

## Therapies for the prevention of stroke and other vascular events in atrial fibrillation and atrial flutter

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Stroke is the major clinical cause of atrial fibrillation (AF). Treatments to reduce the risk of stroke and other vascular events are an important part of AF management. Oral anticoagulation is effective against stroke and has an acceptable risk of adverse events (primarily bleeding). Acetylsalicylic acid is less effective than oral anticoagulants but better tolerated. Anticoagulants are recommended for AF patients with risk factors for stroke.

**Key Words:** *Acetylsalicylic acid; Anticoagulation; Atrial fibrillation; Prevention; Stroke*

### Traitements préventifs de l'AVC et autres complications vasculaires associés à la fibrillation et au flutter auriculaire

L'AVC est la principale cause clinique de la fibrillation auriculaire (FA). Les traitements visant à réduire le risque d'AVC et autres complications vasculaires sont une partie importante de la prise en charge de la FA. L'anticoagulation orale est efficace contre l'AVC et comporte un risque acceptable de réactions indésirables (principalement les saignements). L'acide acétylsalicylique est moins efficace que les anticoagulants oraux, mais elle est mieux tolérée. Les anticoagulants sont recommandés chez les patients qui font de la FA et qui sont exposés à des facteurs de risque d'AVC.

### RECOMMENDATIONS

#### Class I

- 1) All patients with atrial fibrillation (AF) or atrial flutter (AFL) should be stratified for risk of stroke and vascular events, and for risk of bleeding with anticoagulation therapy (level of evidence A).
- 2) Patients with AF or AFL at high risk of stroke should receive oral anticoagulation unless there is an excessive risk of hemorrhage (level of evidence A).
- 3) Patients with AF or AFL at intermediate risk should receive either oral anticoagulation or acetylsalicylic acid (ASA) (75 mg/day to 325 mg/day), and low-risk patients may receive ASA unless there is excessive risk of bleeding (level of evidence B).
- 4) Patients undergoing direct current cardioversion for AF or AFL should receive therapeutic oral anticoagulation for at least three to four weeks before, and at least three to four weeks after, the procedure. Low-risk patients may undergo cardioversion without oral anticoagulation if performed within 48 h of arrhythmia onset. Transesophageal echocardiography (TEE)-guided cardioversion (following protocol from the Assessment of Cardioversion Using Transesophageal Echocardiography

[ACUTE] trial) is an acceptable alternative to oral anticoagulation (level of evidence C).

- 5) When reversal of oral anticoagulation is required (ie, for surgery), therapy should be discontinued five to six days beforehand. Consideration should be given to the use of heparin or low-molecular-weight heparin during this period in higher risk patients (level of evidence C).

### STROKE, VASCULAR EVENTS AND RISK STRATIFICATION

The risk of stroke and vascular events in AF is well documented. AF increases the overall risk of stroke to a rate of 4.5% per year (1). This risk, however, varies by an order of magnitude according to the clinical factors associated with AF. In healthy, young AF patients with no other clinical conditions, the risk of stroke and other vascular events is less than 1% per year (2). On the other hand, in elderly patients with multiple risk factors (such as prior stroke or hypertension), the risk of vascular events may exceed 10% per year (3). Therefore, risk stratification should guide therapy. In 1996, the Canadian Cardiovascular Society (CCS) issued guidelines recommending risk stratification according to the proposal from the AF investigators (4). Subsequently, in 1998, the American College of Chest Physicians issued guidelines that updated this

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**TABLE 1**  
**Risk factor stratification**

High-risk factors	Moderate-risk factors
History of stroke/TIA	Age between 65 and 75 years
Hypertension	Diabetes
Reduced LV function	Coronary artery disease without
Age over 75 years	LV dysfunction
Mitral stenosis	
Prosthetic heart valve	

*LV Left ventricular; TIA Transient ischemic attack*

approach, incorporating new information regarding the value of echocardiography. The risk stratification outlined by the American College of Chest Physicians in 1998 is widely accepted, comprehensive and recommended (5). Patients are divided into low, medium and high categories of risk based on clinical parameters. Tables 1 and 2 present this risk stratification system.

Intermittent AF is associated with a risk of stroke that is similar to that of permanent AF. In an analysis of patients involved in the Stroke Prevention in Atrial Fibrillation (SPAF) trials (6), the annual risk of stroke was found to be 3.2% in patients with intermittent AF and 3.3% in those with permanent AF. Patients with a single episode of AF can, in general, be considered to be similar to patients with recurrent AF. The minimum duration of AF that requires antithrombotic therapy is unknown. It has recently been recognized that AF recurrence is often not symptomatic, even in patients with a history of highly symptomatic episodes. Physicians should not rely on symptoms to assess the value of using antithrombotic therapy in AF. Although data regarding AFI are sparse, there is considerable overlap between AFI and AF within patients. It appears prudent to manage patients with AFI in a manner similar to that recommended for AF.

