Society Guidelines

Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Implementing GRADE and Achieving Consensus

Anne M. Gillis, MD, FRCPC,a Allan C. Skanes, MD, FRCPC,b and the CCS Atrial Fibrillation Guidelines Committeec

aDepartment of Cardiac Sciences, University of Calgary and Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada
bDivision of Cardiology, University Hospital, University of Western Ontario, London, Ontario, Canada
cFor a complete listing of committee members, see page 30.

ABSTRACT
This article describes the process of the Canadian Cardiovascular Society 2010 atrial fibrillation (AF) guidelines update. Guideline development was based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system of evaluation. GRADE separates the quality of evidence (very low, low, moderate, or high quality) from the strength of recommendations (strong or conditional, ie, weak). GRADE allows acknowledgement of values and preferences in the provision of clinical care as well as costs of interventions in determining the strength of recommendations. Disclosures of relationships with industry or other potential conflicts of interest were reported at the outset and annually. Each recommendation was approved by at least a two-thirds majority of the voting panel (those with a significant conflict recusing themselves from voting on those specific recommendations).

Atrial fibrillation (AF) is the most common sustained arrhythmia treated in clinical practice and is associated with substantial morbidity. Indeed, the lifetime risk of developing AF in individuals older than 40 years is 1 in 4.1 The Canadian Cardiovascular Society (CCS) last published a set of recommendations on the diagnosis and management of AF in 2005.2 Since then, major advances in the management of AF have occurred, including the results of clinical trials providing guidance on pharmacologic therapies for management of AF,3-5 antithrombotic therapies for prevention of systemic thromboembolism,6,7 the continuing evolution of catheter ablation for treatment of AF,8-10 and the development of a simple semiquantitative scale that closely approximates patient-reported subjective measures of quality of life of AF have occurred, including the results of clinical trials providing guidance on pharmacologic therapies for management of AF,3-5 antithrombotic therapies for prevention of systemic thromboembolism,6,7 the continuing evolution of catheter ablation for treatment of AF,8-10 and the development of a simple semiquantitative scale that closely approximates patient-reported subjective measures of quality of life

received for publication November 4, 2010. Accepted November 11, 2010.
Corresponding author: Dr Anne M. Gillis, Department of Cardiac Sciences, The University of Calgary, 3280 Hospital Dr NW, Calgary, Alberta, Canada T2N 4N1. Tel: 403-220-6841; fax: 403-270-0313.
E-mail: mgillis@ucalgary.ca
The disclosure information of the authors and reviewers are available from the CCS on the following Web sites: www.ccs.ca and www.ccsguidelineprograms.ca.
This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific

RÉSUMÉ
Dans cet article, nous décrivons le processus de mise à jour des lignes directrices de 2010 en matière de fibrillation auriculaire (FA) de la Société Canadienne de Cardiologie. L’élaboration des lignes directrices repose sur le système d’évaluation Grading of Recommendations Assessment, Development and Evaluation (GRADE). Le système d’évaluation GRADE distingue la qualité de la preuve (très faible, faible, moyenne ou élevée) de la force des recommandations (forte ou conditionnelle, i.e. faible). Le système d’évaluation GRADE permet de reconnaître les valeurs et les préférences en ce qui a trait à la prestation des soins cliniques, ainsi que les coûts des interventions, pour déterminer la force des recommandations. Les relations du groupe d’experts avec l’industrie ou autres conflits d’intérêts potentiels ont été divulguées initialement et annuellement. Chaque recommandation a été approuvée par au moins les deux tiers du groupe d’experts (ceux qui étaient en conflit d’intérêt se sont abstenus de voter sur certaines recommandations).

A complete list of the Primary and Secondary Panel Members are listed in the Appendix on page 30.
in AF. In 2009, the CCS convened a primary panel of experts to undertake a comprehensive review of current knowledge and management strategies in the field of AF and to develop an up-to-date evidence-based set of recommendations, easily available to primary care physicians, emergency room physicians, internists, and cardiologists, on the diagnosis and management of patients with AF. The guidelines are broadly applicable across a spectrum of practice environments. It is expected that optimized management of AF may improve quality of life and reduce rates of stroke and hospitalization for AF-related causes across all levels of care in a large population of patients.

Simultaneous with the evolution in treatments for AF, the CCS has been implementing a unique Canadian knowledge translation (KT) model for disseminating guidelines. Known as the CCS closed-loop model for KT, it has the aim of improving the uptake and integration of guidelines into clinical practice. The model involves assembling a multidisciplinary primary panel to draft guidelines and then using a multi-pronged, multimedia approach to dissemination. Dissemination strategies involve regional and national face-to-face, interactive, case-based workshops and a dedicated Web site featuring practical tools and tips for end users as well as synchronous and asynchronous e-learning programs. Feedback from KT program participants and guideline end users drives the selection and development of new content for subsequent annual guideline updates, which are then disseminated and evaluated as part of a regular annual cycle. This cyclical approach to guideline development, dissemination, and evaluation results in a powerful compendium of guidelines that address a specific topic and are highly relevant to and highly valued by care providers. The CCS experienced success with this model through applying it to heart failure beginning in 2005. As AF emerged as a major topic requiring updated, comprehensive, multidisciplinary guidelines, the CCS has embarked on this second closed-loop KT program.

A primary working group was formed and met face-to-face in October 2009 to agree on the process of achieving consensus, to address issues related to real or perceived conflict of interest related to specific recommendations, to discuss the process of weighing the strength of a recommendation and the quality of evidence supporting the recommendation, to identify the full membership of the primary panel, to finalize topics for guideline development, and to develop writing groups for each topic. Conflicts were disclosed prior to forming the writing groups. The Appraisal of Guidelines for Research and Evaluation was used to guide primary panel structure and guideline development. Membership of the primary panel was expanded to include wide representation (from primary care, internal medicine, emergency medicine, and general cardiology, in addition to cardiology and electrophysiology) and to increase the proportion of panel members having no conflict of interest or relationships with industry to 5 of 19 members (26%). Writing groups were developed with specific attention to content expertise and conflict of interest. It was decided that each recommendation must be approved by a two-thirds majority of the voting panel (those with a significant conflict recusing themselves from voting on those specific recommendations).

The working groups undertook a review of the English language literature, using MEDLINE or Cochrane library searches and a critical appraisal of the evidence focusing predominantly on the results of randomized clinical trials and systematic reviews. In the absence of such data, recommendations were based on the results of large cohort studies or smaller clinical studies. The recommendations were finalized by informed consensus through one face-to-face meeting, conference calls, e-mail correspondence, and final review by all members of the primary panel. Specifically, the writing group presented each preliminary recommendation with its attendant supporting evidence in summary form. Following discussion, an anonymous vote was obtained in which a two-thirds majority was considered consensus. Failing consensus, further discussion was directed at areas of divergence of opinion until either consensus was reached or it was deemed by the chair(s) that consensus would not be reached and a recommendation could not be made. A two-thirds majority was achieved in all cases. The primary panelists were principally responsible for the document, but an independent secondary panel reviewed the recommendations and provided feedback. All members of the primary panel formally approved the final document prior to submission to the Guidelines Committee and CCS Executive for review and approval.

As outlined in a separate communication, this is the first CCS Guidelines Panel to use the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system of evaluation, replacing the American College of Cardiology and American Heart Association scale for level of evidence that was used previously. In the past, guidelines have been criticized as being inconsistent in how they rate quality of evidence and strength of recommendations, which may lead to confusion in interpretation of the recommendations and failure to adhere to the guidelines. GRADE (www.gradeworkinggroup.org) was created by a group of international guideline developers, including a large Canadian representation to address the shortcomings of other rating systems. The approach separates the quality of evidence (very low, low, moderate, or high quality; see Table 1), from the strength of recommendations (strong or conditional, ie, weak; see Table 2). GRADE allows acknowledgment of values and preferences in the provision of clinical care, as well as of the cost of therapies, in determining the strength of recommendations. GRADE has already been adopted by more than 45 international organizations, including the World Health Organiza-

### Table 1. GRADE: Rating quality of evidence

<table>
<thead>
<tr>
<th>Quality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Future research unlikely to change confidence in estimate of effect; eg, multiple well-designed, well-conducted clinical trials</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research likely to have an important impact on confidence in estimate of effect and may change the estimate; eg, limited clinical trials, inconsistency of results or study limitations</td>
</tr>
<tr>
<td>Low</td>
<td>Further research very likely to have a significant impact on the estimate of effect and is likely to change the estimate; eg, small number of clinical studies or cohort observations</td>
</tr>
<tr>
<td>Very low</td>
<td>The estimate of effect is very uncertain; eg, case studies, consensus opinion</td>
</tr>
</tbody>
</table>

Modified and reprinted with permission from Guyatt, et al. GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
tion, the American College of Physicians, the Cochrane Collaboration, the American College of Chest Physicians, and many others.

The updated guidelines are published in 7 articles:

1. Etiology and Initial Investigations
2. Management of Recent-Onset Atrial Fibrillation and Flutter in the Emergency Department
3. Rate and Rhythm Management
4. Catheter Ablation for Atrial Fibrillation/Atrial Flutter
5. Surgical Therapy
6. Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter
7. Prevention and Treatment of Atrial Fibrillation Following Cardiac Surgery

A specific chapter on atrial tachyarrhythmias in the congenital heart disease population was not undertaken at this time but is planned for a future update.

References

13. Kerr CR. CCS guidelines and position statements are important, but do they make the GRADE? Can J Cardiol 2010;26:177-8.

Table 2. Factors determining the strength of the recommendation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence</td>
<td>The higher the quality of evidence, the greater the probability that a strong recommendation is indicated; eg, strong recommendation that patients with AF at moderate to high risk of stroke be treated with oral anticoagulants.</td>
</tr>
<tr>
<td>Difference between desirable and undesirable effects</td>
<td>The greater the difference between desirable and undesirable effects, the greater the probability that a strong recommendation is indicated; eg, strong recommendation that patients with AF ≥ 48-h duration receive oral anticoagulation therapy for at least 3 wk prior to planned cardioversion and 4 wk following.</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>The greater the variation or uncertainty in values and preferences, the higher the probability that a conditional recommendation is indicated; eg, aspirin may be a reasonable alternative to oral anticoagulant therapy in patients at low risk of stroke.</td>
</tr>
<tr>
<td>Cost</td>
<td>The higher the cost, the lower the likelihood that a strong recommendation is indicated; eg, conditional recommendation for catheter ablation as first-line therapy for AF.</td>
</tr>
</tbody>
</table>
### Appendix 1. Primary and secondary panel members

