

Atrial Fibrillation and Thromboembolism: A Decade of Progress in Stroke Prevention

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Atrial fibrillation is associated with a sixfold increased risk for stroke. More than a dozen published randomized trials of anticoagulants or antiplatelet agents for stroke prevention provide solid evidence on which to base antithrombotic prophylaxis. Adjusted-dose warfarin reduces risk for stroke by about 60% compared with placebo, aspirin reduces this risk (primarily for nondisabling stroke) by about 20% compared with placebo, and warfarin reduces it by about 40% compared with aspirin. Warfarin provides maximal protection against stroke at international normalized ratios of 2.0 to 3.0. Risk stratification of patients with atrial fibrillation identifies those who potentially benefit most or least from anticoagulation; this is important because a substantial percentage of patients with atrial fibrillation have relatively low rates of stroke if they are given aspirin. Many elderly patients with recurrent intermittent atrial fibrillation experience high rates of stroke and benefit from anticoagulation. The value of precordial or transesophageal echocardiography in addition to clinical risk stratifiers for stratifying stroke risk is controversial. Altered hemostasis favoring thrombosis may contribute to formation of atrial appendage thrombus, but these conditions remain ill defined.

The past decade has brought unprecedented progress toward understanding thromboembolism in patients with atrial fibrillation and has changed the clinical perspective of a prevalent cardiac arrhythmia into an important opportunity for stroke prevention. Making the most of this promise calls for appreciation of the epidemiology of atrial fibrillation and the concept of risk specificity in the face of diverse therapeutic options.

By the late 1970s, nonvalvular atrial fibrillation was identified as an independent risk factor for stroke (1–4), and millions of people with this common cardiac dysrhythmia were designated as having substantial risk for cardiogenic embolism (5). One of every six strokes occurs in a patient with atrial fibrillation, and about 10% of all ischemic strokes are probably due to embolism of left atrial thrombi. In the past decade, randomized clinical trials assessed the efficacy of antithrombotic therapies for stroke prevention in patients with nonvalvular atrial fibrillation. Eighteen trials involving more than 10 000 participants with atrial fibrillation have compared anticoagulants and antiplatelet agents, alone and in combination, with placebo and with each other (6). The remarkable pace of development has revolutionized management of this long-neglected dysrhythmia and makes detection of atrial fibrillation an important opportunity for stroke prevention. We present recent advances, discuss controversies, and explore new ideas about stroke and its prevention in patients with nonvalvular atrial fibrillation. We searched the MEDLINE database using the key words *atrial fibrillation*, *thromboembolism*, *antithrombotic therapy*, *anticoagulation*, *stroke*, *warfarin*, and *aspirin*.

Antithrombotic Therapy for Stroke Prevention

Adjusted-dose warfarin is highly efficacious for prevention of stroke in patients with atrial fibrillation (**Table 1**). Meta-analysis of six randomized trials that considered all stroke (both ischemic and hemorrhagic) according to the intention-to-treat principle showed a relative risk reduction of 62% (95% CI, 48% to 72%) for adjusted-dose warfarin compared with placebo (6). This relative risk reduction was similar for both primary and secondary prevention and for both disabling and nondisabling strokes. According to on-treatment analysis (which excludes patients who were not taking warfarin at the time of stroke), the efficacy of warfarin for prevention of ischemic stroke exceeded 80%. Thus, adjusted-dose warfarin has the remarkable potential to reverse almost entirely the increased risk for cardioembolic stroke that accompanies atrial fibrillation.

Ann Intern Med. 1999;131:688-695.

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Anticoagulation increases the frequency and severity of major extracranial and intracranial hemorrhage; intensity of anticoagulation and patient age are the strongest, most consistent predictors of major bleeding (7–10). The benefit of anticoagulation was not substantially offset by major hemorrhage in the randomized trials, in which participants with a mean age of 69 years were carefully selected on the basis of absence of risk factors for bleeding and were managed according to strict clinical protocols. It is unclear whether the relatively low rates of major hemorrhage observed in clinical trials apply generally to patients with atrial fibrillation in clinical practice (whose mean age is about 75 years) (5, 11). Additional studies of the tolerability of anticoagulation in elderly patients with atrial fibrillation are needed.

