Strategies for stroke prevention in atrial fibrillation

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Stroke is among the most potentially devastating consequences of atrial fibrillation. In patients with atrial fibrillation, stroke usually is presumed to be due to thromboembolism arising from the left atrium or left atrial appendage (Figure 1). Atrial fibrillation is the most common cause of cardiogenic stroke and one of the most potent risk factors for stroke in the elderly. It also has been associated with an approximately 15% risk for silent cerebral infarction.

Risk of stroke in atrial fibrillation

Risk factors for stroke in atrial fibrillation have been well identified. These include advanced age (>60 to 65 years), prior transient ischemic attack or stroke, hypertension, coronary artery disease, congestive heart failure, left ventricular dysfunction, diabetes mellitus, increased left atrial size, rheumatic mitral valve disease, prosthetic valves, mitral annular calcification, increased wall thickness, and thyrotoxicosis.1-3 Risk for thromboembolism also has been associated with echocardiographic findings of increased spontaneous echocardiographic contrast in the left atrium, decreased velocities in the left atrial appendage, left atrial or left atrial appendage thrombi, and complex aortic atheroma. The risk of thromboembolic events tends to cluster near the onset of the arrhythmia; the incidence of embolism decreases over subsequent years. Patients with paroxysmal atrial fibrillation appear to be at similar risk as patients with chronic, persistent atrial fibrillation.

Warfarin and aspirin in atrial fibrillation

Randomized controlled trials have definitively established the efficacy of adjusted-dose warfarin anticoagulation in the prevention of stroke in patients with atrial fibrillation. A pooled analysis from five primary prevention trials reported a 68% reduction in stroke risk with warfarin.4 Only a borderline significant reduction in risk was reported with aspirin. Results from randomized studies and meta-analyses consistently show a higher relative risk reduction with warfarin compared to aspirin.4-7 Moreover, warfarin is the only treatment to date reported to improve mortality in patients with atrial fibrillation. A 33% reduction in mortality with warfarin use was reported in a combined analysis of randomized studies of warfarin versus control.1 Warfarin also was associated with a 31% relative reduction in all-cause mortality in another large study of patients with nonvalvular atrial fibrillation.8

Recommendations for long-term antithrombotic therapy

Guidelines for long-term antithrombotic therapy emphasize the use of anticoagulation with warfarin for patients with risk factors (Tables 1 and 2).2,9 Warfarin or aspirin can be used in some low-risk patients between ages 60 and 75 years. Aspirin 325 mg/day may be recommended for patients ≥65 years with no risk factors, including hypertension. These recommendations apply to paroxysmal as well as chronic persistent atrial fibrillation.

Anticoagulation prior to cardioversion

The risk of emboli after cardioversion has been reported to be up to approximately 5%.9 For atrial fibrillation lasting for >48 hours, anticoagulation with warfarin for 3 to 4 weeks should be achieved prior to elective cardioversion and continued at least until sinus rhythm has been maintained for 4 weeks. Heparin followed by oral anticoagulation may be used for patients requiring emergency cardioversion. A transesophageal echocardiography (TEE)-guided protocol with short-term anticoagulation may allow earlier cardioversion with less bleeding than the conventional anticoagulation approach.10 It is recommended for patients with new-onset atrial fibrillation, high-risk patients for stroke and bleeding, and in-patients. For atrial fibrillation lasting <48 hours, pericardioversion anticoagulation usually is advised, especially in cases at high risk for stroke.

The importance of achieving therapeutic prothrombin time/international normalized ratios (PT/INR) for several weeks prior to cardioversion has been emphasized by recent studies. The incidence of left atrial or left atrial appendage thrombi has been reported to be 13.8% in the absence of prolonged anticoagulation.10 Another study reported an incidence of 9.9% if a subtherapeutic PT/INR (<2.0) was recorded within 3 weeks of DC cardioversion.11 Moreover, the incidence of thromboembolic events has been correlated

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with the intensity of anticoagulation at DC cardioversion. Incidence was 0% for PT/INR ≥2.5, 0.93% for PT/INR 1.5 to 2.4, and 1.2% for unmeasured or PT/INR <2.5. Thus, therapeutic PT/INRs are critical at and prior to cardioversion attempts.

Thromboembolic risk: A lifelong need for management

Anticoagulation should be continued long term beyond 4 weeks after cardioversion in the presence of any stroke risk factors. Recent trials, including the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, have demonstrated that thromboembolic risk is not reduced despite a rhythm control approach. AFFIRM showed no reduction in thromboembolism. In the Rate Control versus Electrical Cardioversion (RACE) for Persistent Atrial Fibrillation trial, thromboembolism incidence was higher in the rhythm control group. In both studies, most events occurred on subtherapeutic or no anticoagulation. These findings emphasize that in patients with atrial fibrillation and risk factors for stroke, continued anticoagulation is important even with a rhythm control strategy, despite apparent achievement and maintenance of sinus rhythm.