#### Primary panel members

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anne M. Gillis, MD, FRCP(C)</td>
<td>Cochair Dept of Cardiac Sciences, University of Calgary, Libin Cardiovascular Institute of Alberta</td>
</tr>
<tr>
<td>Allan Skanes, MD, FRCP(C)</td>
<td>Cochair Division of Cardiology, University of Western Ontario</td>
</tr>
<tr>
<td>Stuart Connolly, MD, FRCP(C)</td>
<td>Member Division of Cardiology, Department of Medicine, McMaster University</td>
</tr>
<tr>
<td>John Cairns, MD, FRCP(C)</td>
<td>Member Faculty of Medicine, University of British Columbia</td>
</tr>
<tr>
<td>Jafna Cox, BA, MD, FRCP(C), FACC</td>
<td>Member Division of Cardiology, Dalhousie University</td>
</tr>
<tr>
<td>Paul Durian, MD, MSc, FRCP(C)</td>
<td>Member Division of Cardiology, University of Toronto</td>
</tr>
<tr>
<td>Jeff Healey, MD, FRCP(C)</td>
<td>Member Division of Cardiology, Medicine Department, McMaster University</td>
</tr>
<tr>
<td>Laurent Macle, MD, FRCP(C)</td>
<td>Member Electrophysiology Service, Montreal Heart Institute, Université de Montréal</td>
</tr>
<tr>
<td>Sean McMurtuy, MD, PhD, FRCP(C)</td>
<td>Member Division of Cardiology, University of Alberta</td>
</tr>
<tr>
<td>Brent Mitchell, MD, FRCP(C)</td>
<td>Member University of Calgary, Libin Cardiovascular Institute of Alberta</td>
</tr>
<tr>
<td>Stanley Nattel, MD, FRCP(C)</td>
<td>Member Montreal Heart Institute, Université de Montréal</td>
</tr>
<tr>
<td>Pierre Page, MD, FRCPS</td>
<td>Member Montreal Heart Institute, Université de Montréal</td>
</tr>
<tr>
<td>Ratika Parkash, MD, MSc, FRCP(C)</td>
<td>Member Division of Cardiology, Dalhousie University</td>
</tr>
<tr>
<td>P. Timothy Pollak, MD, PhD FRCP(C)</td>
<td>Member Department of Cardiac Sciences, and Physiology &amp; Pharmacology, University of Calgary</td>
</tr>
<tr>
<td>Michael Stephenson, MD, CCFP, FCFP</td>
<td>Member Representative of The College of Family Physicians of Canada, Ancaster, Ontario</td>
</tr>
<tr>
<td>Ian Stiell, MD, MSc, FRCP(C)</td>
<td>Member Department of Emergency Medicine, Ottawa Hospital Research Institute, University of Ottawa</td>
</tr>
<tr>
<td>Mario Talajic, MD, FRCP(C)</td>
<td>Member Montreal Heart Institute, Université de Montréal</td>
</tr>
<tr>
<td>Teresa Tsang, MD, FRCP(C)</td>
<td>Member Division of Cardiology, University of British Columbia</td>
</tr>
<tr>
<td>Arul Verma, MD, FRCP(C)</td>
<td>Member Heart Rhythm Program, Southlake Regional Health Centre</td>
</tr>
<tr>
<td>Jan Brozek, MD, PhD</td>
<td>Special Collaborator Departments of Clinical Epidemiology &amp; Biostatistics and Medicine, McMaster University</td>
</tr>
<tr>
<td>Grant Stotts, MD, FRCP(C)</td>
<td>Special Collaborator University of Ottawa, The Ottawa Hospital, Representative of the Canadian Stroke Network</td>
</tr>
</tbody>
</table>

#### Secondary panel members

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm Arnold, MD, FRCP(C)</td>
<td>Member Division of Cardiology, University of Western Ontario</td>
</tr>
<tr>
<td>David Bewick, MD, FRCP(C)</td>
<td>Member St. John’s, New Brunswick</td>
</tr>
<tr>
<td>Vidal Esebag, MD, MSc, FRCP(C)</td>
<td>Member Department of Cardiology, McGill University Health Center</td>
</tr>
<tr>
<td>Milan Gupta, MD, FRCP(C)</td>
<td>Member Division of Cardiology, Brampton Civic Hospital</td>
</tr>
<tr>
<td>Brett Heilbron, MBChB, FRCP(C)</td>
<td>Member St. Paul’s Hospital Heart Centre, University of British Columbia</td>
</tr>
<tr>
<td>Charles Kerr, MD, FRCP(C)</td>
<td>Member St. Paul’s Hospital Heart Centre, University of British Columbia</td>
</tr>
<tr>
<td>Bob Kimiz, MD, FRCS(C)</td>
<td>Member Division of Cardiac Surgery, University of Western Ontario</td>
</tr>
<tr>
<td>Jan Surkes, BA (hon) MD FRCP(C)</td>
<td>Member Department of Medicine, Langley Memorial Hospital, Langley, BC</td>
</tr>
<tr>
<td>George Wyse, MD, PhD, FRCP(C)</td>
<td>Member Department of Cardiac Sciences, University of Calgary, Libin Cardiovascular Institute of Alberta</td>
</tr>
</tbody>
</table>

30 Canadian Journal of Cardiology

Volume 27 2011
ABSTRACT
The initial evaluation of patients with atrial fibrillation (AF) should include a comprehensive history, physical examination, and initial investigations. The initial evaluation of patients with AF has several important purposes, including the identification of the etiology of AF, particularly the identification of reversible causes of AF; the description of the pattern of AF; the assessment of the degree of symptomatic impairment due to AF; the assessment of the thromboembolic risk of the patient; and the identification of common comorbidities. Additional investigations may then be undertaken, with the decision guided by the initial evaluation. A comprehensive and systematic initial evaluation forms the foundation for a patient-specific plan for the management of AF.

RÉSUMÉ
L’évaluation initiale des patients présentant une fibrillation auriculaire (FA) devrait comprendre un questionnaire détaillé, un examen physique et un bilan sanguin de base. Cette première évaluation a pour but d’identifier l’étiologie (et particulièrement les causes réversibles) de la FA, de décrire le type de FA (paroxystique, persistante ou permanente), d’évaluer le degré de symptomatologie du patient, d’identifier ses co-morbidités et d’évaluer son risque thromboembolique. L’indication d’investigations supplémentaires et le plan de traitement spécifique au patient dépendent de cette évaluation initiale qui doit être complète et systématique.

Initial Evaluation of AF
The initial evaluation of a patient with atrial fibrillation (AF) should consist of a comprehensive history (including social, drug, and family history), physical examination, and initial investigations (Table 1). This evaluation has many important purposes, including assessing the degree of symptomatic impairment due to AF, developing a therapeutic strategy for symptom relief, assessing and managing thromboembolic risk, establishing prognosis, and, where possible, identifying the underlying etiology of AF. The identification of the etiology of AF during the initial investigation is particularly important for several reasons:

Funding Information

Received for publication November 9, 2010. Accepted November 9, 2010.

Corresponding author: Jeff S. Healey, Population Health Research Institute, McMaster University, DBCVSRI Building, Hamilton Health Sciences-General Site, 237 Barton St E, Room C3-121, Hamilton, Ontario, L8L 2X2 Canada. Tel.: 905-527-0271, ext 40319; fax: 905-523-9165.
Email address: Jeff.Healey@phri.ca

The disclosure information of the authors and reviewers is available from the CCS on the following Web sites: www.ccs.ca and www.ccsguidelineprograms.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.
Table 1. Baseline evaluation of atrial fibrillation for all patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination</td>
<td>Establish pattern (new onset, paroxysmal, persistent, or permanent)</td>
</tr>
<tr>
<td>Establish severity (including impact on quality of life)</td>
<td></td>
</tr>
<tr>
<td>Identify etiology</td>
<td></td>
</tr>
<tr>
<td>Identify reversible causes (hyperthyroidism, ventricular pacing,</td>
<td></td>
</tr>
<tr>
<td>supraventricular tachycardia, exercise, etc)</td>
<td></td>
</tr>
<tr>
<td>Identify risk factors whose treatment could reduce recurrent AF or</td>
<td></td>
</tr>
<tr>
<td>improve overall prognosis (ie, hypertension, sleep apnea, left</td>
<td></td>
</tr>
<tr>
<td>ventricular dysfunction, etc)</td>
<td></td>
</tr>
<tr>
<td>Social history to identify potential triggers (ie, alcohol, intensive</td>
<td></td>
</tr>
<tr>
<td>aerobic training, etc)</td>
<td></td>
</tr>
<tr>
<td>Elicit family history to identify potentially heritable causes of AF</td>
<td></td>
</tr>
<tr>
<td>(particularly in lone AF)</td>
<td></td>
</tr>
<tr>
<td>Determine thromboembolic risk</td>
<td></td>
</tr>
<tr>
<td>Determine bleeding risk to guide appropriate antiplatelet or</td>
<td></td>
</tr>
<tr>
<td>antithrombotic therapy</td>
<td></td>
</tr>
<tr>
<td>Review prior pharmacologic therapy for AF, both for efficacy and for</td>
<td></td>
</tr>
<tr>
<td>adverse effects</td>
<td></td>
</tr>
<tr>
<td>Measure blood pressure and heart rate</td>
<td></td>
</tr>
<tr>
<td>Determine patient height and weight</td>
<td></td>
</tr>
<tr>
<td>Comprehensive precordial cardiac examination and assessment of</td>
<td></td>
</tr>
<tr>
<td>jugular venous pressure and carotid and peripheral pulses to detect</td>
<td></td>
</tr>
<tr>
<td>evidence of structural heart disease</td>
<td></td>
</tr>
<tr>
<td>12-Lead electrocardiogram</td>
<td></td>
</tr>
<tr>
<td>Document presence of AF by electrocardiography</td>
<td></td>
</tr>
<tr>
<td>Assess for structural heart disease (myocardial infarction, ventricular</td>
<td></td>
</tr>
<tr>
<td>hypertrophy, atrial enlargement, congenital heart disease) or</td>
<td></td>
</tr>
<tr>
<td>electrical heart disease (ventricular preexcitation, Brugada syndrome)</td>
<td></td>
</tr>
<tr>
<td>Identify risk factors for complications of therapy for AF (conduction</td>
<td></td>
</tr>
<tr>
<td>disturbance, sinus node dysfunction, or repolarization); document</td>
<td></td>
</tr>
<tr>
<td>baseline PR, QT, or QRS intervals</td>
<td></td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
</tr>
<tr>
<td>Document ventricular size, wall thickness, and function</td>
<td></td>
</tr>
<tr>
<td>Evaluate left atrial size (if possible, left atrial volume)</td>
<td></td>
</tr>
<tr>
<td>Exclude significant valvular or congenital heart disease</td>
<td></td>
</tr>
<tr>
<td>(particularly atrial septal defects)</td>
<td></td>
</tr>
<tr>
<td>Estimate ventricular filling pressures and pulmonary arterial pressure</td>
<td></td>
</tr>
<tr>
<td>Complete blood count, coagulation profile, renal, thyroid, and liver</td>
<td></td>
</tr>
<tr>
<td>function</td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile, fasting glucose</td>
<td></td>
</tr>
</tbody>
</table>

1. To identify risk factors for AF, which, if treated, could reduce or eliminate the occurrence of further AF
2. To identify important risk factors, which, if treated, could improve the overall outcome of the patient, independent of AF
3. To aid in assessing the prognosis of AF in the individual patient
4. To assist in the selection of optimal AF therapy in the individual patient

RECOMMENDATION

All patients with AF should undergo a complete history and physical examination, electrocardiogram, echocardiogram, and basic laboratory investigations. Details are highlighted in Table 1 (Strong Recommendation, Low-Quality Evidence).

Other ancillary tests should be considered under specific circumstances. Details included in Table 2 (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places a high value on a comprehensive evaluation of patients with AF and a lower value on initial costs to the health care system.

Documentation of AF and Its Characteristics

It is incumbent upon the physician to document AF in at least one electrocardiogram lead, as the perception of “irregularly irregular” palpitations may be the result of a variety of arrhythmias, including atrial tachycardia, atrial flutter, premature atrial and/or ventricular contractions, or nonarrhythmic causes.

The predominant pattern of AF should be determined, as this is helpful for directing therapy:

1. First detected AF
2. Paroxysmal: AF is self-terminating within 7 days of recognized onset
3. Persistent: AF is not self-terminating within 7 days or is terminated electrically or pharmacologically or
4. Permanent: AF in which cardioversion has failed or in which clinical judgment has led to a decision not to pursue cardioversion

One may not be able to identify the pattern of AF at the time of initial presentation, and the pattern may change over time. An assessment of the nature and severity of symptoms and their impact on quality of life should also be performed. Symptoms associated with AF are highly variable and may include palpitations, dyspnea, dizziness, weakness, or chest pain. The frequency and duration of symptoms vary, as can the severity, with some patients being truly asymptomatic and others having debilitating symptoms. The impact of these symptoms on lifestyle as well as a record of emergency department visits, hospital admissions, and cardioversions should be made, along with a record of all prior interventions (eg, drug therapy, catheter ablation, etc) for AF.