**THERAPEUTIC RECOMMENDATIONS**

The 1996 CCS guidelines (4) recommended oral anticoagulation for patients with AF who were stratified to the high-risk group. These recommendations were based on the results of placebo-controlled trials of anticoagulation in AF. Several trials published in the intervening period have served to solidify these recommendations. A reanalysis of all currently available evidence, including a meta-analysis of placebo-controlled trials and comparative trials (7), showed that oral anticoagulation is a highly effective therapy, resulting in a greater than 60% reduction in stroke. ASA reduces the risk of stroke by approximately 20%. ASA therapy has been evaluated at a variety of doses, from 50 mg/day to 1200 mg/day in patients with AF, without any clear indication that any particular dose is superior (7). The Antithrombotic Trialists' Collaboration supports the use of doses from 75 mg/day to 325 mg/day in a wide variety of patient groups (8). Therefore, this dose range of ASA is preferred when ASA is to be used in AF. Compared with ASA, oral anticoagulation is more effective (50% reduction in stroke, 30% reduction in vascular events), but confers a higher risk of bleeding. In the most recent meta-analysis of oral anticoagulation versus ASA trials (9), oral anticoagulation reduced the risk of stroke by 45% (hazard ratio [HR]=0.55, 95% CI 0.43 to 0.71) and reduced the risk of overall cardiovascular events by 29% (HR=0.71, 95% CI 0.59 to 0.85).

**TABLE 2**  
**Antithrombotic therapy by risk group**

Risk factors	Recommended therapy
Any high-risk factors or more than one moderate-risk factor	Warfarin (target international normalized ratio of 2.5 [range 2.0 to 3.0])
One moderate-risk factor	Acetylsalicylic acid 75 mg/day to 325 mg/day, or warfarin (target international normalized ratio of 2.5 [range 2.0 to 3.0])
No high-risk factors and no moderate-risk factors	Acetylsalicylic acid 75 mg/day to 325 mg/day

Compared with ASA, oral anticoagulation increased the risk of major bleeding by 71% (HR=1.71, 95% CI 1.21 to 2.41). In 1996, the target international normalized ratio (INR) recommended for anticoagulant prophylaxis was between 2.0 to 3.0. Hylek et al (10) have confirmed that this recommendation is appropriate and have emphasized the increased risk of stroke associated with INR values below 2.0.

Several randomized trials (11,12) of oral anticoagulation in AF have used an extensive screening process to eliminate patients at increased risk of hemorrhage. These studies estimated that these criteria would exclude 15% to 30% of patients with AF. The known risk factors for hemorrhage include prior stroke, advanced age and underlying malignancy. As has been noted in a number of guidelines, including the 1996 CCS consensus conference guidelines, the physician must balance the benefits of stroke prevention against the risks of hemorrhage for each patient in which antithrombotic therapy is to be used. ASA therapy may be appropriate for patients in whom the risk-to-benefit ratio of hemorrhage versus stroke prevention is high with oral anticoagulation.

Although the benefit of warfarin in preventing thromboembolic events in patients with AF has been unquestionably demonstrated, many patients do not receive the drug because of the rigours involved in monitoring the INR and maintaining a therapeutic level. These challenges could lead to underutilization and either bleeding or thromboembolism if the INR is too high or too low, respectively. These drawbacks to warfarin have led to the investigation of new agents that act on different phases of the coagulation process, such as direct thrombin inhibition (13,14). Other studies have focused on combinations of antiplatelet agents. The ability to administer drugs without significant drug or food interaction and with consistent dosing would improve patient acceptance of antithrombotic therapy and provide consistent therapeutic efficacy.

**CONVERSION TO SINUS RHYTHM**

Patients undergoing electrical cardioversion of AF or AFI face a risk of thromboembolism that has been estimated to be between 1% and 5% in case series. The 1996 CCS guidelines recommended that patients undergoing electrical cardioversion be treated with therapeutic anticoagulation for at least three to four weeks before and at least three to four weeks after the procedure. Cardioversion within 48 h of the onset of AF could be performed without anticoagulation. Although not based on the results of clinical trials, this recommendation is widely accepted in the international cardiology community. It is reasonable to continue this approach, although caution is now advised for cardioversion of the high-risk AF patient without oral anticoagulation or TEE, even within 48 h of onset. In 2001, the practice

of using TEE to assess the risk of thromboembolism associated with cardioversion was evaluated in the ACUTE study (15), a major clinical trial in which patients with AF lasting more than two days or those with AF with previous AF were randomized to a TEE-guided approach or the conventional approach. Patients randomly assigned to the TEE-guided strategy received anticoagulation with heparin just before TEE, and subsequent cardioversion was refused if no thrombus was identified in the left atria or its appendage. Oral anticoagulation therapy was started and continued for four weeks after cardioversion. Cardioversion was postponed if left atrial thrombus was identified by TEE. Similar outcomes were observed in the two groups for stroke, bleeding and maintenance of sinus rhythm at eight weeks postcardioversion. The TEE-guided approach to

cardioversion provided results that were comparable to the standard approach. In general, there is no reason to prefer TEE, although it is useful when prompt cardioversion is desired.

### TEMPORARY DISCONTINUATION OF ORAL ANTICOAGULATION

It is occasionally necessary to discontinue oral anticoagulation for invasive procedures and elective surgery. In general, INR levels return to normal within five to six days; therefore, discontinuation for this period is recommended, as is an evaluation of the INR on the morning of surgery. In high-risk patients, the risk of stroke during this period would justify the use of heparin or low-molecular-weight heparin until 6 h to 12 h before surgery.

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