Alternative antithrombotic agents for atrial fibrillation

Limitations of warfarin have led to the search for new antithrombotic agents for treatment of atrial fibrillation. Warfarin is associated with bleeding risk, a narrow therapeutic window (minimum PT/INR 2.0 is required for efficacy against stroke and PT/INR >4.0 increases the risk of intracranial hemorrhage), need for frequent monitoring, multiple drug and diet interactions, and influence by hepatic dysfunction, changes in gastrointestinal flora, alcohol intake, and compliance.

Antiplatelet therapy

Antiplatelet agents have been demonstrated to block arterial thrombogenesis. Antiplatelet therapy may be less effective, however, when thrombus formation is related to stasis, as might occur in the venous system or the left atrium. In a randomized study of 70 patients, warfarin reduced markers of thrombogenesis, whereas combination antiplatelet therapy with aspirin and clopidogrel did not. No trial has shown antiplatelet therapy to be equivalent to adjusted-dose warfarin in patients at high risk for embolic events.

New anticoagulants

New agents that have been studied or used for treatment of atrial fibrillation include indirect thrombin inhibitors, acting via antithrombin III, and direct thrombin inhibitors. The indirect thrombin inhibitors include the low-molecular-weight heparins (enoxaparin, dalteparin, tinzaparin, ardeparin) and heparin derivatives (danaparoid). Low-molecular-weight heparin (LMWH) has been used in some studies of atrial fibrillation but is of limited long-term use because of its parenteral route of administration. The direct thrombin inhibitors include hirudin, bivalirudin, lepirudin, argatroban, efegatran, ingogatran, antithrombin III, melagatran, and ximelagatran. Of the direct thrombin inhibitors, ximelagatran is an oral agent that has been the subject of large randomized trials targeting patients with atrial fibrillation.

Low-molecular-weight heparin

Randomized trials assessing efficacy of LMWH for prevention of thromboembolism in atrial fibrillation have been

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>No. of risk factors</th>
<th>Recommendation</th>
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<tr>
<td>High*</td>
<td>1</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Moderate†</td>
<td>&gt;1</td>
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</tr>
<tr>
<td></td>
<td>1</td>
<td>Warfarin or aspirin</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>Aspirin</td>
</tr>
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*High risk factors: Prior transient ischemic attack, systemic embolus, or stroke; hypertension; poor left ventricular function; rheumatic mitral valve disease; prosthetic heart valve; age >75 years.
†Moderate risk factors: Age 65–75 years, diabetes mellitus, coronary artery disease with preserved left ventricular systolic function.
Sparse. In a study of patients with acute ischemic stroke and atrial fibrillation, no significant differences in recurrent stroke, hemorrhage, death rate, or functional outcome were reported in patients treated with dalteparin versus aspirin. In the ongoing ACUTE II study, patients with atrial fibrillation of at least 2 days’ duration undergoing DC cardioversion are being randomized to a TEE-guided unfractionated heparin versus enoxaparin approach. Although not currently indicated by the US Food and Drug Administration (FDA) for use as bridge therapy, LMWH has been frequently used clinically for perioperative and postoperative bridging in patients with atrial fibrillation. Data on need for bridge therapy have been lacking, and guidelines support stopping warfarin for up to 1 week periprocedurally without heparin or LMWH bridging. However, bridge therapy with unfractionated heparin or LMWH may be justified in high-risk patients (e.g., those with mechanical mitral valve prosthesis, prior transient ischemic attack/cerebrovascular accident, or severe stroke in the left atrium).

### Thrombin inhibitors

Melagatran is an intravenous direct thrombin inhibitor that is markedly hydrophilic at intestinal pH, resulting in poor gastrointestinal absorption. Ximelagatran is an oral direct thrombin inhibitor that has an ethyl- and hydroxy-protecting group, which makes it less hydrophilic, leading to better bioavailability independent of food intake. The advantages of ximelagatran over warfarin include ximelagatran’s prompt onset and offset of anticoagulation action, wider therapeutic margin, lower potential for food and drug interactions, and less need for dosage adjustments or coagulation monitoring. Ximelagatran is renally excreted.

In the Stroke Prevention using an ORal Thrombin Inhibitor in atrial fibrillation (SPORTIV) III and V trials, more than 7,000 patients with nonvalvular atrial fibrillation were randomized in open-label and double-blind fashion to adjusted-dose warfarin (PT/INR 2–3) versus fixed-dose ximelagatran (36 mg bid), respectively. Ximelagatran appeared as effective as warfarin in preventing stroke and systemic embolic events. Overall, these trials concluded that ximelagatran is not inferior to warfarin in the prevention of stroke and embolic events and may be associated with a decreased combined incidence of major and minor bleeding. Ximelagatran was associated with increased alanine aminotransferase (ALT) in approximately 6% of patients.