Symptoms at the termination of paroxysms should be sought and if present, symptom–rhythm correlation can be made using an ambulatory electrocardiogram (Holter monitor, event monitor, or loop recorder). Patients with sick sinus syndrome often have sinus pauses, particularly following the termination of AF, which may limit the use of rate- or rhythm-controlling medications and may require the use of permanent pacing. Any supraventricular tachycardia (SVT), including atrial tachycardia and atrial flutter, can lead to the development of AF, and successful ablation of the underlying SVT may eliminate the associated AF. Therefore, it is important to elicit and investigate any history of regular palpitations. This can be further explored using ambulatory electrocardiographic monitoring.

Evaluation of the Impact of AF on Quality of Life

AF causes a greater degree of impairment of quality of life in most patients than is generally appreciated. Although rarely life threatening, AF can cause moderate and sometimes severe distress and substantially alter everyday functioning. In a referral practice, a majority of patients have a quality of life that is similar to that of patients following
myocardial infarction. Impaired quality of life is primarily the result of symptoms from AF but is also influenced by side effects from the AF therapies, illness perceptions, and patient factors such as depression. In the absence of a gold standard method to treat AF patients, improving quality of life and relieving symptoms are often the primary goals in the management of AF patients.

Making treatment plans and assessing treatment effectiveness require a consistent and standardized approach to measuring the impact of overall quality of life of the AF syndrome. In 2005, the Canadian Cardiovascular Society Atrial Fibrillation Guidelines Committee set out to create and validate a standard approach to assessing overall quality of life in AF patients, by developing the Severity in Atrial Fibrillation (SAF) scale (Table 2). This semiquantitative scale ranges from 0 (no impact of AF or its treatment on overall quality of life and patient functioning) to SAF 4 (resulting in a severe impairment of functioning and overall quality of life). A multicentre Canadian study has shown that the results of this scale correlate well with previously validated symptom scores and generic measures of quality of life and that it can be easily applied by a variety of caregivers at the bedside with minimal training.

An increasing recognition that the presence of AF on an electrocardiogram or the frequency and duration of episodes of AF ("the AF burden") are poorly correlated with long-term morbidity and overall quality of life has led to an increasing emphasis on subjective patient-defined outcomes to most effectively assess the usefulness of overall management and specific treatments in AF. An explicit assessment of the effect of AF on QOL, preferably using a scale such as the SAF scale in every patient seen with AF, is recommended and can be used as a baseline to assess the effects of new or changed therapy in individual patients (Table 3). Patients vary widely with respect to severity of symptoms and overall quality of life related to AF. It is difficult to give appropriate counsel and weigh risks and benefits of therapy without an explicit understanding of the consequences of AF and its treatment on the patient’s well-being.

Such an approach serves to emphasize that simply slowing the ventricular rate under the strategy of rate control or restoring and maintaining sinus rhythm using a strategy of rhythm control may not necessarily improve patient well-being and quality of life. Careful evaluation and ongoing reevaluation of the impact of the disorder and its treatment on overall patient well-being are required.

**Table 2. Evaluation of quality of life (QOL) using the CCS SAF scale**

<table>
<thead>
<tr>
<th>SAF score</th>
<th>Impact on quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 0</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Class 1</td>
<td>Minimal effect on QOL</td>
</tr>
<tr>
<td>Class 2</td>
<td>Minor effect on QOL</td>
</tr>
<tr>
<td>Class 3</td>
<td>Moderate effect on QOL</td>
</tr>
<tr>
<td>Class 4</td>
<td>Severe effect on QOL</td>
</tr>
</tbody>
</table>

*The intent of the CCS SAF scale is to capture AF-related symptoms and QOL. However, the scale evaluates not only symptoms that occur during episodes of AF but also the consequences of ongoing treatment for AF (ie, medication-related side effects).*

**Table 3. Additional investigations useful in selected cases**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Potential role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiography</td>
<td>Exclude concomitant lung disease, heart failure, baseline in patients receiving amiodarone</td>
</tr>
<tr>
<td>Ambulatory electrocardiography (Holter monitor, event monitor, loop monitor)</td>
<td>Document AF, exclude alternative diagnosis (atrial tachycardia, atrial flutter, AVNRT/AVRT, ventricular tachycardia), symptom–rhythm correlation, assess ventricular rate control</td>
</tr>
<tr>
<td>Treadmill exercise test</td>
<td>Investigation of patients with symptoms of coronary artery disease, assessment of rate control</td>
</tr>
<tr>
<td>Transesophageal echocardiography</td>
<td>Rule out left atrial appendage thrombus, facilitate cardioversion in patients not receiving oral anticoagulation, more precise characterization of structural heart disease (mitral valve disease, atrial septal defects, cor triatriatum, etc)</td>
</tr>
<tr>
<td>Electrophysiological study</td>
<td>Patients with documented regular supraventricular tachycardia (ie, atrial tachycardia, AVNRT/AVRT, atrial flutter) that is amenable to catheter ablation</td>
</tr>
<tr>
<td>Serum calcium and magnesium</td>
<td>In cases of suspected deficiency (ie, diuretic use, gastrointestinal losses), which could influence therapy (ie, sotalol)</td>
</tr>
<tr>
<td>Sleep study (ambulatory oximetry or polysomnography)</td>
<td>In patients with symptoms of obstructive sleep apnea or in select patients with advanced symptomatic heart failure</td>
</tr>
<tr>
<td>Ambulatory blood pressure monitoring</td>
<td>In cases of borderline hypertension</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>In rare cases of apparent familial AF (particularly with onset at a young age) with additional features of conduction disease, Brugada syndrome, or cardiomyopathy</td>
</tr>
</tbody>
</table>

AVNRT/AVRT, atrioventricular nodal reentrant tachycardia/atrioventricular reentrant tachycardia.

**RECOMMENDATION**

We recommend that the assessment of patient well-being, symptoms, and quality of life be part of the evaluation of every patient with AF (Strong Recommendation, Low-Quality Evidence).

We suggest that the quality of life of the AF patient be assessed in routine care using the CCS SAF scale (Conditional Recommendation, Low-Quality Evidence).
Values and preferences. These recommendations recognize that improvement in quality of life is a high priority for therapeutic decision making.

Identification of the Etiology of AF

AF is a disease of advancing age, whose prevalence increases from 0.1% in patients under age 50 to 10%-15% in those >80 years old.7 This has important public health implications for the aging Canadian population. In most cases, AF is associated with underlying heart disease—most commonly, hypertension, heart failure, left ventricular systolic dysfunction, and valvular heart disease.8-11 Although these conventional risk factors are present in >70% of North American patients,12,13 there are important additional considerations.

First, additional risk factors such as hyperthyroidism,14 Wolff-Parkinson-White syndrome,3,15 and unnecessary ventricular pacing,16-19 although much less prevalent, are important to identify as they have additional deleterious effects and their treatment could eliminate further AF in affected patients. Second, because Canada is a country with a significant immigrant population, it is important to remember that in many patients, AF may be the result of conditions that are much less common among individuals born in North America, such as rheumatic heart disease, complicated hypertension, and pericarditis.20 Third, there are emerging data identifying additional conditions such as obesity, sleep apnea, and alcohol intake as risk factors for the development of AF and its complications.21-23 Finally, there are still approximately 15%-20% of AF patients who do not have identifiable comorbidities.24 While these patients would be classified as having “lone” (idiopathic) AF, some may have a genetic predisposition to AF, an SVT that leads to the development of AF or have AF as a result of high vagal tone, such as secondary to intensive aerobic exercise.25

The underlying etiologic conditions associated with AF should be determined. In Canada, the most important of these risk factors is hypertension.11,13 Careful blood pressure measurement should be conducted, as outlined by the Canadian Hypertension Education Program guidelines for the diagnosis of hypertension.26,27 Clinicians should pursue a diagnosis of hypertension in patients with frequent borderline office readings, particularly those with significant left atrial enlargement or left ventricular hypertrophy. Ambulatory blood pressure monitoring may facilitate this in patients with paroxysmal AF; however, these devices are greatly influenced by the variable heart rate during AF, limiting their sensitivity and specificity in patients with persistent or permanent AF.

Particular effort should also be given to identify potentially reversible causes of AF (Table 4), such as hyperthyroidism and excessive alcohol. Although only 3.1% of AF patients have hyperthyroidism, it is still an important example of a treatable cause.28 Identification of both of these disorders on the patient history may be particularly difficult in the elderly. Other common, conventional risk factors include coronary artery disease with prior myocardial infarction, left ventricular systolic dysfunction, and valvular heart disease. Identification of such structural heart disease is important, as it influences the prognosis of AF and may influence choices of therapy for both rate and rhythm control.

Screening history and physical evaluation for obstructive and nonobstructive sleep apnea should be performed in all patients, and further testing, such as ambulatory oximetry or polysomnography, or appropriate referral to a specialist in sleep medicine should be considered if the history is suggestive of sleep apnea.

RECOMMENDATION

Underlying causes or precipitating factors for AF including hypertension should be identified and treated. Details are highlighted in Table 3 (Strong Recommendation, High-Quality Evidence).

Values and preferences. This recommendation recognizes that therapy of underlying etiology can improve management of AF and that failure to recognize underlying factors may result in deleterious effects.

Determination of Cardiovascular Risk in AF

AF is associated with a 3- to 6-fold increased risk of stroke or non–central nervous system (CNS) systemic embolism.10,29-34. It is thought that ≈15% of all strokes are due to AF and that this increases to 25% for patients >80 years old.10 Both oral anticoagulation and antiplatelet medication reduce the risk of stroke in patients with AF but are associated with an increased risk of bleeding.33,35,36 For this reason, several risk stratification schemes have been developed to identify patients with the highest risk of stroke, in whom the benefit of oral anticoagulant therapy outweighs the risk of bleeding.37,38 Initial investigation of patients with AF should identify risk factors for stroke, as this is necessary to help guide the appropriate use of antico-

Table 4. Potential causes of atrial fibrillation

<table>
<thead>
<tr>
<th>Cardiac causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Heart failure*</td>
</tr>
<tr>
<td>Coronary artery disease with prior myocardial infarction</td>
</tr>
<tr>
<td>Left ventricular dysfunction (systolic and diastolic)*</td>
</tr>
<tr>
<td>Including hypertrophic, dilated, and restrictive cardiomyopathies</td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Congenital heart disease* (early repair of atrial septal defect)</td>
</tr>
<tr>
<td>Pericardial disease</td>
</tr>
<tr>
<td>Postsurgical (particularly cardiac surgery)</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
</tr>
<tr>
<td>AF as a result of ventricular pacing*</td>
</tr>
<tr>
<td>Supraventricular tachycardia (including Wolff-Parkinson-White syndrome, atrial tachycardia, atrial flutter, or other)*</td>
</tr>
<tr>
<td>Genetic/familial</td>
</tr>
<tr>
<td>Noncardiac causes</td>
</tr>
<tr>
<td>Obstructive sleep apnea*</td>
</tr>
<tr>
<td>Obesity*</td>
</tr>
<tr>
<td>Excessive alcohol ingestion (acute or chronic)*</td>
</tr>
<tr>
<td>Hyperthyroidism*</td>
</tr>
<tr>
<td>Vagally mediated (ie, habitual aerobic training)*</td>
</tr>
<tr>
<td>Pulmonary disease (pneumonia, chronic obstructive pulmonary disease, pulmonary embolism, pulmonary hypertension)</td>
</tr>
<tr>
<td>Lone (idiopathic) AF</td>
</tr>
</tbody>
</table>

* Denotes cause for which treatment may prevent the development or recurrence of AF.
agulant and antiplatelet medication. Risk factors include a history of stroke, transient ischemic attack, or non-CNS systemic embolism; hypertension; heart failure; left ventricular ejection fraction $\leq 35\%$; increasing age; and diabetes mellitus. Other moderate risk factors include female gender and peripheral vascular disease.\textsuperscript{37} Many of these same conditions are also associated with an increased risk of bleeding. The initial evaluation of patients with AF should also elicit a bleeding history, prior antiplatelet and anticoagulant use, and degree of INR control\textsuperscript{39} to aid in the determination of the ideal strategy for stroke prevention. For a full discussion, see Cairns et al.\textsuperscript{40} The use of stroke risk stratification schemes is undergoing a period of reevaluation. First, there is increasing appreciation that the same clinical characteristics that predict stroke also predict bleeding\textsuperscript{41} thus patients with a lower risk of stroke are also less likely to have bleeding complications of therapy. Second, there are 2 new therapies that have been shown to prevent stroke in patients with AF: clopidogrel (added to acetylsalicylic acid [ASA])\textsuperscript{34} and dabigatran.\textsuperscript{42} These 2 agents have different bleeding profiles and are substantially easier for patients to take and have far fewer food and drug interactions than warfarin, thus changing the risk/benefit equation for stroke prevention in AF. Regardless of the specific agents used to prevent stroke and the threshold for their use, the identification of stroke risk factors remains vital to properly inform therapy. In contrast, it should be noted the pattern of AF (paroxysmal vs persistent or permanent) does not influence these decisions.\textsuperscript{43} Furthermore, the AFFIRM trial strongly suggests that the apparent suppression of AF with antiarrhythmic medications does not obviate the need for oral anticoagulation in patients with AF and additional risk factors for stroke.\textsuperscript{44}

Traditionally, the prevention of cardiovascular events in patients with AF has focused on the prevention of stroke and non-CNS systemic embolism. It should be noted, however, that in recent clinical trials, the most common adverse cardiovascular event in patients with AF is now the development of heart failure.\textsuperscript{34,41,42} Patients with AF also frequently require hospitalization, and these patients have a particularly high subsequent mortality.\textsuperscript{45} Thus, the appropriate identification and treatment of hypertension and asymptomatic left ventricular systolic dysfunction, as well as the appropriate evidence-based management of heart failure, are also important in the management of patients with AF.

