td>
<td>‡</td>
<td>...</td>
</tr>
</tbody>
</table>

Adapted from Hart et al.\(^{11}\) Stroke includes both ischemic and hemorrhagic stroke.

*Includes 218 participants administered dipyridamole alone or combined with aspirin.

†Estimated mean achieved INRs of 2.6 vs 1.2 from pooling of the 3 trials.\(^{15,16,19}\) An additional small trial compared 2 different intensities of adjusted-dose warfarin.\(^{20}\)

‡Statistically significant heterogeneity of the results (73% risk reduction in SPAF III high-risk AF patients\(^{13}\) vs 0% in AFASAK II low-risk AF patients\(^{15}\) precluded meta-analysis and is likely explained by stroke subtypes; see text).

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**Figure 3.** Benefit of anticoagulation instead of aspirin according to the inherent rate of stroke in 6 randomized trials. The y axis shows the number of strokes prevented yearly per 100 patients treated with warfarin instead of aspirin. The largest reductions are seen in AF patients at highest risk (EAFT, SPAF III) due to both a larger relative risk reduction and the higher intrinsic stroke rate. See Table 1 for trial eponyms.

**Figure 4.** Relationship between anticoagulation intensity and protection from ischemic stroke in patients with AF. Achieving INRs equally distributed in the range of 1.6 to 2.5 is predicted to provide 90% of the protection of INRs between 2.0 and 3.0 for primary prevention of stroke in patients with nonvalvular AF. Data from Hylek et al\(^{24}\) and the Stroke Prevention in Atrial Fibrillation Investigators\(^{13}\) (reprinted with permission of the American College of Physicians).
TABLE 3. Predictors of Ischemic Stroke in Nonvalvular Atrial Fibrillation

<table>
<thead>
<tr>
<th>Consistent independent predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age*</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
</tr>
<tr>
<td>Left ventricular dysfunction†</td>
</tr>
<tr>
<td>Possible independent predictors</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Systolic blood pressure &gt; 160 mm Hg</td>
</tr>
<tr>
<td>Women over age 75</td>
</tr>
<tr>
<td>Postmenopausal hormone replacement therapy</td>
</tr>
<tr>
<td>Regular alcohol use (&gt;14 drinks/2 wk) (decreased risk)</td>
</tr>
<tr>
<td>Coronary artery disease/prior myocardial infarction</td>
</tr>
<tr>
<td>Postoperative status</td>
</tr>
<tr>
<td>Mitral regurgitation (decreased risk)</td>
</tr>
<tr>
<td>Transesophageal echocardiography: appendage thrombi, spontaneous dense echocontrast, reduced appendage flow velocity‡</td>
</tr>
<tr>
<td>Not independently predictive</td>
</tr>
<tr>
<td>Left atrial diameter</td>
</tr>
<tr>
<td>Intermittency (ie, paroxysmal)</td>
</tr>
</tbody>
</table>

From multivariate analyses of prospectively evaluated cohorts or case-control studies, adapted from Hart and Halperin. 29

*Some studies dichotomized at age >65 years while others at age >75 years to confer high risk.
†Clinical congestive heart failure or systolic dysfunction by echocardiography.
‡While predictive, it remains unclear whether independently predictive when other clinical risk factors are considered.

the long-term tolerability of different intensities of anticoagulation.

Stratification of Stroke Risk

Warfarin reduces stroke for all AF patients, but the magnitude of reduction is small for those with low inherent risks of stroke. The stroke rate varies >20-fold among AF patients, from 0.5%/y for young (<65 years old) AF patients without organic heart disease or hypertension (ie, “lone” AF) to 12%/y for AF patients with prior stroke or TIA. Clinical features independently associated with high stroke rates in AF patients have been defined (Table 3) and integrated into several risk stratification schemes. 29,30 Although available schemes have much in common, there are important differences that bear on individual patient management. For example, by some schemes, all AF patients age 75 or older are predicted to be high risk for stroke, whereas other schemes classify up to one third of AF patients of this age as low risk.30

Surprisingly, many elderly patients with recurrent intermittent (ie, paroxysmal) AF have substantial rates of stroke, predicted by similar risk factors that apply to those with sustained AF.31,32 Although it seems likely that transesophageal echocardiographic measures of stasis (ie, appendage ejection fraction and flow velocity, dense spontaneous echo contrast) are independent predictors of embolic risk, the role of transesophageal echocardiography has yet to be adequately defined and integrated into clinical risk stratification.33,34

AF patients with relatively low rates of stroke can be identified.30 In a large prospective study, the Stroke Prevention in Atrial Fibrillation Investigators identified AF patients with a low risk for stroke during treatment with aspirin through the use of specific clinical criteria.35 During a 2-year mean follow-up of 892 AF patients, the observed stroke rates were 2.0%/y for stroke of any severity and 0.8%/y for disabling stroke (Rankin level 2 or worse). A major research imperative, in our view, is additional study of stratification of stroke risk in AF patients, validating application outside of clinical trials. Reliable risk stratification to identify AF patients who benefit most and least from lifelong anticoagulation is an important precursor to the selection of antithrombotic prophylaxis.

Underuse of Anticoagulation in AF

Recent studies have documented the increasing use of warfarin in AF patients: about half of AF patients in North American reports are anticoagulated.36,37 In our view, warfarin is not so much underused as it is poorly used: those at high risk are often not given warfarin in favor of younger, low-risk AF patients who are easier and safer to anticoagulate.38 At least half of AF patients with high risks of stroke who would stand to benefit substantially from anticoagulation are not treated, and this is especially so for those over age 75. Patient values and preferences regarding anticoagulation have not received sufficient attention; patient-perceived thresholds of benefit for choosing anticoagulation vary widely and may not coincide with those in physician-generated guidelines.39

The appropriate use of anticoagulation for the >2 million Americans with nonvalvular AF should consider the individual patient’s absolute risk reduction afforded by warfarin (derived from stroke risk stratification), the estimated bleeding risk, and the patient’s preference after an explanation of the benefits, risks and disutility of anticoagulation therapy.

Our initial commentary in 1988 stated that “while the importance of AF-associated stroke is not in doubt, preventive strategies...remain empiric,” citing major uncertainties about mechanisms of AF-associated stroke, stratification of stroke risk, and optimal antithrombotic prophylaxis.4 We have come very far since then. Evidence-based effective prevention strategies tailored to the individual patient’s risks, benefits, and preferences are now available for most AF patients. Results of randomized trials and high-quality observational and case-control studies have prompted a revolution in antithrombotic management, saving many tens of thousands of persons each year from having a stroke.

References


Key Words: anticoagulants ▪ aspirin ▪ atrial fibrillation ▪ cerebral embolism ▪ cerebrovascular disorders ▪ stroke
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