Stroke prevention in atrial fibrillation:

Current anticoagulation management and future directions

BENJAMIN T. FITZGERALD, MBBS; STEVEN L. COHN, MD; AND ALLAN L. KLEIN, MD

ABSTRACT

Atrial fibrillation (AF) is an important cause of stroke, and stroke risk stratification is critical to the management of patients with AF. Anticoagulation with warfarin is the current standard of care for stroke prevention in these patients, despite the need for close monitoring. Aspirin alone is not as effective. Warfarin is recommended for patients with AF and valvular disease or with AF and one or more stroke risk factors. Other novel anticoagulants and antiplatelet combinations are under investigation. Curative procedures for AF are possible, but their long-term safety and effect on stroke risk are unknown.

Atrial fibrillation (AF) is a significant risk factor for the formation of atrial thrombi, which can lead to systemic emboli, including stroke.[1] For this reason, stroke prevention is a key consideration in managing patients with AF.

Anticoagulation successfully reduces the incidence of stroke in patients with AF,[2–7] but it carries risks of its own and is not accepted or tolerated by all, especially the elderly. There is also a problem with physician acceptance.[8] Other management options are under investigation. This article outlines considerations for stroke risk stratification in patients with AF and reviews stroke prevention options in these patients, with a focus on the role of anticoagulation within the evolving landscape of AF management.

OVERVIEW OF ATRIAL FIBRILLATION

Epidemiology and types of atrial fibrillation

AF is common, occurring in 2% to 5% of individuals 60 years of age or older and contributing to 10% to 20% of strokes in that population.[1,9–11] The prevalence of AF increases with age,[9–11] and the lifetime risk of developing AF is one in four for men and women over age 40.[11] Thus, AF is an important cause of stroke, and its significance increases with the aging process.

The condition encompasses many processes. *Paroxysmal AF* is self-terminating and generally lasts less than 24 hours (by definition, it lasts less than 7 days). *Persistent AF* lasts for longer than a week and is sustained (not self-terminating). Both paroxysmal and persistent AF can be recurrent. *Permanent AF* refers to AF that persists for longer than 1 year. *Lone AF* constitutes arrhythmia without underlying structural heart disease.

Mechanisms of atrial fibrillation

AF results in uncoordinated contraction of the atria, leading to blood stasis and clot formation.[12,13] Low left atrial appendage (LAA) peak velocities (< 20 cm/sec by pulsed-wave Doppler echocardiography) are associated with thrombus formation.[14] Another echocardiographic phenomenon seen in patients with AF is spontaneous echo contrast, ie, smoke-like images thought to represent increased red blood cell aggregation in the setting of low flow. The presence of spontaneous echo contrast is a predisposing factor for thrombus.[15]

AF also appears to activate the clotting system, further promoting thrombus formation. Thrombotic and fibrinolytic markers are increased in AF patients.[12,13]

STROKE RISK FACTORS AND RISK STRATIFICATION

A number of factors increase stroke risk in patients with nonvalvular AF: history of a previous stroke or stroke-like event, increased age, hypertension, diabetes mellitus, and history of heart failure.[16–18] The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators[16] identified female sex, systolic blood pressure greater than 160 mm Hg (with a history of hypertension), and an ejection fraction less than 25% as additional risk factors **(Table 1)**. The SPAF Investigators found that risk increases with each decade of life as one ages, with a relative risk of 1.8 per decade.[16]

From the Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio (BTF, ALK); and the Division of General Internal Medicine, State University of New York Downstate, Brooklyn, N.Y. (SLC).

Address: Allan L. Klein, MD, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk F15, Cleveland, OH 44195; kleina@ccf.org.

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TABLE 1
Stroke risk calculations from two large atrial fibrillation trial groups[16–18]

Level of risk and risk factors	Annualized stroke rate	Strokes per 100 pt-yr*
Stroke Prevention in Atrial Fibrillation (SPAF) Investigators		
High risk	7.1%	5.7
• Female aged > 75 yr		
• Age > 75 yr + hypertension		
• Congestive heart failure		
• Left ventricular ejection fraction < 25%		
• Systolic blood pressure > 160 mm Hg		
Medium risk	2.6%	3.3
• Age < 75 yr + hypertension		
• Diabetes mellitus		
• Hypertension + diabetes mellitus		
Low risk	0.9%	1.5
• None of the above risk factors		
Atrial Fibrillation Investigators (AFI)		
High risk	—	5.4
• Previous stroke		
• Hypertension		
• Diabetes mellitus		
Medium risk	—	2.2
• Age > 65 yr		

*Modified by Gage et al[18] from the SPAF and AFI data.