The Physical Examination and Initial Investigations for AF

The physical findings suggestive of AF include an irregular pulse (that may not be rapid), an irregular jugular venous pulse with loss of a-wave, and variation in the intensity of the first heart sound. The physical examination may also uncover causes of AF, including hypertension, left ventricular systolic dysfunction, heart failure, valvular heart disease, congenital heart disease (ie, fixed-split S2 in patient with an atrial septal defect), or hyperthyroidism.

A number of routine investigations are warranted in all patients presenting with a history of AF (see Table 1). An electrocardiogram is useful both in AF and sinus rhythm. Evidence of left atrial enlargement, left ventricular hypertrophy, preexcitation, conduction disease, or myocardial infarction should be sought. A transthoracic echocardiogram is also invaluable and should be performed in all patients with AF. This will identify left ventricular hypertrophy or systolic dysfunction, significant valvular or congenital heart disease, and, rarely, complications such as left atrial appendage thrombus. All of these are necessary for making appropriate decisions regarding the use of rate- and rhythm-controlling agents and anticoagulant medications. An evaluation of left atrial size should also be conducted, as this provides important information about the likelihood of AF recurrence or the development of persistent or permanent AF, which can help guide optimal therapy for symptom improvement. In certain cases, such as the assessment of valvular or congenital heart disease or the exclusion of left atrial appendage thrombus, transesophageal echocardiography may be required.

Routine blood work should be performed at the time of the initial evaluation of patients with AF. A complete blood count and coagulation studies should be performed as they will inform decisions about the use of anticoagulant and antiplatelet medications. Serum electrolytes and creatinine should also be determined because antiarrhythmic and newer anticoagulant medications may be more likely to cause adverse effects in those with electrolyte disorders or renal insufficiency. Serum creatinine and a urinalysis may also identify chronic kidney disease, another common complication of hypertension, the most prevalent risk factor for AF. Liver function tests should also be performed at baseline, both to aid in the identification of excessive alcohol intake and as a baseline for potentially hepatotoxic medications, such as amiodarone, that are frequently administered in the treatment of AF. A lipid profile is recommended in most patients as part of an overall assessment of cardiovascular risk.

Ambulatory electrocardiography monitoring is not routinely required but has a number of important purposes, such as initial documentation of AF, identification of other forms of SCT, assessment of ventricular rate control, and the correlation of patient’s symptoms with both rhythm and heart rate. Although not routinely recommended, exercise testing may supplement ambulatory monitoring in certain patients with exercise-related symptoms. Invasive electrophysiological studies should be considered in those patients with idiopathic AF at a young age, particularly in those with documented SVT other than AF or symptoms suggestive of such arrhythmias.

References


RÉSUMÉ

La fibrillation auriculaire (FA) est la forme d’arythmie la plus fréquemment rencontrée à la salle d’urgence. La plupart des patients présentant une FA ou un flutter auriculaire d’apparition récente peuvent être traités en toute sécurité au service des urgences sans nécessiter d’hospitalisation. Les priorités du traitement à l’urgence incluent une évaluation rapide de l’état hémodynamique ainsi que l’identification et le traitement de la cause sous-jacente et/ou des facteurs précipitants. Le patient doit être soigneusement questionné sur ses symptômes, pour tenter de déterminer le début d’apparition de l’arythmie. Le risque d’accident vasculaire cérébral (AVC) doit être déterminé dans tous les cas, en utilisant, par exemple, le score de CHADS2. Chez les patients hémodynamiquement stables et présentant une FA ou un flutter auriculaire d’apparition récente, une stratégie soit de contrôle de la fréquence ventriculaire soit de conversion et maintien du rythme sinusal doit être adoptée, en tenant compte de nombreux éléments comme la durée de la FA et la sévérité des symptômes. Si l’on retient une stratégie de conversion et maintien du rythme sinusal, la cardioversion pourra être électrique ou pharmacologique. Avant cardioversion chez les patients non anticoagulés, il faudra être certain que la durée de l’épisode de FA ou de flutter

Atrial fibrillation (AF) is the most common arrhythmia managed by emergency physicians and accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances.1

In Canada, the estimated overall rate of hospitalization with AF is 583 per 100,000 population.2 Hospital admissions for AF have increased by 66% over the past 20 years due to an aging specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia managed by emergency physicians. There is increasing evidence that most patients with recent-onset AF or atrial flutter (AFL) can be safely managed in the emergency department (ED) without the need for hospital admission. The priorities for ED management of recent-onset AF/AFL include rapid assessment of potential hemodynamic instability and identification and treatment of the underlying or precipitating cause. A careful evaluation of the patient’s history should be performed to determine the time of onset of the arrhythmia. All patients should be stratified using a predictive index for the risk of stroke (eg, CHADS2). For stable patients with recent-onset AF/AFL, a strategy of either rate control or rhythm control could be selected based on multiple factors including the duration of AF and the severity of symptoms. If a strategy of rhythm control has been selected, either electrical or pharmacologic cardioversion may be used. Before proceeding to cardioversion in the absence of systemic anticoagulation, physicians must be confident that the duration of AF/AFL is clearly <48 hours and that the patient is not at a particularly high risk of stroke. When the duration of AF/AFL is >48 hours or uncertain, rate control should be optimized first and
The patients should receive therapeutic anticoagulation for 3 weeks before and 4 weeks after planned cardioversion. Adequate follow-up of patients with recent-onset AF/AFL is recommended to identify structural heart disease and evaluate the need for long-term antithrombotic or antiarrhythmic therapy.

Population and a rising prevalence of chronic heart disease. The overall mortality rate for patients with AF is approximately double that for patients in normal sinus rhythm. The rate of ischemic stroke among patients with nonvalvular AF averages 5% per year, 2 to 7 times that of the population without AF. Atrial flutter (AFL) may also occur in the patient with AF or may present as an isolated arrhythmia. The goals of therapy and management approaches for AFL are similar to those for AF.

The decision regarding the initial strategy of rate versus rhythm control depends upon multiple factors including patient and physician preference, clarity of the history of onset of symptoms, type and duration of AF, severity of symptoms, associated cardiovascular disease and medical conditions, and age.

Evidence for Emergency Department Management

Variation in practice within Canadian EDs has been observed, and this variation likely reflects a lack of high-quality evidence to guide the acute management of recent-onset AF patients. Standard guidelines and textbooks are unable to offer clear evidence-based direction for emergency physicians. Particularly controversial is the issue of using rhythm control or rate control. The very large AFR-FIRM and AF-CHF clinical trials compared rate and rhythm control but did not explore the optimal management for recent-onset AFL patients presenting to the ED with <48 hours of symptoms. In the United States, patients are often admitted to hospital under the cardiology service or discharged home after rate-control therapy only. One Canadian site has described 2 cohorts of patients successfully treated with rhythm control with good results. Other studies of rhythm control in the ED have been small or did not include both pharmacologic and electrical cardioversion as an option.

The overall mortality rate for patients with AF is approximately double that for patients in normal sinus rhythm. The rate of ischemic stroke among patients with nonvalvular AF averages 5% per year, 2 to 7 times that of the population without AF. Atrial flutter (AFL) may also occur in the patient with AF or may present as an isolated arrhythmia. The goals of therapy and management approaches for AFL are similar to those for AF.

In the emergency department (ED), physicians often manage patients with either recent-onset (first detected or recurrent) or those with permanent AF/AFL. In the case of permanent AF/AFL, cardioversion has previously failed or clinical judgment has led to a decision not to pursue cardioversion, and ED care focuses on rate control and treatment of underlying conditions. When AF terminates spontaneously within 7 days of recognized onset, it is designated paroxysmal; when sustained beyond 7 days, AF is designated persistent. This chapter will focus on those with symptomatic, recent-onset episodes of AF/AFL (either newly detected, recurrent paroxysmal, or recurrent persistent episodes), the most common arrhythmia managed in the ED. There are 2 competing strategies for management: rate-control and rhythm-control treatment. The rate-control approach consists of ventricular rate control, oral anticoagulation, no attempt to return the patient to sinus rhythm in the ED, and delayed cardioversion after 4 weeks, if indicated. With the rhythm-control approach, attempts are made to cardiovert patients to sinus rhythm in the ED, either pharmacologically or electrically, and then discharge them home in sinus rhythm.

**Emergency Department Management of Recent-Onset AF/AFL**

**Overall approach**

The priorities for ED management of recent-onset AF/AFL (Fig. 1) include rapid assessment of potential hemodynamic instability, the identification and treatment of the underlying or precipitating cause, and a careful assessment of the patient’s history with particular attention to the risk of thromboembolism. At this time, evidence equally supports a strategy of rate control or rhythm control for stable patients with known onset of AF/AFL within 48 hours. Both approaches are presented here. The decision regarding the initial strategy of rate versus rhythm control depends upon multiple factors including patient and physician preference, clarity of the history of onset of symptoms, type and duration of AF, severity of symptoms, associated cardiovascular disease and medical conditions, and age.

**RECOMMENDATION**

We recommend that in stable patients with recent-onset AF/AFL, a strategy of rate control or rhythm control could be selected (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** This recommendation places a high value on the randomized controlled trials investigating rate control as an alternative to rhythm control for AF/AFL, recognizing that these trials did not specifically address the ED environment.

**Assessment**

Uncommonly, patients with recent-onset AF/AFL will present with hemodynamic instability and must be immediately cardioverted as described later. Most patients are stable, presenting with palpitations, chest tightness, or weakness, although some patients, especially the elderly, are often unaware that they have a tachyarrhythmia or when it started. A careful history should be taken to determine the time of onset, if known, and particularly to determine if it was within the past 48 hours. Other important points to determine include previous episodes and treatment, associated cardiac conditions, current antiarrhythmic agents, anticoagulation and current INR level, rhythm on most recent ECG, and risk of thromboembolism per the CHADS2 score (see Table 1 and Therapies for Prevention of Stroke and Vas-
circular Events). AF may be related to acute, temporary causes including alcohol use (eg, “holiday heart syndrome”), myocardial ischemia or infarction, myocarditis or pericarditis, pulmonary embolism or other pulmonary diseases, hyperthyroidism, and other metabolic disorders. In such cases, successful treatment of the underlying condition may promote the resolution of AF. Routine chemistry and hematology are indicated as well as, in some cases, troponin and thyroid-stimulating hormone levels. Transesophageal echocardiography, if available, is useful to exclude the presence of left atrial clot in patients in whom the onset of arrhythmia is unclear and cardioversion is desired.