The target intensity of anticoagulation involves a tenuous balance between prevention of ischemic stroke and accentuation of major bleeding. Achieving the lowest adequate intensity of anticoagulation is particularly important for elderly patients, who have higher risks for bleeding. Maximum protection against ischemic stroke in atrial fibrillation is probably achieved by maintaining the international normalized ratio (INR) between 2.0 and 3.0 (12–14). International normalized ratios between 1.6 and 2.5 are associated with substantial, if incomplete, efficacy, estimated to be 90% of that achieved with higher-intensity anticoagulation (15). Two randomized trials with target INRs between 1.4 and 2.8 (estimated mean achieved INR, 2.0 to 2.1) reported the largest relative risk reductions for ischemic stroke in patients with atrial fibrillation (16, 17). Preliminary results of a recent trial in which patients with atrial fibrillation and previous stroke were randomly assigned to target INR ranges of 2.2 to 3.5 compared with 1.5 to 2.1 found a greater rate of major hemorrhage with higher-intensity anticoagulation (18). For patients with nonvalvular atrial fibrillation, INRs from 1.6 to 3.0 are efficacious and relatively safe. For most patients younger than 75 years of age and for secondary prevention, we aim for an INR of 2.5 (target range, 2.0 to 3.0); for primary prevention in most older patients, we seek a lower target INR of 2.0 (target range, 1.6 to 2.5). In recent clinical trials, INRs achieved during follow-up were more often below than above the target range. Low-intensity anticoagulation requires special efforts to minimize the time spent below the target range (during which protection against stroke is sharply reduced).

Aspirin offers modest protection against stroke for patients with atrial fibrillation. Meta-analysis of six randomized trials showed a relative risk reduction for all stroke of 22% (CI, 2% to 38%) (6). The effect of aspirin on stroke in these trials was less

Table 1. Antithrombotic Therapies for Stroke Prevention in Atrial Fibrillation: Key Results of Meta-Analysis of 16 Randomized Trials*

Therapy	Trials	Participants	Relative Risk Reduction (95% CI)	
			<i>n</i>	%
Adjusted-dose warfarin compared with placebo	6	2900	62 (48 to 72)	
Aspirin compared with placebo	6	3119	22 (2 to 38)	
Adjusted-dose warfarin compared with aspirin	5	2837	36 (14 to 52)	
Adjusted-dose warfarin compared with low-dose warfarin	3	893	38 (–20 to 68)	
Aspirin compared with low-dose warfarin	2	934	15 (–42 to 49)	

* Adapted from Hart and colleagues (6). Stroke includes both ischemic and hemorrhagic stroke.

consistent than that of warfarin (6, 19). When analysis was restricted to disabling strokes, aspirin use was associated with a smaller relative risk reduction (13% [CI, –19% to 36%]) (6). Aspirin may be more efficacious for reducing noncardioembolic strokes than cardioembolic ischemic strokes in patients with atrial fibrillation (20), but cardioembolic strokes are, on average, more disabling than noncardioembolic strokes in atrial fibrillation (21). Noncardioembolic strokes make up a substantial portion of strokes in relatively low-risk patients with atrial fibrillation. The greater the risk for disabling cardioembolic stroke in patients with atrial fibrillation, the less protection aspirin affords (21).