TABLE 2
$CHADS_2$ scores, stroke risk, and risk levels[18,19]

$CHADS_2$ score*	Stroke risk per 100 pt-yr	$CHADS_2$ risk level	Warfarin recommended
0	1.9	Low	No
1	2.8	Low	No
2	4.0	Moderate	Yes
3	5.9	Moderate	Yes
4	8.5	High	Yes
5	12.5	High	Yes
6	18.2	High	Yes

*The $CHADS_2$ stroke risk index assigns 1 point for each of four risk factors (congestive heart failure, hypertension, age > 75 years, diabetes mellitus) and 2 points for a previous stroke.

Other clinical risk factors for AF include valvular heart disease, coronary artery disease, and obstructive sleep apnea.[1] Echocardiographic risk factors include left atrial enlargement, low LAA volume or flow velocity, the presence of left atrial or LAA thrombus or spontaneous echo contrast, valvular disease, left ventricular dysfunction or hypertrophy, and the presence of ascending aortic and aortic arch thrombus or plaque.[1,14,15]

Stroke rates vary significantly according to the patient's risk profile.[16–18] Patients at high risk may benefit from intervention,[2,3,5] whereas those at lower risk may not. Estimating the level of stroke risk is a critical part of assessing patients with AF.

The SPAF Investigators and Atrial Fibrillation Investigators identified risk factors and used clinical trial data to estimate stroke rates according to those factors **(Table 1)**.[16,17] Gage et al[18] identified independent risk factors for stroke and devised a scoring system, the $CHADS_2$ index, to assess the risk level for a given patient **(Table 2)**. The index assigns 1 point to each of four risk factors (congestive heart failure, hypertension, advanced age, and diabetes) and 2 points for a previous stroke-like event. The $CHADS_2$ index was validated with the $CHADS_2$ database and shown to be more accurate in predicting stroke rates in a Medicare population **(Table 2)** than the classifications from the SPAF Investigators or the Atrial Fibrillation Investigators.[18,19]

The most comprehensive but most complicated risk score for AF is based on Framingham Heart Study data and predicts 5-year risk of stroke or the composite of stroke and death on the basis of a patient's risk factors. This risk-analysis scoring system is available as an Excel spreadsheet on the National Institutes of Health Web site at **www.nhlbi.nih.gov/about/framingham/stroke.htm**.[20]

A RANGE OF MANAGEMENT OPTIONS

A variety of options are available for the prevention of stroke in patients with AF, including oral anticoagulation (warfarin or warfarin plus aspirin), antiplatelet therapy (aspirin, clopidogrel, ticlopidine, or dipyridamole), restoration of sinus rhythm, and procedural options (LAA ligation or amputation, LAA occlusion, surgical treatment for AF, or pulmonary vein ablation).

PHARMACOLOGIC OPTIONS

Oral anticoagulant therapy

Anticoagulation with warfarin has been shown to be beneficial in patients with AF and rheumatic valvular heart disease.[2]

A number of trials have evaluated warfarin for the primary prevention of stroke in patients with nonvalvular AF.[4,6,7,16,21–23] In these studies, warfarin (dosed to achieve an international normalized ratio [INR] between 2.0 and 5.0) significantly reduced the incidence of stroke and stroke-like events compared with placebo, aspirin, or aspirin combined with low-dose warfarin (INR < 2.0). Compared with placebo, warfarin reduced the annual rate of vascular events from 5%–8% to approximately 2% (relative risk reduction

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TABLE 3

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Please see original source table (table 1) in: *McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. Ann Intern Med 2003; 139:1018–1033.*

of 62%).[4,6,7,16,21,22] However, warfarin increased the risk of intracranial hemorrhage relative to placebo, with rates ranging from 0.3% to 1.8% for INRs from 2.0 to 4.5. When the target INR was 2.0 to 3.0, rates of intracranial hemorrhage were only 0.3% to 0.6%.[6,16,21,22] Rates of major bleeding were 0.2% to 0.5% annually. Rates of minor bleeding also increased significantly with warfarin therapy.[6,7,16,21,22]

In patients with nonvalvular AF at moderate to high risk of stroke, warfarin is the recommended therapy for primary stroke prevention unless it is contraindicated; the target INR should be 2.0 to 3.0.[24–26] This includes patients with persistent or paroxysmal AF with one or more significant risk factors **(Tables 1 and 2)**.[19,24–26]