Unstable patients

If recent-onset AF/AFL has caused hemodynamic instability with hypotension, acute coronary syndrome, or florid pulmonary edema, then patients must undergo immediate electrical cardioversion. This is a relatively uncommon presentation of recent-onset AF/AFL, and physicians must ensure that the patient is not in long-standing persistent AF/AFL, as attempts to cardiovert such patients are likely to fail and may increase morbidity. In this case, the rapid AF may be secondary to an acute decompensation of an underlying condition such as sepsis or hypovolemia. Generally, unstable patients need not be given an anticoagulant either before or following cardioversion if the duration of AF/AFL is known to have occurred <48 hours. However, if the duration of AF/AFL is ≥48 hours or unknown or the patient is at particularly high risk of stroke (eg, mechanical valve, rheumatic valve disease, recent stroke, or transient ischemic attack), we suggest administering the patient intravenous unfractionated heparin or low-molecular-weight heparin before cardioversion if possible or immediately thereafter if even a brief delay is unacceptable. Such a patient should then be bridged with heparin and started on a course of oral anticoagulants for ≥4 weeks postcardioversion.

RECOMMENDATION

We recommend for patients with acute hemodynamic instability secondary to rapid recent-onset AF/AFL, immediate electrical conversion to sinus rhythm (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the immediate management of hemodynamic instability and a lower value on anticoagulation status under these circumstances. It is also recognized that this is a relatively rare circumstance and that, in most cases, stroke risk and anticoagulation status can be considered prior to immediate cardioversion.

Rate control

Criteria for adequate rate control vary. A sustained, uncontrolled tachycardia over weeks may lead to deterioration of left
ventricular function, a condition called tachycardia-related cardiomyopathy, so it is important that adequate rate control be achieved.29 Physicians should attempt to reduce the heart rate to target rates of <100 beats per minute (bpm) at rest and <110 bpm during moderate exercise (such as a walk test). The most commonly used drugs are intravenous diltiazem, verapamil, and metoprolol (Table 2). Digoxin is not considered a first-line agent for rate control because of slow onset of action and it affects only resting heart rate. It may be useful in patients with heart failure and left ventricular systolic dysfunction or as an adjunctive agent, allowing lower doses of beta-blockers or calcium channel blockers to be used. At discharge from the ED, physicians should ensure the patient is placed on oral rate-control medications and the appropriate prophylaxis for stroke.

### Rhythm control

Cardioversion in the absence of systemic anticoagulation carries a risk of thromboembolism when AF/AFL has been present for >48 hours. When the duration of AF/AFL has been <48 hours, cardioversion appears to have an acceptably low risk of thromboembolism except in particularly high-risk groups.30,31 Such high-risk situations include the presence of a mechanical valve, rheumatic valve disease, or recent stroke or transient ischemic attack unless the patient is already on oral anticoagulation with a therapeutic INR. There is no evidence that the risk of thromboembolism or stroke differs between pharmacologic and electrical cardioversion. Before proceeding to immediate cardioversion in the absence of systemic anticoagulation, physicians must be confident that the onset of AF/AFL is clearly <48 hours and that the patient is not at a particularly high risk of stroke. Most patients in the ED are acutely aware of the time of onset of symptoms but some are not. In such situations, a transesophageal echocardiogram may be used to establish the safety of immediate cardioversion. If patients are on warfarin, it is important to ensure that their INR has been therapeutic for ≥3 consecutive weeks.1,32

Rate-control drugs have not been shown to enhance the rate of conversion when a rhythm-control approach is used. Physicians and patient preferences dictate whether to start rhythm-control treatment with drugs or with electrical cardioversion. Initial use of antiarrhythmic agents may also prevent immediate recurrence of AF after electrical cardioversion.33,34 All patients undergoing pharmacologic or electrical cardioversion require continuous electrocardiographic monitoring and temporary pacing capability. Prevention of thromboembolism for patients managed with rhythm control is discussed later.

Spontaneous conversion of recent-onset AF to sinus rhythm within 24 hours is common. Some emergency physicians have the patients return the following day for cardioversion at that time if spontaneous conversion has not occurred.5,35 In this scenario, after documentation of appropriate rate control, patients at low risk of stroke can be discharged on rate control alone to return the following day for reevaluation. Patients who remain in AF can then undergo DC cardioversion at this time as long as the total duration of AF remains <48 hours.

### Pharmacologic cardioversion

Physicians may consider several drugs for the pharmacologic cardioversion of recent-onset AF/AFL in the ED13,15,16,36,37 (Table 3). Procainamide is administered intravenously over 60 minutes at a dose of 15-17 mg/kg and occasionally is accompanied by transient hypotension. A recent report described the successful use of procainamide in the ED, where this drug was 60% effective for conversion of recent-onset AF.38 This study showed procainamide to have an excellent safety profile, even for patients already taking oral antiarrhythmic agents. Oral propafenone or flecainide, both Class IC agents, can be safely administered in the ED but can be expected to have slower onset of action than intravenous drugs.39-41 The Class III agent ibutilide is administered intravenously as long as the total duration of AF remains ≤48 hours in whom a strategy of rhythm control has been selected:

- We recommend that rate-slowing agents alone are acceptable while awaiting spontaneous conversion (Strong Recommendation, Moderate-Quality Evidence).
- We recommend that synchronized electrical cardioversion or pharmacologic cardioversion may be used when a decision is made to cardiovert patients in the emergency department. See Table 2 for drug recommendations (Strong Recommendation, Moderate-Quality Evidence).
- We suggest that antiarrhythmic drugs may be used to pretreat patients before electrical cardioversion in ED in order to decrease early recurrence of AF and to enhance cardioversion efficacy (Conditional Recommendation, Low-Quality Evidence).

### Values and preferences

These recommendations place a high value on determination of the duration of AF/AFL as a determinant of stroke risk with cardioversion. Also, individual considerations of the patient and treating physician are recognized in making specific decisions about method of cardioversion.

### Table 2. Recommended intravenous drugs for heart rate control in the ED

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem*</td>
<td>0.25 mg/kg IV bolus over 10 min; repeat at 0.35 mg/kg IV</td>
<td>Hypotension, bradycardia</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>2.5-5 mg IV bolus over 2 min; up to 3 doses</td>
<td>Hypotension, bradycardia</td>
</tr>
<tr>
<td>Verapamil*</td>
<td>0.075-0.15 mg/kg over 2 min</td>
<td>Hypotension, bradycardia</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.25 mg IV each 2 h; up to 1.5 mg</td>
<td>Bradycardia, digitalis toxicity</td>
</tr>
</tbody>
</table>

* Calcium-channel blockers should not be used in patients with heart failure or left ventricular dysfunction.

In hemodynamically stable patients with AF/AFL of known duration <48 hours in whom a strategy of rhythm control has been selected:

- We recommend that rate-slowing agents alone are acceptable while awaiting spontaneous conversion (Strong Recommendation, Moderate-Quality Evidence).
- We recommend that synchronized electrical cardioversion or pharmacologic cardioversion may be used when a decision is made to cardiovert patients in the emergency department. See Table 2 for drug recommendations (Strong Recommendation, Moderate-Quality Evidence).
- We suggest that antiarrhythmic drugs may be used to pretreat patients before electrical cardioversion in ED in order to decrease early recurrence of AF and to enhance cardioversion efficacy (Conditional Recommendation, Low-Quality Evidence).
Adenosine transiently slows heart rate, does not cardiovert AF, and is associated with a significant risk of ventricular arrhythmias in Wolff-Parkinson-White syndrome with AF (see Rapid Preexcitation later). Recent trials of vernakalant have demonstrated high clinical efficacy of this intravenous agent for conversion of recent-onset AF. Recent clinical trials of oral vernakalant for the conversion of AF have demonstrated clinical success rates of 75% to 90% at 5 minutes. However, the drug is currently not available in the United States for this indication. In the United States, electrical cardioversion is the preferred option for the acute management of AF. Synchronized electrical cardioversion is highly effective and is associated with a significant risk of ventricular arrhythmias in Wolff-Parkinson-White syndrome with AF (see Rapid Preexcitation later). Recent trials of vernakalant have demonstrated high clinical efficacy of this intravenous agent for conversion of recent-onset AF. This atrial selective antiarrhythmic drug was recently approved for use in the European Union, but in North America it is currently available only for investigational use.

**Electrical cardioversion**

Synchronized electrical cardioversion is highly effective and physicians have the option of pretreating with antiarrhythmic drugs or proceeding directly to electrical shock. In a series of 660 patients, one Canadian site described 91.0% successful electrical cardioversion in the ED, after pretreatment with intravenous procainamide. Patients had no serious adverse events and their ED lengths of stay averaged only 4-6 hours. Current guidelines recommend starting with a higher energy level, such as 150-200 joules for biphasic waveform devices in order to increase the likelihood of initial success and thus limit the cumulative energy dose with multiple attempts at cardioversion. Likewise, an anterior-posterior pad positioning may be more effective than an anterior-lateral approach. Sedation typically involves rapid acting agents such as intravenous fentanyl, propofol, and midazolam.

---

**Table 3. Recommended drugs for pharmacologic conversion in the ED**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Efficacy</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td>15-17 mg/kg IV over 60 min</td>
<td>++</td>
<td>5% Hypotension</td>
</tr>
<tr>
<td>Class IC*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>450-600 mg PO</td>
<td>+++</td>
<td>Hypotension, 1:1 flutter, bradycardia</td>
</tr>
<tr>
<td>Flecainide</td>
<td>300-400 mg PO</td>
<td>+++</td>
<td>Hypotension, 1:1 flutter, bradycardia</td>
</tr>
<tr>
<td>Class III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibutilide</td>
<td>1-2 mg IV over 10-20 min Pretreat with MgSO4 1-2 mg IV</td>
<td>++</td>
<td>2.3% Torsades de pointes</td>
</tr>
</tbody>
</table>

* Class IC drugs should be used in combination with AV nodal blocking agents (beta-blockers or calcium channel inhibitors). Class IC agents should also be avoided in patients with structural heart disease.

---

**RECOMMENDATION**

We recommend that electrical cardioversion may be conducted in the ED with 150-200 joules biphasic waveform as the initial energy setting (Strong Recommendation, Low-Quality Evidence).

**Values and preferences.** This recommendation places a high value on the avoidance of repeated shocks and the avoidance of ventricular fibrillation that can occur with synchronized cardioversion of AF at lower energy levels. It is recognized that the induction of VF is a rare but easily avoidable event.

**Rapid preexcitation during AF**

AF occurring in the setting of Wolff-Parkinson-White syndrome (Fig. 2) is a precarious situation because rapid atrioventricular conduction through the accessory pathway may precipitate ventricular fibrillation. In these patients, drugs that block atrioventricular conduction (digoxin, calcium channel blockers, beta-blockers, and adenosine) are contraindicated because they do not slow conduction.

---

**Figure 2.** Electrocardiogram of rapid ventricular preexcitation (Wolff-Parkinson-White syndrome) during atrial fibrillation. Note very rapid (up to 300 bpm) irregular wide QRS complexes.
through the accessory pathway and, therefore, may precipitate VF. We recommend urgent electrical cardioversion if the patient is hemodynamically unstable or intravenous antiarrhythmic agents procainamide or ibutilide in stable patients. Amiodarone should be used with caution in the case of preexcited AF as several case reports have described the occurrence of VF after intravenous administration.45

**RECOMMENDATION**

We recommend, in patients with rapid ventricular preexcitation during AF (Wolff-Parkinson-White syndrome): Urgent electrical cardioversion if the patient is hemodynamically unstable (Strong Recommendation, Low-Quality Evidence). Intravenous antiarrhythmic agents procainamide or ibutilide in stable patients (Strong Recommendation, Low-Quality Evidence).