With the advantages of fixed dosing, lack of monitoring requirements, and possibly less bleeding potential, it was hoped ximelagatran would become the preferred oral therapy for stroke and embolism prevention in patients with atrial fibrillation and additional risk factors. However, several potential caveats should be noted. Efficacy in patients with valvular disease, as well as in stroke prevention for cardioversion, remains to be established. The fixed-dosing regimen may have some limitations at the extremes of weight, particularly in obese patients. Because ximelagatran is renally excreted, dosage adjustments in renal insufficiency may need to be established. The significance of liver function test abnormalities, however, were concerning to an FDA panel, which recently recommended against approval of ximelagatran pending further studies. A reversing agent is not readily available. Nevertheless, effects should not be nearly as long lasting as with warfarin, and the onset of action should be much quicker.

### Nonpharmacologic approaches

Left atrial appendage occlusion has been studied using transvenous endovascular occlusion devices, as well as thoracoscopic or surgical appendectomy, ligation, and stapling.

#### Percutaneous left atrial appendage occlusion

Devices that can be percutaneously delivered to occlude the left atrial appendage have been devised. Early clinical experience with the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device was reported in

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<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommendation</th>
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<tbody>
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<td>&lt;60 years</td>
<td>No heart disease; no risk factors</td>
<td>ASA 325 mg qd or no therapy</td>
</tr>
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<td></td>
<td>Heart disease; no risk factors</td>
<td>ASA 325 mg qd</td>
</tr>
<tr>
<td>60–75 years</td>
<td>No risk factors</td>
<td>ASA 325 mg qd</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus or coronary artery disease</td>
<td>OAC INR 2.0–3.0, ASA 81–162 mg qd optional</td>
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<tr>
<td>&gt;75 years</td>
<td>Risk factors or Thyrotoxicosis</td>
<td>OAC INR ~2.0</td>
</tr>
<tr>
<td>Any age</td>
<td>High risk factors</td>
<td>OAC INR 2.0–3.0 (2.5–3.5 or higher may be appropriate)</td>
</tr>
</tbody>
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Risk factors: Heart failure, left ventricular ejection fraction <0.35, hypertension.

High risk factors: Rheumatic heart disease (mitral stenosis), prosthetic heart valves, prior thromboembolism, persistent atrial thrombus on transesophageal echocardiography.

ASA = acetylsalicylic acid; OAC = oral anticoagulation.

15 patients with chronic atrial fibrillation who were at high risk for stroke and were poor candidates for warfarin. The device consists of nitinol struts covered with an e-PTFE membrane that is delivered via a percutaneous transseptal catheter to the left atrial appendage. Successful occlusion was achieved in 100%, with hemopericardium in one patient. Longer-term studies are ongoing.

**Surgical left atrial appendage ligation or occlusion**

Left atrial appendage ligation has been performed during concomitant cardiac surgical procedures. However, ligation often is incomplete by echocardiography. In a study of 50 patients who underwent mitral valve surgery with left atrial appendage ligation and TEE 6 days to 13 years after the procedure, incomplete ligation was detected in more than one third of patients. Spontaneous echocardiographic contrast was observed in half of patients, and almost one fourth of patients had thromboembolic events. A large randomized trial of left atrial occlusion during routine coronary artery bypass graft surgery for long-term stroke prevention is ongoing. Left atrial appendage occlusion will be achieved via suturing or vascular stapling. A pilot trial of 100 patients with TEE performed at least 6 weeks after surgery will be performed to verify the efficacy of surgical methods.

Until further studies show benefits in stroke reduction, unless patients are undergoing cardiac surgery, left atrial appendage occlusion methods may best be reserved for high-risk patients with contraindications to anticoagulation.

**Summary**

Currently, warfarin is the standard for stroke reduction in atrial fibrillation. Warfarin reduces the risk of systemic embolism and stroke in atrial fibrillation and is indicated as long-term treatment for patients with atrial fibrillation and risk factors for stroke, even when a rhythm control strategy is being used. Unless contraindications to anticoagulation develop, warfarin should not be stopped in these patients, even if atrial fibrillation is paroxysmal or if sinus rhythm appears to be maintained. Warfarin should be maintained at therapeutic levels (PT/INR 2.0–3.0) for best efficacy and safety. Therapeutic PT/INRs ≥2.0 are particularly important at and prior to cardioversion attempts. Aspirin may be used in some low-risk patients with lone atrial fibrillation, no additional risk factors, and age <65 years.

New therapies may revolutionize the approach to stroke reduction in atrial fibrillation and include thrombin inhibitors and, in selected patients, left atrial occlusion techniques. However, safety and efficacy, particularly compared to warfarin, need to be established prior to routine use of these treatments.

**References**