Adjusted-dose warfarin is clearly more efficacious than aspirin for prevention of stroke in patients with atrial fibrillation, as suggested by indirect comparisons and by a 36% relative risk reduction (CI, 14% to 52%) seen in meta-analysis of five randomized trials (6). Because of differences in the proportions of cardioembolic and noncardioembolic events, this overall estimate may obscure important differences in relative risk reduction between patients with atrial fibrillation who have high risk for stroke and those who have low risk for stroke (21). Randomized trials involving high-risk patients with atrial fibrillation (stroke rate > 6% per year) show large relative risk reductions with adjusted-dose warfarin relative to aspirin (13, 22), whereas the relative risk reductions are consistently smaller in trials involving patients with atrial fibrillation who have lower stroke rates (23–25). Thus, warfarin may be most beneficial for patients with atrial fibrillation who are at higher intrinsic risk for thromboembolism and have a higher proportion of disabling cardioembolic strokes; this agent offers only modest reductions over aspirin in both the relative risk and absolute rates of stroke in patients with atrial fibrillation who are at low risk.

Combining low-dose warfarin (INR < 1.5) with aspirin adds little additional protection against stroke compared with aspirin alone in patients with atrial fibrillation (13, 23). Adding warfarin therapy to aspirin therapy at higher anticoagulation intensities may accentuate intracranial hemorrhage in elderly patients with atrial fibrillation (26). For patients with atrial fibrillation who sustain cardioembolic events while receiving low-intensity anticoagulation (INR < 2.5), we currently favor increasing the anticoagulation intensity up to a maximum target INR of 3.0 to 3.5 rather than routinely adding antiplatelet agents. The value of antiplatelet agents other than aspirin for prevention of stroke in atrial fibrillation remains to be determined (6).

Stroke Risk Stratification

Most patients with atrial fibrillation never experience a clinical stroke. The stroke rate varies more than 20-fold, from 0.5% per year (27, 28) for young patients without organic heart disease ("lone atrial fibrillation") to 12% per year for patients with atrial fibrillation who have had stroke (13, 22, 29). Hence, identification of risk factors for stroke in nonvalvular atrial fibrillation is important because it allows individualized antithrombotic prophylaxis to be given according to stroke risk. Numerous studies have examined risk factors for stroke in atrial fibrillation, and multivariate analyses reveal several consistent, independent predictors of ischemic stroke (Table 2) (17, 28–42).

Mechanisms linking these risk factors to ischemic stroke in atrial fibrillation are incompletely defined. The strong association between hypertension and stroke in atrial fibrillation is primarily mediated by

embolism originating as thrombus in the atrial appendage (44). Hypertension in patients with atrial fibrillation is associated with reduced atrial appendage flow velocity, spontaneous echocontrast in the left atrium, and thrombus formation (44–46). Whether sustained control of systemic hypertension reduces the risk for cardioembolic stroke in patients with atrial fibrillation is a vital question because the ventricular abnormalities associated with hypertension in elderly persons are often multifactorial and difficult to reverse (47, 48). Hypertension also increases the risk for noncardioembolic stroke in atrial fibrillation (20, 29), and this type of stroke may be particularly amenable to prophylaxis with aspirin (19, 20, 49).

Advancing age increases risk for stroke in atrial fibrillation for many reasons. Aging in patients with atrial fibrillation is associated with left atrial enlargement, reduced atrial appendage flow velocity, and spontaneous echocontrast, each of which predisposes patients to left atrial thrombus formation (45, 46, 50). In addition, age is a risk factor for atherosclerosis, including complex aortic arch plaque in patients with atrial fibrillation, which is associated with noncardioembolic strokes in atrial fibrillation (51). Levels of prothrombin activation fragment F1·2, an index of in vivo thrombin generation, increase with age in the general population (52) and in patients with atrial fibrillation (53), suggesting an age-related prothrombotic diathesis. In the Stroke Prevention in Atrial Fibrillation (SPAF) studies, age was a more potent risk factor when combined with other risk factors, such as hypertension or female sex (29); women older than 75 years of age with atrial fibrillation are at particular risk for cardioembolic strokes (49).

Left ventricular systolic dysfunction, as indicated by a history of heart failure or precordial echocardiographic measurements, predicts ischemic stroke in patients with atrial fibrillation who are not receiving antithrombotic therapy (30, 31, 39, 40). However, this association was not evident in recent analyses of moderate-risk patients with atrial fibrillation who were given aspirin (29, 36). Available inferences about mechanisms are contradictory: Left ventricular systolic dysfunction has been associated both with left atrial thrombus and with noncardioembolic stroke in patients with atrial fibrillation (20, 54).