Antiplatelet therapy

For patients in whom warfarin is not an option, aspirin may be an alternative. The SPAF trials demonstrated a benefit for aspirin over placebo except in patients older than 75 years of age.[3,23] A recent meta-analysis[27] suggested a trend towards a benefit with aspirin relative to placebo **(Table 3)**. Aspirin may have a role for stroke risk reduction in low-risk patients. Aspirin combined with low-dose warfarin is not as effective as adjusted-dose warfarin (target INR of 2.0 to 3.0)[7,22,27,28] **(Table 3)**.

In patients who continue to have events despite appropriately dosed warfarin (INR 2.0 to 3.0), some physicians have advocated adding aspirin to the conventional warfarin regimen, although this has not been assessed in a clinical trial setting.

Combinations of aspirin and other antiplatelet agents (clopidogrel, ticlopidine, dipyridamole) have not yet been shown to be effective for patients with nonvalvular AF. Several trials are under way to assess the combination of aspirin and clopidogrel relative to warfarin. However, a study assessing the effect of aspirin and clopidogrel on platelet function and coagulation did not show equivalent effects on coagulation relative to warfarin,[29] suggesting that warfarin is likely to be superior for stroke prevention in this setting. Aspirin and clopidogrel may have a role in low-risk to moderate-risk patients, but this also needs to be tested. The combination could also be considered in patients for whom warfarin is not acceptable.

Warfarin has been shown to have a beneficial effect for patients who have had a recent cerebrovascular ischemic event associated with AF (ie, secondary prevention).[5,23] The secondary prevention data for aspirin from the European Atrial Fibrillation Trial suggest that it is a safe but less effective option than warfarin but better than placebo.[5]

Guidelines and pharmacologic therapy

A number of guidelines for the prevention of stroke in AF have been devised.[24–26] **Table 4** outlines the risk-based approach recommended in recent guidelines from the American College of Cardiology, American Heart Association, and European Society of Cardiology.[24] These guidelines are generally similar to the 2004 recommendations from the American College of Chest Physicians.[26] The American Academy of Family Physicians and American College of Physicians suggest defining risk for stroke according to the $CHADS_2$ classification **(Table 2)**.[19] Key recommendations from these guidelines are summarized in the "Recommendations" section below.

Perioperative bridging therapy

One of the dilemmas of warfarin therapy is what to do when a patient requires an intervention for which anticoagulation poses significant risk. In these situations, the risk of stroke resulting from warfarin discontinuation needs to be assessed. For those at low risk of thromboembolism, warfarin can be stopped for 4 to 5 days before the procedure and restarted after the procedure is completed. In high-risk patients, warfarin can be stopped and, once the INR has dropped below 2.0, intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin can be started. The US Food and Drug Administration has not approved these

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TABLE 4

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agents for this indication, but guidelines do list them as options.[26] If low-molecular-weight heparin is used, it should be stopped 12 to 24 hours before the procedure. Unfractionated heparin can be discontinued several hours before the procedure. These medications and warfarin should be restarted as soon as adequate hemostasis is achieved. Unfractionated or low-molecular-weight heparin should be continued at least until the warfarin is therapeutic.[24–26]

Emerging antithrombotic therapies

Warfarin has a narrow therapeutic window and complex and variable pharmacodynamics and pharmacokinetics. It also interacts with many drugs and foods and requires regular blood level monitoring. As a result, there has been much interest in finding agents to replace warfarin.

Direct thrombin inhibitors. Ximelagatran is the first oral agent in the direct thrombin inhibitor class of anticoagulants. At a fixed dose, it has been shown to be noninferior to warfarin for stroke prevention in patients with nonvalvular AF.[30–32] It appears to have similar risks of intracranial bleeding and major bleeding relative to warfarin but a lower risk of minor hemorrhage.[31,32]

Unfortunately, ximelagatran has been shown to raise serum transaminase and bilirubin levels in 5% to 10% of patients. These abnormalities have been reported to improve whether or not the medication is continued.[30–32] However, recent analyses suggest that deaths due to liver failure have occurred.[33,34] These deaths may be preventable with more careful follow-up of transaminase levels, but more data are needed. The FDA also recently raised concerns over a possible increase in coronary events in patients receiving ximelagatran compared with those receiving warfarin, but these data are inconsistent.[34] As a result of these safety concerns, ximelagatran has not currently been approved by the FDA.