AV nodal blocking agents (digoxin, calcium channel blockers, beta-blockers, adenosine) are contraindicated (Strong Recommendation, Low-Quality Evidence).

**Values and preferences.** These recommendations place a high value on avoidance of the degeneration of preexcited AF to ventricular fibrillation. It is recognized that degeneration can occur spontaneously or it can be facilitated by the administration of specific agents that in the absence of ventricular preexcitation would be the appropriate therapy for rate control of AF.

**Practical tip.** Identification of preexcited AF can be challenging and should be considered with any very rapid (240-300 bpm) sustained, highly irregular wide complex tachycardia (Fig. 2). Spontaneous degeneration of preexcited AF to VF can occur in the absence of administration of medication. As such, DC cardioversion is most often the preferred option when preexcited AF is very rapid.

**Prevention of thromboembolism**

Perhaps the most important and controversial aspect of ED management for recent-onset AF/AFL is ensuring that patients do not sustain a stroke. Physicians should be familiar with the CHADS2 risk scoring system54,55 (Table 1). If warfarin is prescribed, patients need careful follow-up to minimize the risk of bleeding.56,57 Dabigatran is a promising new oral anticoagulant that reversibly inhibits thrombin and can be used with a fixed-dose regimen without the need for routine coagulation monitoring.58,59

**a. Duration of AF/AFL 48 hours or high-risk patient.** In stable patients with AF/AFL >48 hours or of uncertain duration in which a strategy of rhythm control has been selected, rate control should first be optimized. The patient should also receive therapeutic warfarin (INR 2-3) or dabigatran for 3 weeks before and at least 4 weeks after attempted cardioversion.1,52 Antithrombotic therapy should be continued indefinitely if symptoms suggest that AF/AFL has been recurrent or if AF/AFL persists, using either aspirin or oral anticoagulants as appropriate based on the patient’s risk of thromboembolism. If sinus rhythm is achieved and sustained for 4 weeks, the need for ongoing antithrombotic therapy should be based on the risk of stroke. If rhythm control is not anticipated, aspirin is sufficient for those with a CHADS2 score of 0, whereas oral anticoagulants are preferred if the CHADS2 score is 1 and strongly recommended if the CHADS2 score is ≥2 (see Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter).60 If the patient is at particularly high risk of stroke (eg, mechanical valve, rheumatic valve disease, recent stroke or transient ischemic attack), even when the duration of new-onset AF/AFL is <48 hours, we recommend that cardioversion be delayed and that oral anticoagulants be prescribed for 3 weeks before and at least 4 weeks postcardioversion. Subsequent antithrombotic therapy should be based on balancing the risks of stroke and bleeding.

**b. Duration of AF/AFL 48 hours and not high risk.** In stable patients with AF of known duration <48 hours in whom a strategy of rhythm control has been selected, we recommend that hemodynamically stable patients with AF/AFL of ≥48 hours’ or uncertain duration for whom a strategy of rhythm control has been selected should have rate control optimized and receive therapeutic oral anticoagulants (OAC) therapy (warfarin [INR 2-3] or dabigatran) for 3 weeks before and at least 4 weeks postcardioversion.

Following attempted cardioversion:

1. If AF/AFL persists or recurs or if symptoms suggest that the presenting AF/AFL has been recurrent, the patient should have antithrombotic therapy continued indefinitely (using either OAC or aspirin as appropriate).

2. If sinus rhythm is achieved and sustained for 4 weeks, the need for ongoing antithrombotic therapy should be determined based on the risk of stroke, and in selected cases, expert consultation may be required (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** These recommendations place a high value on minimizing stroke risk by rate control, appropriate anticoagulation and delayed cardioversion, and a lower value on symptomatic improvement associated with immediate cardioversion.

**RECOMMENDATION**

We recommend that hemodynamically stable patients with AF/AFL of ≥48 hours’ or uncertain duration for whom a strategy of rhythm control has been selected should have rate control optimized and receive therapeutic oral anticoagulants (OAC) therapy (warfarin [INR 2-3] or dabigatran) for 3 weeks before and at least 4 weeks postcardioversion.

Following attempted cardioversion:

1. If AF/AFL persists or recurs or if symptoms suggest that the presenting AF/AFL has been recurrent, the patient should have antithrombotic therapy continued indefinitely (using either OAC or aspirin as appropriate).

2. If sinus rhythm is achieved and sustained for 4 weeks, the need for ongoing antithrombotic therapy should be determined based on the risk of stroke, and in selected cases, expert consultation may be required (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** These recommendations place a high value on minimizing stroke risk by rate control, appropriate anticoagulation and delayed cardioversion, and a lower value on symptomatic improvement associated with immediate cardioversion.
RECOMMENDATION

We recommend that hemodynamically stable patients with AF/AFL of known duration <48 hours for whom a strategy of rhythm control has been selected may generally undergo cardioversion without prior or subsequent anticoagulation. However, if the patient is at particularly high risk of stroke (eg, mechanical valve, rheumatic heart disease, recent stroke, or transient ischemic attack), cardioversion should be delayed and the patient should receive OAC for 3 weeks before and at least 4 weeks post-cardioversion.

Following attempted cardioversion:

If AF or AFL persists, recurs, or if symptoms suggest that the presenting AF/AFL has been recurrent, antithrombotic therapy (OAC or aspirin as appropriate) should be commenced and continued indefinitely.

If NSR is achieved, the need for ongoing antithrombotic therapy should be determined based on the risk of stroke according to CHADS2, score and early consultant follow-up should be arranged (Strong Recommendation, Low-Quality Evidence).

Values and preferences. These recommendations place a high value on minimizing stroke risk by appropriate anticoagulation prior to cardioversion in all patients except those at very low risk of stroke due to a short duration of AF/AFL. A lower value is placed on symptomatic improvement associated with immediate cardioversion in patients who are deemed not to be at very low risk of stroke despite an apparent short duration of AF/AFL.

c. Transesophageal echocardiography. If the onset of symptoms is not clearly <48 hours or there is a particularly high risk of stroke, we suggest that patients may undergo cardioversion guided by transesophageal echocardiography, as an alternative to anticoagulation prior to cardioversion. Patients with no identifiable left atrial thrombus may undergo immediate cardioversion. Prior to cardioversion, pretreatment with heparin must be initiated and continued until a therapeutic level of oral anticoagulation has been established. Oral anticoagulation must be continued for a minimum of 4 weeks (as discussed). For patients in whom thrombus is identified by transesophageal echocardiography, oral anticoagulation should be prescribed for ≥3 weeks and transesophageal echocardiography repeated to confirm the resolution of thrombus before proceeding to cardioversion.

RECOMMENDATION

When the duration of an episode of AF/AFL is uncertain, we suggest that patients may undergo cardioversion guided by transesophageal echocardiography, as an alternative to anticoagulation prior to cardioversion. However, anticoagulation needs to be simultaneously started and maintained for ≥4 weeks post-cardioversion (Conditional Recommendation, High-Quality Evidence).

Values and preferences. This recommendation places a higher value on the symptomatic improvement with immediate cardioversion as well as avoidance of precardioversion anticoagulation. A lower value is placed on the small risks associated with transesophageal echocardiography.

Disposition and follow-up

Most patients with recent-onset AF/AFL may be discharged home from the ED within a period of 6-12 hours, once adequate rate or rhythm control has been achieved. We recommend hospital admission of symptomatic patients with decompensated heart failure or myocardial ischemia. Occasionally, admission may be required for highly symptomatic patients in whom adequate rate or rhythm control cannot be achieved.

RECOMMENDATION

We recommend hospital admission for highly symptomatic patients with decompensated heart failure or myocardial ischemia (Strong Recommendation, Low-Quality Evidence).

We suggest limiting hospital admission to highly symptomatic patients in whom adequate rate control cannot be achieved (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the need for monitoring of the response to therapy and its reassessment, as well as ancillary investigation and treatment not available in the ED in patients with complex medical conditions associated with AF/AFL. A lower value is placed on the attendant costs of admission to hospital in patients with complex medical conditions associated with AF/AFL.

Adequate follow-up is recommended to identify structural heart disease and the possible need for long-term anticoagulation or antiarrhythmic therapy. Patients with newly detected AF/AFL should have outpatient echocardiography and referral to a cardiologist or internist. Adequate and early follow-up are necessary to safely monitor the INR of patients discharged on warfarin. The need for long-term antithrombotic therapy may be reviewed by the appropriate consultant, weighing the risks and benefits. Long-term rhythm management should also be reviewed by a consultant, based on the estimated probability of recurrence, the symptoms during AF, and other factors.

RECOMMENDATION

We suggest that after conversion to sinus rhythm has been achieved, whether antiarrhythmic drug therapy is indicated should be based on the estimated probability of recurrence and the symptoms during AF. Long-term therapy will need to be determined by an appropriate outpatient consultation (Conditional Recommendation, Low-Quality Evidence).
Values and preferences. This recommendation places a high value on minimizing the risk of infrequent but serious side effects associated with long-term antiarrhythmic drugs. A high value is also placed on the appropriate use of specialty care to make patient-specific decisions to minimize these risks. A lower value is placed on the avoidance of symptoms associated with subsequent episodes of AF/AFL if antiarrhythmic drugs cannot be avoided.

Conclusion

Physicians frequently encounter ED patients with recent-onset AF/AFL and may safely manage these patients with either a rate-control or rhythm-control strategy. Immediate specialist consultation or admission to hospital is not often necessary. Careful consideration of the risks of thromboembolism is a priority and appropriate follow-up is important. There is a need for more evidence to specifically guide the unique management of patients in the ED with recent-onset AF.

References


ARTICLE IN PRESS

Canadian Journal of Cardiology 27 (2011) 47–59

Society Guidelines

Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Rate and Rhythm Management

Anne M. Gillis, MD, FRCPC,a Atul Verma, MD, FRCPC,b Mario Talajic, MD, FRCPC,c Stanley Nattel, MD, FRCPC,c Paul Dorian, MD, FRCPC,d and the CCS Atrial Fibrillation Guidelines Committeee

a University of Calgary/Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada
b Southlake Regional Health Centre, Newmarket, Ontario, Canada
'Montreal Heart Institute, Université de Montréal and McGill University, Montreal, Québec, Canada
d St Michael’s Hospital and University of Toronto, Toronto, Ontario, Canada

ABSTRACT

The goals of atrial fibrillation (AF) and atrial flutter (AFL) arrhythmia management are to alleviate patient symptoms, improve patient quality of life, and minimize the morbidity associated with AF and AFL. Arrhythmia management usually commences with drugs to slow the ventricular rate. The addition of class I or class III antiarrhythmic drugs for restoration or maintenance of sinus rhythm is largely determined by patient symptoms and preferences. For rate control, treatment of persistent or permanent AF and AFL should aim for a resting heart rate of <100 beats per minute. Beta-blockers or nondihydropyridine calcium channel blockers are the initial therapy for rate control of AF and AFL in most patients without a history of myocardial infarction or left ventricular dysfunction. Digoxin is not recommended as monotherapy for rate control in active patients. Digoxin and dronedarone may be used in combination with other agents to optimize rate control. The first-choice antiarrhythmic drug for maintenance of sinus rhythm in patients with non structural heart disease can be any one of dronedarone, flecainide, propafenone, or sotalol. In patients with abnormal ventricular function but left ventricular ejection fraction <40%, and in some cases, left ventricular dysfunction and congestive heart failure. The approach to the management of AF and AFL includes, in parallel, identification and treatment

Atrial fibrillation (AF) and atrial flutter (AFL) are often associated with rapid and irregular ventricular rates causing palpitations, dyspnea, fatigue, reduced exercise tolerance, other symp-

Received for publication November 4, 2010. Accepted December 3, 2010.