Estimating the inherent risk for stroke in individual patients with atrial fibrillation is an important precursor to antithrombotic management; this process identifies those who will potentially benefit most or least from lifelong anticoagulation. Four stratification schemes to predict the risk for ischemic stroke have been proposed, based on analyses of prospectively followed cohorts of patients with atrial fibrillation in clinical trials (Table 3) (28, 29,

Table 2. Independent Predictors of Ischemic Stroke in Nonvalvular Atrial Fibrillation*

Predictor	Reference
Consistent predictors	
Advanced age	28, 29, 32, 33, 36, 40, 41
Hypertension	28–30, 32, 35, 36, 42
Previous stroke or transient ischemic attack	28–30, 33, 35, 36, 38
Left ventricular dysfunction†	30, 31, 34, 35, 39, 40
Possible predictors	
Diabetes mellitus	28–30
Systolic blood pressure > 160 mm Hg‡	29, 33, 34, 38
Women, especially older than 75 years of age	29, 32, 35
Postmenopausal hormone replacement therapy	29
Regular alcohol use (>14 drinks in 2 wk)§	29
Coronary artery disease or previous myocardial infarction	28, 37, 42
Moderate to severe mitral regurgitation§	41, 43

* From multivariate analyses of prospectively evaluated cohorts or case-control studies.

† Clinical congestive heart failure or systolic dysfunction according to echocardiography.

‡ In some analyses, systolic blood pressure >160 mm Hg remained an independent predictor after adjustment for hypertension.

§ Associated with decreased risk.

Table 3. Risk Stratification Schemes for Stroke Prevention in Nonvalvular Atrial Fibrillation*

Study, Year (Reference)	High-Risk Criteria	Moderate-Risk Criteria	Low-Risk Criteria
Untreated patients Atrial Fibrillation Investigators, 1994 (28)	Age ≥ 65 y History of hypertension Diabetes Previous stroke or transient ischemic attack	—	Age < 65 y, no high-risk criteria
Laupacis et al. [American College of Chest Physicians Consensus], 1998 (56)	Age > 75 y History of hypertension Previous stroke or transient ischemic attack Left ventricular dysfunction† > 1 moderate risk factor	Age 65–75 y Diabetes Coronary disease Thyrotoxicosis	Age < 65 y, no risk factors
Aspirin-treated patients SPAF III, 1995 (55)	Women > 75 y Systolic blood pressure > 160 mm Hg Previous stroke or transient ischemic attack Left ventricular dysfunction‡	History of hypertension, no high-risk criteria	No high-risk criteria, no history of hypertension
SPAF exploratory analysis 1999 (29)	Women > 75 y Systolic blood pressure > 160 mm Hg Hypertension plus age > 75 Previous stroke or transient ischemic attack	Hypertension and age ≤ 75 y Diabetes No high-risk criteria	No high-risk or moderate-risk criteria

* SPAF = Stroke Prevention in Atrial Fibrillation.

† Moderate to severe left ventricular systolic dysfunction on echocardiography or recent congestive heart failure.

‡ Impaired left ventricular function included recent congestive heart failure or left ventricular fractional shortening $\leq 25\%$ by M-mode echocardiography.

55, 56). Although the criteria overlap, differences between these stratification schemes often create dilemmas for management of individual patients. For example, men older than 75 years of age without hypertension or previous stroke had an observed stroke rate of 1.2% per year (CI, 0.4% to 3.2%) and were categorized as having low risk by one scheme (29), whereas all patients older than 75 years of age with atrial fibrillation are considered to be at high risk in other schemes (28, 56). In one population-based cohort of patients with atrial fibrillation who are older than 65 years of age, the proportion classified as having high risk varied from 45% to 76%, depending on the criteria used (57).