Factor Xa inhibitors. Another novel class of anticoagulants is the factor Xa inhibitors, or pentasaccharides. Fondaparinux, currently the only commercially available member of this class, is administered once daily by subcutaneous injection and has potential utility for stroke prevention in patients with AF. The long-acting, once-weekly subcutaneous agent idraparinux is in early phase 3 trials. Oral factor Xa inhibitors are still in phase 2 trials.

If a safe and effective oral agent becomes available, it will have the potential to revolutionize stroke prevention in patients with AF.

Rate control vs rhythm control

Another area of controversy is which of two strategies—maintenance of sinus rhythm ("rhythm control") or controlling the heart rate and continuing anticoagulation ("rate control")—is more beneficial for patients with AF. A number of studies have shown no mortality or stroke benefit with rhythm control,[35–39] and the AFFIRM trial[35] suggested a trend toward lower mortality with rate control. The main reason for these results has been the inability to maintain sinus rhythm in patients managed with rhythm control, and the subsequent thromboembolic events that occurred during AF after patients were taken off anticoagulant therapy.[35–37] There are, however, hemodynamic benefits to being in

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TABLE 5
Summary of trials comparing rate control and rhythm control in patients with atrial fibrillation

Trial	N	Mean age (yr)	Follow-up	End point	Outcome
PIAF[39]	252	61	1 yr	Symptoms	No significant difference between rate and rhythm control groups
RACE[37]	522	68	2.3 yr	Composite*	No significant difference between rate and rhythm control groups
AFFIRM[35]	4,060	69.7	5 yr	Mortality	Trend toward lower mortality in rate control group (hazard ratio of 1.15 for rhythm group [95% CI, 0.99–1.34], $P = .08$)
STAF[36]	200	66	19.6 mo	Composite†	No significant difference between rate and rhythm control groups
HOT CAFE[38]	205	60.8	12 mo	Symptoms	No significant difference between rate and rhythm control groups
				Mortality	No significant difference between rate and rhythm control groups
				Hospitalizations	62% absolute risk reduction in rate control group ($P < .001$)
				LV function	Improvement in rhythm control group ($P < .01$)
				Exercise capacity	Improvement in rhythm control group ($P < .01$)

* Death, heart failure, and thromboembolic events

† Mortality, need for cardiopulmonary resuscitation, cerebrovascular events, and thromboembolic events

PIAF = Pharmacological Intervention in Atrial Fibrillation; **RACE** = Rate Control versus Electrical Cardioversion; **AFFIRM** = Atrial Fibrillation Follow-up Investigation of Rhythm Management; **STAF** = Strategies of Treatment of Atrial Fibrillation; **HOT CAFE** = How to Treat Chronic Atrial Fibrillation

sinus rhythm.[37,38] The trials investigating this problem enrolled patients with no symptoms or minimal symptoms. In patients for whom AF produces significant symptoms, restoration of sinus rhythm is still appropriate. The important message of these trials **(Table 5)**[35–39] is that in patients for whom a strategy of achieving sinus rhythm is chosen, continued anticoagulation should be recommended for the prevention of stroke.

CURATIVE APPROACHES TO ATRIAL FIBRILLATION

Surgical occlusion of the LAA may be attempted for patients with AF who are undergoing cardiac surgery for an indication other than AF. One study has shown a significant reduction of embolic events in patients who received this procedure compared with those who did not.[40] However, the significant risk of incomplete occlusion with this procedure (≈20%) may result in further thromboembolic events.[40]

Occlusion of the LAA can also be achieved percutaneously. This has been done safely and effectively without significant effect on the left atrium or the pulmonary veins.[41] Long-term safety data are not yet available, however, and the effect on stroke prevention is not yet known.

The maze procedure is a surgical intervention in which small incisions are made in the atria to interrupt the pathways that produce AF. It eliminates AF in more than 90% of patients.[42] Pulmonary vein ablation can also be done during or instead of the maze procedure. A small percentage of patients may require medical therapy or permanent pacemaker implantation for sinus node injury.[42] The maze procedure has been shown to significantly lower stroke rates both acutely (0.7% perioperative stroke rate) and over the long term (0.4% stroke rate over follow-up of up to 11.5 years).[43]

Percutaneous catheter ablation for AF is a procedure in evolution. Current techniques involve pulmonary vein isolation and atrial ablation. Success rates range from 60% to 90% during short-term follow-up. Long-term risks are not yet fully determined but so far seem minimal.[44–46] Nonrandomized trials have shown significantly improved survival, less heart failure, and less stroke with pulmonary ablation compared with conventional therapy.[44,46] Catheter ablation appears to offer substantial promise, at least for highly symptomatic patients.

