Atrial Fibrillation and Stroke
Revisiting the Dilemmas

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Atrial fibrillation is a common cardiac dysrhythmia of the elderly, and stroke is its most devastating complication. Six years ago in Stroke, we discussed controversies surrounding the prevention of stroke in patients with nonvalvular atrial fibrillation (AF). Since then, six recent randomized trials have changed the approach to stroke prevention for AF patients. Above all else, the randomized trials have confirmed the magnitude of the problem: AF raises the risk of stroke in more than 1.5 million Americans to a degree approaching that which follows transient ischemic attack (TIA). The rate of ischemic stroke among people with AF averages 5%/y, approximately six times that of people without AF. Additionally, considering TIAs (often causing radiographic evidence of brain infarction) and clinically occult "silent" strokes detected radiographically, the rate of brain ischemia accompanying nonvalvular AF exceeds 7%/y.

The absolute rate of stroke in AF patients varies importantly with coexistent cardiovascular disease, and therefore stratification of AF patients into those at high and low risk of thromboembolism has become a crucial determinant of optimal antithrombotic prophylaxis. AF increases in prevalence and risk with age, and more than half of AF-associated strokes occur in patients aged older than 75 years. Special consideration of these older patients is therefore a critical aspect of an effective stroke prevention strategy.

Most ischemic strokes associated with AF are probably due to embolism of stasis-induced thrombi forming in the left atrium and particularly its appendage. Transesophageal echocardiography shows left atrial thrombi more frequently in AF patients with ischemic stroke than in AF patients without stroke. Nevertheless, perhaps 25% of AF-associated strokes are due to intrinsic cerebrovascular diseases, other cardiac sources of embolism, or atheromatous pathology in the proximal aorta. Approximately half of elderly AF patients have chronic hypertension (a major risk factor for cerebrovascular disease), and approximately 12% of elderly AF patients harbor cervical carotid artery stenosis. But the frequency of carotid stenosis is not substantially greater in AF patients with stroke, and carotid stenosis is a minor contributing factor to the increased stroke risk associated with AF. Although atherosclerotic carotid lesions may contribute to stroke risk through thromboembolic mechanisms unrelated to the severity of luminal stenosis, the available data do not support routine screening of AF patients without symptoms of brain ischemia for cervical carotid stenosis.

Subgroups of AF Patients With High and Low Rates of Stroke

Identification of subpopulations with relatively high or low absolute rates of stroke determines which AF patients gain the greatest benefit from long-term anticoagulation with warfarin, offsetting its risk, expense, and inconvenience. Because clinical classification of ischemic strokes according to etiologic subtypes is imperfect and not adequately validated, risk stratification is presently based on combined analysis of all ischemic strokes. Schemes for stratification of risk in AF patients have been extensively pursued, using clinical and echocardiographic parameters. Two prospective studies encompass sufficient numbers of patients and stroke events for meaningful multivariate analysis, and these provide the most reliable basis for risk stratification available. The differences in the findings (involving age and congestive heart failure) are not substantially conflicting, as clinical variables frequently overlap (heart failure, hypertension, and diabetes are all more frequent in older patients). Intermittent (or paroxysmal) AF does not appear to be an independent predictor of thromboembolic risk. Other studies support the notion that stroke in AF patients is directly related to coexistent heart disease, hypertension, age, and perhaps female sex. Still missing from these stratification models are firm links to stroke mechanism and cohesive pathophysiological correlations.

Transesophageal echocardiography offers better visualization of the left atrium and its appendage than precordial echocardiography and more often identifies atrial thrombi and spontaneous echogenic contrast ("smoke" probably indicative of stasis) in AF patients...
with thromboembolism than in those without thromboembolism.16 The sensitivity and specificity of this technique for detection of small thrombi in the atrial appendage are unclear. The predictive value of these findings for subsequent stroke has yet to be validated by adequate clinical studies, and available data are insufficient to justify routine transesophageal echocardiography to stratify thromboembolic potential in our view. A large multicenter clinical trial (Stroke Prevention in Atrial Fibrillation [SPAF] III) is evaluating the role of transesophageal echocardiography in AF.28

Antithrombotic Therapy for Stroke Prevention

Anticoagulation with the oral vitamin K antagonist warfarin is highly effective for reducing ischemic stroke in AF patients. Five recent randomized clinical trials using prothrombin time international normalized ratio (INR) ranges between approximately 1.8 and 4.2 showed a mean reduction in ischemic stroke of nearly 70% in patients assigned anticoagulation (Fig 1); on-therapy analysis indicated an even greater benefit.2 The incremental risk of severe bleeding was less than 1%/y among anticoagulated patients, a selected group followed up carefully according to clinical trial protocols.