Corresponding author: Dr Anne M. Gillis, University of Calgary, Cardiac Sciences, 3280 Hospital Drive N.W., Calgary, Alberta, Canada T2N 4Z6. Tel: +1-403-220-6841, fax: +1-403-270-0313. E-mail: amgillis@ucalgary.ca

The disclosure information of the authors and reviewers is available from the CCS on the following Web sites: www.ccs.ca and www.ccsguidelineprograms.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, and appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.
of precipitating causes, antithrombotic therapy based on risk factors for stroke, drug therapy to control ventricular rates, and antiarrhythmic therapy as required to restore and/or maintain sinus rhythm with the major goal of alleviating patient symptoms and minimizing the morbidity associated with AF (Fig. 1). Arrhythmia management usually commences with drugs to slow the ventricular rate. The addition of class I or class III antiarrhythmic drugs for restoration or maintenance of sinus rhythm is largely determined by patient symptoms and preferences as, to date, none of the large randomized trials has demonstrated that pharmacologic therapy to maintain sinus rhythm has improved survival or reduced the risk of stroke.

AF may be classified as newly detected, paroxysmal (self-terminating episodes lasting <7 days), persistent (non–self-terminating episodes lasting >7 days), or permanent (no further attempts or no initial attempt to restore sinus rhythm to be undertaken). The nature of AF is recurrent and frequently progressive (Fig. 2). Although a treatment strategy of rate control or rhythm control may be selected initially, the treatment strategy may change over time if the selected treatment strategy has been unsuccessful, as the arrhythmia progresses, or as the patient’s condition changes (Fig. 1). Thus, treatment strategies and their effectiveness, safety, and acceptability must be constantly reevaluated. Factors that might influence a decision for rate control versus rhythm control are summarized in Table 1.

AFL may also occur in the patient with AF or may present as an isolated arrhythmia. The goals of therapy and management approaches for AFL are similar to those for AF.

Figure 1. Overview of AF management. If a strategy of rate or rhythm control is not successful, crossover to the alternate strategy may be required. AF, atrial fibrillation; OAC, oral anticoagulation.

Figure 2. Interrelationships among categories of AF. Arrows indicate most common forms of progression. AF, atrial fibrillation. Adapted and reprinted with permission from Fuster V, et al. Circulation 2006; 114(7):e257-e354. ©2006 American Heart Association, Inc.
Referral for Specialty Care

Most patients with a history of AF or AFL should be considered for referral to a cardiologist or an internist with an interest in cardiovascular disease for an expert opinion on management of AF or AFL, as well as any underlying cardiovascular conditions. Patients aged \( \leq 35 \) years with symptomatic AF should be referred to an arrhythmia specialist to rule out other forms of supraventricular tachycardia that may trigger AF (so-called “tachycardia-induced atrial fibrillation”).

Referral for Specialty Care

Values and preferences. These recommendations place a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL and other clinical outcomes with the potentially greater adverse effects of class I or class III antiarrhythmic drugs compared with rate-control therapy.

Rate Control of AF and AFL

Rate control is an important part of therapy for all patients with AF or AFL. The primary goal of rate control is to improve symptoms and prevent deterioration of cardiac function associated with excessively rapid ventricular rates during AF or AFL. In addition, therapy for rate control should aim to improve exercise tolerance, QOL, and to avoid hospitalization. Tachycardia-induced cardiomyopathy refers to a condition characterized by reversible left ventricular systolic dysfunction occurring in patients with chronic rapid heart rates. This complication can occur in some patients with AF or AFL and very rapid ventricular rates (eg, >120/min for most or all of the time) and is totally or partially reversible and preventable with adequate rate control.\(^{12}\)

Heart rate targets

In the past, adequate heart rate control had been empirically defined as \( \leq 80 \) beats per minute (bpm) at rest.\(^{3,6,8,13,14}\) A recent study randomized patients to strict (\( \leq 80 \) bpm at rest and \( \leq 110 \) bpm during moderate exercise) or lenient (\( <110 \) bpm at rest) rate-control strategies.\(^{15}\) No difference in the primary outcome (composite of cardiovascular death, heart failure hospitalization, stroke, systemic embolism, bleeding, and arrhythmic events) was found, and the lenient strategy rate goal was achieved in a larger proportion of patients, with lower drug doses and fewer combinations of drugs, resulting in far fewer visits to achieve the intended target.\(^{15}\) Relatively few patients randomized to lenient rate control had resting heart rates \( >100 \) to 110 bpm. Furthermore, at the end of the first year, average resting heart rates were \( 86 \pm 15 \) and \( 75 \pm 12 \) bpm in the lenient and strict rate-control arms, respectively, and the difference of 10 to 11 bpm remained through the remainder of the trial. Thus, although the definition of lenient seems quite liberal, in the trial itself the difference in heart rates in the 2 groups was quite small. Since few patients had resting heart rates \( >100 \) bpm and previous studies cannot conclusively show the safety of resting heart rates \( >100 \) bpm, we recommend that a heart rate target of \( <100 \) bpm at rest be used for most patients. In all cases, the heart rate target may need modification based on patient symptoms and preferences. Patients with persistent or permanent AF or AFL who have exertional symptoms possibly due to excessive heart rates should have an assessment of rate response to exercise. Activity heart rate assessment can be achieved in a variety of ways, including recording heart rate after brisk hall walking or stair climbing, 24-hour ambulatory monitoring, or formal exercise testing. Correlation of symptoms and heart rate may also be achieved by patient-activated electrocardiogram (ECG) rhythm strips (“event recorders”). In all patients, it is reasonable to verify that symptoms are caused by rapid ventricular rates. Finally, it should be noted that rate control in paroxysmal AF is empirical, and heart rate targets are impractical for these briefer episodes of AF.
small comparative drug trials have been performed but have not shown major advantages of one agent over another. In small, mostly blinded randomized trials, beta-adrenoceptor blockers led to lower heart rates at rest and exercise but no change or a decrease in exercise capacity. Calcium channel blockers were less effective at heart rate lowering on exercise but led to an increase or no change in exercise capacity. In one study, beta-adrenoceptor blockers added to digoxin did not result in improved QOL, whereas calcium blockers resulted in small improvements in physical and emotional function.

Digitalis prolongs AV nodal refractoriness by enhancing vagal tone. During exercise, vagal tone is withdrawn, and therefore digitalis controls the heart rate less effectively than beta-adrenoceptor blockers or calcium channel blockers during exercise. Digitalis should thus be avoided as the sole agent in active patients. On its own, digoxin does not routinely control the heart rate and frequently has to be combined with another rate-slowing drug. Drug combinations are frequently effective when treatment with a single agent fails. Dronedarone is a newly released analogue of amiodarone with significant rate-controlling properties which may also be useful in selected patients. Amiodarone has significant rate-controlling properties in addition to its antiarrhythmic actions and may be used in refractory patients. However, because of the risk of toxicity associated with long-term use, it should be used only when other rate-control strategies are not feasible or are insufficient.

### Table 2. Drugs for heart rate control

<table>
<thead>
<tr>
<th>Class</th>
<th>Dose</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>50-150 mg orally daily</td>
<td>Bradycardia, hypotension, fatigue, depression</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>2.5-10 mg orally daily</td>
<td>As per atenolol</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>25-200 mg orally twice a day</td>
<td>As per atenolol</td>
</tr>
<tr>
<td>Nadolol</td>
<td>20-160 mg orally daily to twice a day</td>
<td>As per atenolol</td>
</tr>
<tr>
<td>Propranolol*</td>
<td>80-240 mg orally 3 times a day</td>
<td>As per atenolol</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil*</td>
<td>120 mg orally daily to 240 mg orally twice a day</td>
<td>Bradycardia, hypotension, constipation</td>
</tr>
<tr>
<td>Diltiazem*</td>
<td>120-480 mg orally daily</td>
<td>Bradycardia, hypotension, ankle swelling</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.125-0.25 mg orally daily</td>
<td>Bradycardia, nausea, vomiting, visual disturbances</td>
</tr>
</tbody>
</table>

* Sustained release preparations are available and generally preferred to prolong the dose interval and improve patient convenience or compliance.

**RECOMMENDATION**

We recommend beta-blockers or nondihydropyridine calcium channel blockers as initial therapy for rate control of AF or AFL in most patients without a past history of myocardial infarction or left ventricular dysfunction (Strong Recommendation, Moderate-Quality Evidence).

We suggest that digoxin not be used as initial therapy for active patients and be reserved for rate control in patients who are sedentary or who have left ventricular systolic dysfunction (Conditional Recommendation, Moderate-Quality Evidence).

We suggest that digoxin be added to therapy with beta-blockers or calcium channel blockers in patients whose heart rate remains uncontrolled (Conditional Recommendation, Moderate-Quality Evidence).

We suggest that dronedarone may be added for additional rate control in patients with uncontrolled ventricular rates despite therapy with beta-blockers, calcium channel blockers, or digoxin (Conditional Recommendation, Moderate-Quality Evidence).

We suggest that amiodarone for rate control should be reserved for exceptional cases in which other means are not feasible or are insufficient (Conditional Recommendation, Low-Quality Evidence).

**Values and preferences.** These recommendations recognize that selection of rate-control therapy needs to be individualized on the basis of the presence or absence of underlying structural heart disease, the activity level of the patient, and other individual considerations.

**Rate control in specific patient populations**

Beta-blockers are preferred as a rate-control agent in patients after myocardial infarction and in patients with congestive heart failure. Calcium channel blockers should be avoided in these populations but may be preferred in patients with chronic pulmonary disease and at risk of bronchoconstriction. Digitalis may be useful as monotherapy in sedentary patients and is often useful in combination with beta-blockers or calcium channel blockers.

**Practical tip.** Carvedilol is a less-potent β-adrenergic blocking agent compared to metoprolol. Carvedilol is less effective for rate control of AF compared to metoprolol.
RECOMMENDATION

We recommend beta-blockers as initial therapy for rate control of AF or AFL in patients with myocardial infarction or left ventricular systolic dysfunction (Strong Recommendation, High-Quality Evidence).

Values and preferences. This recommendation places a high value on the results of multiple randomized clinical trials reporting the benefit of beta-blockers to improve survival and decrease the risk of recurrent myocardial infarction and prevent new-onset heart failure following myocardial infarction, as well as the adverse effects of calcium channel blockers in the setting of heart failure.

Nonpharmacologic Treatment

Some patients may require the implantation of a permanent pacemaker to manage drug-exacerbated symptomatic bradycardia, particularly in patients with paroxysmal AF and sinus node disease associated with symptomatic sinus pauses, and thus safely allow adequate pharmacologic control of rapid ventricular rates. Isolated nocturnal pauses are often observed in asymptomatic patients with persistent or permanent AF and do not constitute an indication for pacing.

AV junction ablation requiring the implantation of a permanent pacemaker should be considered in patients with refractory symptoms associated with excessive heart rates despite adequate trials of rate-control drugs, including combination drug therapy. This procedure results in adequate rate control in virtually all patients and has been associated with improvements in clinical symptoms, exercise tolerance, QOL, and ventricular function. Biventricular pacing should be considered after AV junction ablation in patients with left ventricular systolic dysfunction. In selected patients, control of AF by left atrial or pulmonary vein catheter ablation to restore sinus rhythm can be considered as an alternative to AV nodal ablation requiring permanent pacing.

Practical tip. As an alternative to AV junction ablation, an attempt at restoration of sinus rhythm via electrical or pharmacologic cardioversion may be warranted to control heart rate in cases in which this can be achieved, such as in the setting of persistent AF or AFL.

RECOMMENDATION

We recommend AV junction ablation and implantation of a permanent pacemaker in symptomatic patients with uncontrolled ventricular rates during AF despite maximally tolerated combination pharmacologic therapy (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the results of many small randomized trials and one systematic review reporting significant improvements in QOL and functional capacity as well as a decrease in hospitalizations for AF following AV junction ablation in highly symptomatic patients.