Pacemaker implantation has a role in the management of AF. Options include physiologic pacing, dual-site atrial pacing, and overdrive pacing. Whether these options reduce stroke is currently unknown.[45] Atrioventricular node ablation and permanent pacemaker implantation is another strategy for patients with highly symptomatic AF that is unresponsive to other therapies. It does not cure AF or prevent stroke, however, and patients still require anticoagulation.

Implantable atrial defibrillators have been developed, but patient acceptance has been low. Most patients are conscious at the time of defibrillation. Even with low defibrillation outputs, patients have found the discharge uncomfortable.[45] These devices are still experimental, and their effect on stroke rates is unknown.

THE ROLE OF ECHOCARDIOGRAPHY

Transesophageal echocardiography (TEE) images the heart with a high level of resolution and readily detects thrombus in the left atrium and LAA.[47] It also can identify other echocardiographic risk factors for thrombus and emboli. The ACUTE trial[47] showed that TEE safely permits cardioversion in patients with new-onset

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TABLE 6
Factors that guide cardioversion management in hemodynamically stable patients with atrial fibrillation

Patient factors that call for a TEE-guided strategy	Patient factors that call for conventional management
New-onset atrial fibrillation	Chronic or therapeutic anticoagulation
Uncertain anticoagulation status, subtherapeutic anticoagulation levels, or absence of anticoagulation therapy	High likelihood of spontaneous/chemical conversion with inciting factors for atrial fibrillation
Symptoms	Absence of symptoms or minimal symptoms
Hemodynamic effects, congestive heart failure, ischemia	Contraindications or intolerance to TEE
Hospitalized patients	Outpatient status
Elevated risk for long-term bleeding	Low risk for bleeding
Difficulty complying with anticoagulation therapy	Compliance with anticoagulation therapy
High risk for left atrial stroke*	Low risk for left atrial thrombi†

TEE = transesophageal echocardiography
*Valvular heart disease, left ventricular dysfunction, prior left atrial/left atrial appendage thrombi, prior stroke, advanced age, systolic hypertension
†No valvular heart disease, normal left ventricular function, no clinical risk factors for stroke

AF, for whom prolonged anticoagulation is not planned, when no left atrial or LAA thrombus has been identified **(Table 6)**. Postcardioversion embolic events occurred at a rate similar to that in patients treated conventionally (warfarin to an INR of 2.0 to 3.0 for at least 3 weeks before cardioversion), but with significantly fewer bleeding events.[47] Warfarin is still required for at least 3 weeks after cardioversion, owing to variability in the return to fully coordinated function, but the total duration of anticoagulation can be significantly reduced. TEE-guided cardioversion is an effective alternative to conventional management.[47,48]

TEE and intracardiac echocardiography can also be used to ensure the safety of other procedures for AF before those procedures are performed.[48] Echocardiography can guide the placement of percutaneous devices and surgical closure of intracardiac shunts, which may lessen stroke risk.[48]

RECOMMENDATIONS

Stroke prevention is possible and essential for almost all patients with AF. Warfarin remains the treatment of choice for patients in whom it is not contraindicated. It is the most effective approach currently available to prevent systemic thromboembolism. The desired treatment range is an INR of 2.0 to 3.0 (target of 2.5). Warfarin is recommended for patients with AF and valvular disease or with AF and at least one risk factor (see the guidelines discussed above[19,24–26] and **Tables 2 and 4**). It is also recommended in patients who have had a previous stroke or stroke-like event. However, warfarin is not indicated for young patients without risk factors (lone AF). Aspirin may have a role in this group. For patients already on therapeutic warfarin who continue to have recurrent events, the addition of aspirin may be beneficial. For patients with infrequent AF, the effectiveness of anticoagulation is unknown.

Attempting cardioversion for patients with persistent AF is quite reasonable. However, warfarin should be continued long-term in these patients for the prevention of stroke.

For patients with recurrent and significantly symptomatic AF despite attempts at reversion to sinus rhythm, a curative procedure can be contemplated. For patients requiring open heart surgery, a surgical approach at the same time may be warranted. Catheter-based techniques are emerging and may be the wave of the future. Whether these patients still require anticoagulation is currently unknown.

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