Whether such low bleeding risks can be achieved in general clinical practice is an important, unresolved issue.29 Safe anticoagulation monitoring requires use of the INR, which corrects for variable thromboplastin sensitivities. Low-intensity anticoagulation (INR range, 2 to 3) clearly confers benefit,2,30 and there is no doubt that warfarin is highly effective in subgroups of AF patients who carry a high inherent risk of thromboembolism (Table 1).2,29,31

The safety and tolerability of long-term anticoagulation to conventional levels has not been completely defined among patients older than 75 years, who account for more than half of AF-associated strokes. All but one of the placebo-controlled anticoagulation trials enrolled AF patients who were, on average, substantially younger.2 The single placebo-controlled trial involving AF patients with a mean age of 75 years reported an overall withdrawal rate from anticoagulation of 38% after 1 year, and the attrition rate among the oldest patients was probably even higher.32 The risk of major hemorrhage during anticoagulation (INR range, 2.0 to 4.5; mean, 2.7) in another trial was substantially greater among AF patients older than 75 years than among younger patients anticoagulated to similar intensities.31 Although the elderly have a greater risk of AF-associated stroke, the benefit of anticoagulation is offset somewhat by this greater toxicity, and the

| TABLE 1. Risk Stratification in Atrial Fibrillation*: Independent Predictors of Thromboembolic Risk |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| SPAF-I Placebo19 | AFI Pooled Analysis2 | SPAF Echo Analysis11 |
| No. of patients | 568 | 1236 | 568 |
| No. of events | 46 | 81 | 46 |
| High-risk variables | Hx of hypertension | Hx of hypertension | Hx of hypertension |
| Prior stroke/TIA | Prior stroke/TIA | Prior stroke/TIA |
| Diabetes | Diabetes | Recent heart failure |
| Recent heart failure | Age >65 years | LA >2.5 cm² |
| Thromboembolic rate (95% CI) | | |
| Low-risk variables | 1.4%/y (0.05-3.7) | 1.0%/y (0.3-3.1) | 1.0%/y (0.2-4.0) |
| High-risk variables | >7%/y | >5%/y | >6%/y |
| Percentage at low risk | 38 | 15 | 26 |
| SPAF indicates Stroke Prevention in Atrial Fibrillation study; AFI, Atrial Fibrillation Investigators; CI, confidence interval; Hx, history; TIA, transient ischemic attack; LA, left atrial size by M-mode echocardiography; and LV dysfunction, left ventricular dysfunction by two-dimensional echocardiography. |
| *Prospectively acquired data analyzed by multivariable techniques. The SPAF-I placebo data set10 is included in the pooled analysis of clinical trials by the AFI.2 |

![](image-url)
inability of the very elderly to sustain long-term anticoagulation is a noteworthy finding of several trials.31,32

Intracerebral hemorrhage is the most feared and most often fatal complication of warfarin in elderly patients, occurring in 0.3%/y of AF patients given warfarin in recent clinical trials.2 Predictors and precipitants of warfarin-related intracerebral bleeding have not been consistently identified in the literature. In one study the rate of intracerebral bleeding was 1.5%/y in AF patients with a mean age of 80 years and with a mean INR of 2.6, and advanced age was predictive of its occurrence.31 The rate of intracerebral hemorrhage in AF patients older than 75 years was substantially lower in combined analysis of other clinical trials, in which anticoagulation intensity was generally lower.2,30 Although it is uncertain whether the intensity of anticoagulation is related to intracerebral bleeding,33 a lower intensity of anticoagulation (INR approximately 2) may be sensible in older AF patients until ongoing trials addressing alternatives are completed.

The efficacy of aspirin, a platelet inhibitory agent, for stroke prevention in AF patients is less clear and more controversial.2,24 The effect of aspirin in doses between 75 and 325 mg/d has been assessed in three placebo-controlled trials with a statistically significant pooled risk reduction of approximately 25% (range, 14% to 44%) in aspirin-treated patients.34,35 Aspirin was significantly less effective than warfarin in two of these trials analyzed along intention-to-treat paradigms34,35 and according to on-treatment (efficacy) analysis of the third (Fig 2).31 There is no compelling evidence that a specific dose of aspirin between 75 and 325 mg/d confers more or less benefit. Aspirin thus appears active for preventing stroke in AF patients but substantially less effective than warfarin. Aspirin is inexpensive, easily administered, and produces less bleeding toxicity than anticoagulation in elderly patients.31

Selecting Optimal Antithrombotic Therapy to Prevent Stroke

Platelet inhibitors and anticoagulants may influence cardioembolic and noncardioembolic sources of stroke differently.17 Aspirin may have a greater prophylactic impact on noncardioembolic mechanisms than on strokes of presumed cardioembolic origin in AF patients.17 Aspirin is particularly effective in younger AF patients with a history of diastolic hypertension.36 The efficacy of platelet inhibitors for reducing venous thrombosis in the lower extremities (a situation in which stasis is a major contributing factor) has been suggested by a recent meta-analysis.37 Most AF-related stroke, particularly in elderly women, seems attributable to cardiogenic embolism, and this type of stroke is more effectively prevented by anticoagulation.36 AF patients with high rates of stroke during aspirin therapy are typically older women and patients with impaired left ventricular function, where cardiogenic embolism is the predominant mechanism of cerebral infarction.36,39 These pathophysiological constructs nevertheless require further study before they can be confidently applied to patient management.