By these schemes, most patients with atrial fibrillation who are older than 75 years of age are predicted to have a high risk for stroke; low-risk patients are generally younger and free of hypertension. Contrary to the conventional wisdom, elderly patients with recurrent (> 1 episode) intermittent atrial fibrillation seem to have a risk for stroke similar to that seen in patients with sustained atrial fibrillation (58). Independent tests of the reliability of these schemes have been limited to participants in research trials (55, 57), and additional studies of stroke risk stratification outside clinical trials are needed. Community-based cohorts of patients with atrial fibrillation are generally older and include more women than men, and the reliability of risk stratification schemes may differ (11, 57). Because of the rapid pace of development and a lack of consensus about risk stratification, uncertainty remains about which patients with atrial fibrillation should receive anticoagulation, as reflected by surveys reporting wide variations in warfarin use. Ef-

forts to achieve consensus and additional studies of risk stratification are essential. On the basis of available evidence, the American College of Chest Physicians Consensus (56) and the SPAF study (55) criteria seem to be the most robust guidelines for current clinical use (Table 3).

Patients with atrial fibrillation who are at high risk for stroke ($\geq 6\%$ per year), particularly those who have previously had stroke or transient ischemic attack, have the largest absolute reduction in stroke with adjusted-dose warfarin instead of aspirin (Table 4). Selection of anticoagulation instead of aspirin for 1000 patients with atrial fibrillation who have previously had stroke would prevent at least 40 strokes per year (number needed to treat, 25). In contrast, warfarin therapy would prevent only 4 to 12 strokes per year per 1000 patients at low (about 1% per year) or moderate (about 3% per year) risk for stroke (NNT, 250 and 80, respectively). Those who question the reliability of available risk stratification schemes in clinical practice advocate anticoagulation in all but the small fraction of patients with atrial fibrillation who are at the lowest risk. Assuming an average annual stroke rate of 4% with aspirin therapy, this policy of warfarin use would prevent about 16 strokes per 1000 patients per year. This corresponds to about 60 patients needed to treat each year for prevention of any stroke and about 100 patients needed to treat to prevent a disabling stroke. Of note, new thromboembolic risk factors were identified in 6% of patients per year who were categorized as low risk in one study (55); therefore, periodic reassessment to detect risk factors that favor the use of warfarin is important to minimize stroke.

Table 4. Effect of Risk Stratification on Stroke Reduction by Warfarin Compared with Aspirin in Atrial Fibrillation

Risk Stratification	Annual Stroke Rate with Aspirin Therapy	Treatment with Warfarin Instead of Aspirin	
		Number Needed to Treat for 1 y To Prevent 1 Stroke	Number of Strokes Saved Yearly per 1000 Given Warfarin
	%	n	
Primary prevention*			
Low risk	1	250	4
Moderate risk	3	83	12
High risk	6	42†	24†
Secondary prevention	10	25†	40†

* For stratification schemes, see Table 3.

† Calculations are based on a 40% relative risk reduction with adjusted-dose warfarin over aspirin from meta-analysis (Table 1). We suspect that this overestimates the benefit of warfarin therapy in low-risk patients and importantly underestimates it for high-risk patients.

Echocardiography

Precordial echocardiography has become a standard part of the evaluation of patients with atrial fibrillation to exclude occult mitral stenosis, but the perceived value of cardiac ultrasonography when added to clinical risk factors for stratifying stroke risk in nonvalvular atrial fibrillation is not entirely clear. An analysis of placebo recipients in the SPAF I study (31) found that both left atrial diameter and left ventricular systolic dysfunction were independent predictors of thromboembolic events and that these echocardiographic features enhanced prediction when combined with clinical risk factors. When these data were pooled with those from placebo recipients in two other trials, left ventricular systolic dysfunction was confirmed as an independent predictor of stroke, but the relation of stroke to left atrial diameter was not statistically significant (39). Confounding the association between left atrial diameter and thromboembolic risk is that substantial mitral regurgitation, which enlarges the left atrium, is associated with reduced risk for stroke, probably by improving stasis (43). Analyses of patients with atrial fibrillation who are taking aspirin have failed to show independent associations between either left atrial diameter or ventricular systolic dysfunction and stroke (29, 34, 36). Left ventricular diastolic dysfunction may correlate more closely than systolic wall-motion abnormalities with atrial stasis and thromboembolism, but echocardiographic methods for evaluation of diastolic performance are less well established. These limitations and interactions may explain in part why studies to date of precordial echocardiographic variables for prediction of stroke risk have yielded conflicting results and why the value of precordial echocardiography in addition

to clinical risk factors for stratification of risk for stroke remains unsettled (39, 59).

Transesophageal echocardiography (TEE) allows sonographic imaging of the left atrium, its appendage, and the thoracic aorta that is superior to that obtained with precordial echocardiography. Transesophageal echocardiography-based studies have yielded valuable insights into the mechanisms of stroke and the effects of anticoagulation. Most intracardiac thrombi in nonvalvular atrial fibrillation are located in the atrial appendage and are strongly associated with reduced appendage flow velocity and spontaneous echocontrast, both indices of stasis (45, 54, 60). A left atrial appendage thrombus predicts subsequent stroke and resolves during anticoagulation (36, 60, 61) but is a relatively insensitive and nonspecific predictor of subsequent stroke in patients with atrial fibrillation (36, 60). Spontaneous echocontrast detected by TEE, an indicator of stasis, arises when flow velocity is reduced and is accentuated when increased fibrinogen predisposes to erythrocyte rouleaux formation (45, 46). An appendage thrombus is rare in the absence of spontaneous echocontrast and is frequently detected (in about 25% of cases) when contrast is optically dense (60).

Transesophageal echocardiographic findings have clarified the relation between several clinical risk factors and stroke in patients with atrial fibrillation. Age, for example, is an independent predictor of reduced appendage flow velocity (45), spontaneous echocontrast (46), and aortic arch atheroma (51). Hypertension is associated with atrial stasis that engenders cardioembolic stroke (44–46), and left ventricular systolic dysfunction is associated with atrial thrombus (54). However, it is unclear whether observations from TEE add to the predictive value of clinical risk factors for stroke (36, 60). Among high-risk patients with atrial fibrillation, those without dense spontaneous echocontrast still have a substantial rate of stroke, which is reduced by adjusted-dose warfarin (60). In patients with atrial fibrillation who have had recent ischemic stroke, TEE may help discriminate cardioembolic from noncardioembolic mechanisms, but adjusted-dose warfarin is currently recommended for all cases involving secondary prevention. At present, there is no clear indication for use of routine TEE to select patients with nonvalvular atrial fibrillation for long-term antithrombotic therapy, but the last word is yet to be written on this controversial topic (62).

Aortic Arch Plaque

Aortic arch atheromatous plaque is associated with stroke in elderly persons (63–67) and was re-

cently shown to be an independent predictor of stroke in patients with atrial fibrillation (44, 60, 68). Complex aortic plaque is found in about 15% of patients with atrial fibrillation who are at low risk for stroke compared with 35% of those at high risk (44). Its presence is associated with advancing age, systolic hypertension, diabetes, tobacco smoking, and mitral annular calcification (51). Patients with atrial fibrillation and complex aortic plaque have marked reduction in stroke during treatment with warfarin (60). It is unclear whether thrombi on the surface of aortic plaque are the direct cause of stroke in patients with atrial fibrillation who have these lesions: The strongest correlation with stroke has been with plaque situated distal to the origin of the arteries supplying the brain (51). Furthermore, aortic arch plaque has been independently associated with atrial thrombus (51), spontaneous echocontrast (46), and reduced appendage flow velocity (45). The mechanistic link between aortic plaque and atrial stasis remains to be defined.