The risk of thromboembolism in AF patients aged 75 years or younger given aspirin is relatively low, below 3%/y.31,32 Among these younger AF patients, those prospectively identified as at low risk based on clinical criteria had an extremely low rate of thromboembolism averaging 0.5%/y (95% confidence interval, 0.1%/y to 1.9%/y; Table 2) when treated with aspirin.38 Pending the results of ongoing confirmatory studies, it is our view that low-risk AF patients can be treated with aspirin 325 mg/d to prevent stroke, but they must be observed carefully for the development of risk factors for thromboembolism (including systolic hypertension greater than 160 mm Hg, episodes of minor cerebral ischemia, and changes in ventricular function).31,39 High-risk patients deemed safe candidates for anticoagulation should be treated with warfarin. For high-risk AF patients aged 75 years or younger, an INR range of 2.0 to 3.0 is effective and fairly safe; for those aged older than 75 years, a lower target INR of 2.0 seems more sensible. AF patients who cannot safely take warfarin should be given aspirin; the value of other antiplatelet agents has not been assessed in this situation.41

Secondary Prevention of Stroke in AF Patients

Conventional wisdom holds that most ischemic strokes in AF patients are large and disabling, but it is
now clear that minor stroke and TIA are frequent accompaniments of AF.2 AF-related stroke carries a particularly high mortality rate, related to advanced patient age and associated heart disease.18,42 Previously unrecognized AF discovered in a patient with acute stroke might be a consequence of brain infarction mediated by other processes.43 Recent studies indicate that the risk of early recurrent stroke (within 2 weeks) is lower in AF patients than thought a decade ago.18,43 Initiating oral anticoagulation within a few days after submassive infarcts is a reasonable practice; delaying warfarin for 1 week or more in AF patients with large infarcts may also be prudent to avoid accentuating secondary brain hemorrhage. Prophylaxis against deep venous thrombosis with low-dose, subcutaneous heparin in those with lower limb paresis is safe.18

Once ischemic stroke has occurred in a patient with AF, diagnostic evaluation is aimed at identifying those who require chronic anticoagulation for secondary prevention (most patients) or carotid endarterectomy (few patients). Carotid sonography discloses ipsilateral cervical arterial stenosis in approximately 15% of AF patients with stroke.17,18 Precordial echocardiography is seldom helpful in defining stroke mechanism because left atrial thrombi are not reliably detected. Whether or not carotid artery stenosis or atrial thrombi are identified by ultrasound studies, anticoagulation is warranted for secondary prevention of stroke or TIA in AF patients whenever it can be used safely, because the rate of recurrent stroke is high, exceeding 10%/y without treatment.18 A large randomized trial found warfarin (INR range, 2.5 to 4.0) highly effective, superior to aspirin, and relatively safe.18 In AF patients with brain ischemia harboring ipsilateral carotid artery stenosis, carotid endarterectomy followed by chronic anticoagulation should be considered.

Restoration of Sinus Rhythm to Prevent Stroke

There is no solid clinical evidence that cardioversion followed by prolonged maintenance of sinus rhythm reduces thromboembolism in AF patients.44,45 However, based on the pathophysiological concept that most AF-associated strokes are due to embolism of stasis-induced thrombi from the left atrial appendage, resumption of atrial contractility should logically reduce thromboembolic risk. Atrial enlargement and some perturbation of flow dynamics may persist chronically even after successful cardioversion. Further, AF often recurs after iatrogenic cardioversion, and thromboembolism before recognition of recurrence is a potential problem. Because of these uncertainties, it is unclear whether efforts to restore and maintain sinus rhythm for the purpose of preventing stroke are worthwhile. This choice is influenced by the toxicity of anticoagulation versus antiarrhythmic therapy. Quinidine, the most commonly used antiarrhythmic agent to suppress AF, has been possibly associated with increased mortality,35,47 and other antiarrhythmic agents may be preferred.44 Clinical studies of this crucial issue are needed.45 At present, the decision to restore sinus rhythm to prevent stroke is complex, fraught with uncertainties, and must consider the likelihood of long-term suppression of AF and the relative toxicity of antithrombotic versus antiarrhythmic drugs.

Persisting Management Dilemmas

The volume of sound scientific data that have recently emerged regarding prevention of stroke in AF patients represents a considerable research achievement. We know now that the majority of strokes in AF patients can be prevented, more reliably, in fact, than almost any other common type of brain ischemia. AF can today be seen not only as a marker of a patient’s risk of stroke but also as a valuable opportunity for effective clinical intervention. Even so, many issues remain unresolved. Lower-intensity regimens of anticoagulation, which should cause less bleeding, and combinations of anticoagulants plus platelet inhibitory agents are under study to establish efficacy. These efforts are particularly important for AF patients aged older than 75 years, for whom conventional anticoagulation may carry substantial toxicity.31 Better characterization of the role of aspirin and of low-risk patients awaits clarification of stroke mechanisms in AF. The links between risk stratification schemes, pathophysiology, and stroke mechanisms have not been fully elucidated. The value of transesophageal echocardiography for risk stratification and for evaluation of acute stroke patients requires further study.46 Whether perturbations in intrinsic hemostatic balance cause or contribute to stroke in AF is unknown. Ongoing clinical trials38 may yet answer these questions during this “decade of the brain.”

References


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