Disturbances of Hemostasis

Hemostatic conditions favoring thrombosis have long been postulated to contribute to stroke in patients with atrial fibrillation. More than a dozen case-control and cohort studies have reported abnormalities of coagulation, platelet activation, fibrinolytic capacity, or endothelial function favoring thrombosis in patients with atrial fibrillation, particularly those with stroke (69-73). These hemostatic abnormalities may be explained by associated vascular disease in patients with atrial fibrillation, may occur secondary to thrombosis in the atrium, or may be induced by the rhythm itself. Resolution of some hemostatic perturbations with reversion to sinus rhythm suggests that the dysrhythmia itself may provoke hemostatic changes favoring thrombosis (73). Refuting this paradigm is the lack of evidence that patients with atrial fibrillation have higher risk for venous thromboembolism, as might be expected if atrial fibrillation induced a prothrombotic state. Specific hemostatic perturbations that independently predict subsequent stroke in clinical studies are yet to be identified.

Estrogen replacement therapy emerged as an independent risk factor for ischemic stroke in exploratory analyses of SPAF III study participants (29). Postmenopausal hormone replacement therapy seems to increase the risk for venous thromboembolism (74), and the identification of hormone replacement therapy as an independent predictor of stroke in patients with atrial fibrillation supports the contribution of prothrombotic hemostatic factors. The genetic marker for the factor V Leiden genetic

mutation was not associated with ischemic stroke in a cohort of low-risk patients with atrial fibrillation taking aspirin, but the power to detect a relation was limited (75).

Restoration of Sinus Rhythm To Prevent Stroke

On the basis of the pathophysiologic notion that most strokes associated with atrial fibrillation result from embolism of stasis-induced thrombus originating the left atrial appendage, restoration and maintenance of atrial contraction should logically reduce thromboembolic risk. Left ventricular dysfunction can improve after cardioversion (76), potentially reducing embolic risk and favoring cerebral hemodynamics (77). Although this potential benefit is often considered in decisions to attempt cardioversion in patients with atrial fibrillation (78), it is uncertain how effectively maintenance of sinus rhythm reduces risk for thromboembolism in patients with atrial fibrillation. Relapse of atrial fibrillation is frequent even when cardioversion is initially successful (79). In addition, if aortic arch atheroma contribute to stroke in high-risk patients with atrial fibrillation (44), restoration of sinus rhythm may not reduce the stroke rate to low levels. Ongoing clinical trials assessing the benefits of cardioversion of atrial fibrillation do not involve withdrawal of anticoagulation after reversion to sinus rhythm (80) and thus fail to address whether successful cardioversion obviates the need for anticoagulation.

Conclusions

Investigators around the world have made unprecedented advances in understanding thromboembolism associated with atrial fibrillation, revolutionizing disease management in the process. In particular, much has been learned about antithrombotic therapies to prevent stroke in patients with atrial fibrillation: Adjusted-dose warfarin is highly efficacious; aspirin is modestly efficacious (reducing mainly non-disabling, noncardioembolic strokes); warfarin is much more efficacious than aspirin; and low-intensity warfarin (INR < 1.5), alone or combined with aspirin, offers little protection. All patients with atrial fibrillation should be evaluated for factors associated with additional risk and their stroke risk should be estimated. Patients at high risk for stroke and many of those at moderate risk should be considered for anticoagulation.

Critical issues involving prevention of stroke for millions of persons with atrial fibrillation remain to be resolved by the next generation of studies.

Reliable schemes to predict stroke risk must be refined and validated, and optimal antithrombotic prophylaxis awaits better understanding of the mechanisms linking predictors to stroke. A crucial question is whether sustained control of hypertension reduces the risk for cardioembolic stroke in patients with atrial fibrillation. New antithrombotic agents that are more efficacious than aspirin and more easily administered than warfarin are needed. The impact of restoration and maintenance of sinus rhythm on risk for stroke, cognition, quality of life, and need for anticoagulation must also be determined.

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Note: Both authors were participants in the Stroke Prevention in Atrial Fibrillation I, II, and III clinical trials.

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