Rhythm Control of AF and AFL

It is important to emphasize that compared with rate control alone, the strategy of maintaining sinus rhythm has never been shown to decrease mortality or reduce the incidence of thromboembolic complications in AF patients compared to rate control alone. Thus, the decision to pursue sinus rhythm maintenance should be directed to patients who remain symptomatic with AF or AFL despite adequate rate control (Table 1). Symptoms may include palpitations, fatigue, exercise intolerance, or symptoms of heart failure. In these patients, restoration and maintenance of sinus rhythm can alleviate these symptoms and improve QOL. Improvement in patient QOL and function, and not the total elimination of AF, should always be the focus of rhythm control. The benefits of any antiarrhythmic drug therapy must also be balanced against the side effects and toxicities of such therapy. If drug therapy fails to achieve a meaningful improvement in patient QOL, then alternatives to the strategy of pharmacologic rhythm control should be considered, including catheter ablation of AF or rate control alone.

Practical tip. When pursuing a rhythm-control strategy for AF, there needs to be a reasonable expectation of maintenance of sinus rhythm.

RECOMMENDATION

We recommend the optimal treatment of precipitating or reversible predisposing conditions of AF prior to attempts to restore or maintain sinus rhythm (Strong Recommendation, Low-Quality Evidence).

We recommend a rhythm-control strategy for patients with AF or AFL who remain symptomatic with rate-control therapy or in whom rate-control therapy is unlikely to control symptoms (Strong Recommendation, Moderate-Quality Evidence).

We recommend that the goal of rhythm-control therapy should be improvement in patient symptoms and clinical outcomes, and not necessarily the elimination of all AF (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. These recommendations place a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL and other clinical outcomes with the potentially greater adverse effects of the addition of class I or class III antiarrhythmic drugs to rate-control therapy.

Mechanism of action of antiarrhythmic drugs

The mechanisms underlying AF are complex, likely differing among patients and even within individual patients as a function of the evolution of their cardiac condition. It has been hypothesized that AF is initiated by arrhythmogenic foci, often originating in the pulmonary veins. However, AF is maintained by multiple small reentrant wavelets, sometimes described as “rotors.” Formation and persistence of these wavelets is favoured by a shortened atrial refractory period and action potential duration, which occur during AF. The primary action of many antiarrhythmic medications is to lengthen refractory periods by prolonging action potential duration, to inhibit the formation of wavelets responsible for AF maintenance, or to reduce the phase-0 sodium current to destabilize AF-maintaining rotors.
Both drugs also have noncompetitive beta-blocking and calcium channel blocking effects, including both class I and class III mechanisms of action.35 Other antiarrhythmic drugs are less efficacious but have fewer side effects compared with amiodarone.42 These drugs still carry some risk however, particularly in patients with underlying heart disease.45 Thus, the choice of which antiarrhythmic agent to use long-term should be guided by evidence-based outcomes (where available) and the safety and efficacy profile of each agent in the context of the specific clinical profile of the patient (see Table 3 and Figs. 4 and 5).

In patients with normal ventricular function, the first-choice antiarrhythmic drug can be either dronedarone, flecainide, or propafenone, block sodium channels.35 This slows atrial conduction, lengthens atrial refractoriness, and suppresses automaticity.36 By destabilizing AF-maintaining rotors, this class of drugs can prevent the persistence of AF.33-35 Class III drugs such as sotalol or dofetilide block potassium channels and thus prolong action potential duration.37 With sufficient action potential prolongation, class III drugs prevent AF recurrence.

Class I drugs, such as flecainide and propafenone, block sodium channels.35 This slows atrial conduction, lengthens atrial refractoriness, and suppresses automaticity.36 By destabilizing AF-maintaining rotors, this class of drugs can prevent the persistence of AF.33-35 Class III drugs such as sotalol or dofetilide block potassium channels and thus prolong action potential duration.37 With sufficient action potential prolongation, class III drugs prevent AF recurrence.

Antiarrhythmic drug therapy to maintain sinus rhythm

In the absence of an antiarrhythmic drug, the recurrence rate of AF is about 75% over 1 year.8 Thus, recurrences are very likely once the AF process starts. If a decision is made to pursue a long-term strategy of rhythm control, patients will often require maintenance oral antiarrhythmic drug therapy. While antiarrhythmic drugs will not completely eliminate AF, they can substantially reduce AF burden and improve QOL. Reduction of AF burden by itself without demonstration of alleviated symptoms or reduced morbidity is insufficient to recommend the routine use of class I or class III antiarrhythmic drugs. Ideally, such therapy should also reduce other, more quantitative outcomes such as hospitalization or even mortality, but to date, only limited data exist to support the notion that rhythm-control therapy can accomplish such goals.39-41

The dosages, efficacy, side effects, and some practical tips about the various antiarrhythmic drugs are summarized in Table 3. The choice of drugs to use depends on an individual patient’s profile and the presence or absence of underlying structural heart disease, as summarized in Figures 4 and 5. Of all the currently available antiarrhythmic drugs, amiodarone has been demonstrated to have the highest efficacy in reducing AF burden.42,43 Unfortunately, it also has numerous important noncardiac side effects, which prevent it from being used as an agent of first choice.44 Other antiarrhythmic drugs are less efficacious but have fewer side effects compared with amiodarone.42 These drugs still carry some risk however, particularly in patients with underlying heart disease.45 Thus, the choice of which antiarrhythmic agent to use long-term should be guided by evidence-based outcomes (where available) and the safety and efficacy profile of each agent in the context of the specific clinical profile of the patient (see Table 3 and Figs. 4 and 5).

In patients with normal ventricular function, the first-choice antiarrhythmic drug can be either dronedarone, fleca-
EMBARGOED

Furthermore, a specific agent in order to avoid paradoxically increasing the ventricular drugs for suppression of AF have not been made. Propafenone patients with decompensated heart failure (see below). It is possible that the rate-control effects of dronedarone contributed to the reduction in hospitalizations for AF reported in ATHENA.

In patients with abnormal ventricular function but left ventricular ejection fraction >35%, dronedarone, sotalol, and amiodarone are all reasonable choices (Fig. 5). However, in patients with left ventricular ejection fraction <35%, amiodarone, is the only drug usually recommended because of its low risk of proarrhythmia in heart failure. Sotalol or dronedarone could be considered for treatment of AF in dronedarone patients with a left ventricular ejection fraction <35% and in the absence of symptoms of severe heart failure, particularly if they have an implantable cardioverter defibrillator. There is an increased risk of proarrhythmia in heart failure patients taking sotalol, likely because of downregulation of potassium currents and loss of repolarization reserve with heart failure. However, sotalol is used selectively by heart rhythm specialists in patients protected by an implantable defibrillator. The ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease) trial found that dronedarone may increase the risk of mortality in recently decompensated heart failure patients in recently decompensated individuals (New York Heart Association classes III and IV) who were hospitalized.

Although the American College of Cardiology, American Heart Association, and European Society of Cardiology 2006 AF guidelines do not recommend the use of propafenone, flecainide, or sotalol in the setting of hypertension and documented left ventricular hypertrophy, the writing group felt that the scientific data supporting this recommendation is weak. Certainly, concern about the use of these drugs due to increased risk of proarrhythmia is warranted if abnormalities of repolarization are noted in the ECG. However, in this setting the choice of antiarrhythmic drug should be individualized on the basis of the patient profile and consideration of the risks and benefits of each drug.

Figure 4. Antiarrhythmic drug choices for prevention of atrial fibrillation in patients without structural heart disease. Antiarrhythmic drugs are presented in alphabetical order. Given the side effect profile of amiodarone, its use is generally reserved for occasions when other drug choices have been demonstrated to be ineffective, contraindicated, or not well-tolerated. CAD, coronary artery disease; AV, atrioventricular.

Figure 5. Antiarrhythmic drug choices for prevention of AF in patients with depressed left ventricular systolic function. Dronedarone is contraindicated in patients with acutely decompensated heart failure. Sotalol may be used with caution in selected patients with mild to moderate reduction in left ventricular ejection fraction.

Dronedarone is generally well-tolerated, with a relatively low incidence of side effects or proarrhythmia. In the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 Mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Flutter) trial, dronedarone was shown to reduce hospitalization and cardiovascular mortality in AF patients. The panel chose not to make a specific recommendation that dronedarone should be the first antiarrhythmic drug considered for prevention of AF since dronedarone’s efficacy for maintenance of sinus rhythm is comparable to other modestly effective rhythm-control agents (flecainide, propafenone, and sotalol). Also, dronedarone has been shown to be harmful in patients with decompensated heart failure (see below).

In patients with abnormal ventricular function but left ventricular ejection fraction >35%, dronedarone, sotalol, and amiodarone are all reasonable choices (Fig. 5). However, in patients with left ventricular ejection fraction <35%, amiodarone, is the only drug usually recommended because of its low risk of proarrhythmia in heart failure. Sotalol or dronedarone could be considered for treatment of AF in dronedarone patients with a left ventricular ejection fraction <35% and in the absence of symptoms of severe heart failure, particularly if they have an implantable cardioverter defibrillator. There is an increased risk of proarrhythmia in heart failure patients taking sotalol, likely because of downregulation of potassium currents and loss of repolarization reserve with heart failure. However, sotalol is used selectively by heart rhythm specialists in patients protected by an implantable defibrillator. The ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease) trial found that dronedarone may increase the risk of mortality in recently decompensated heart failure patients in recently decompensated individuals (New York Heart Association classes III and IV) who were hospitalized.

Although the American College of Cardiology, American Heart Association, and European Society of Cardiology 2006 AF guidelines do not recommend the use of propafenone, flecainide, or sotalol in the setting of hypertension and documented left ventricular hypertrophy, the writing group felt that the scientific data supporting this recommendation is weak. Certainly, concern about the use of these drugs due to increased risk of proarrhythmia is warranted if abnormalities of repolarization are noted in the ECG. However, in this setting the choice of antiarrhythmic drug should be individualized on the basis of the patient profile and consideration of the risks and benefits of each drug.

Dronedarone is generally well-tolerated, with a relatively low incidence of side effects or proarrhythmia. In the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 Mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Flutter) trial, dronedarone was shown to reduce hospitalization and cardiovascular mortality in AF patients. The panel chose not to make a specific recommendation that dronedarone should be the first antiarrhythmic drug considered for prevention of AF since dronedarone’s efficacy for maintenance of sinus rhythm is comparable to other modestly effective rhythm-control agents (flecainide, propafenone, and sotalol). Also, dronedarone has been shown to be harmful in patients with decompensated heart failure (see below).

In patients with abnormal ventricular function but left ventricular ejection fraction >35%, dronedarone, sotalol, and amiodarone are all reasonable choices (Fig. 5). However, in patients with left ventricular ejection fraction <35%, amiodarone, is the only drug usually recommended because of its low risk of proarrhythmia in heart failure. Sotalol or dronedarone could be considered for treatment of AF in dronedarone patients with a left ventricular ejection fraction <35% and in the absence of symptoms of severe heart failure, particularly if they have an implantable cardioverter defibrillator. There is an increased risk of proarrhythmia in heart failure patients taking sotalol, likely because of downregulation of potassium currents and loss of repolarization reserve with heart failure. However, sotalol is used selectively by heart rhythm specialists in patients protected by an implantable defibrillator. The ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease) trial found that dronedarone may increase the risk of mortality in recently decompensated heart failure patients in recently decompensated individuals (New York Heart Association classes III and IV) who were hospitalized.

Although the American College of Cardiology, American Heart Association, and European Society of Cardiology 2006 AF guidelines do not recommend the use of propafenone, flecainide, or sotalol in the setting of hypertension and documented left ventricular hypertrophy, the writing group felt that the scientific data supporting this recommendation is weak. Certainly, concern about the use of these drugs due to increased risk of proarrhythmia is warranted if abnormalities of repolarization are noted in the ECG. However, in this setting the choice of antiarrhythmic drug should be individualized on the basis of the patient profile and consideration of the risks and benefits of each drug.
As previously discussed, the goal of antiarrhythmic drug therapy should be reduction (not necessarily elimination) of AF burden with concomitant improvement in QOL. If a patient has occasional breakthroughs of AF, but few symptoms, therapy may be considered successful. Antiarrhythmic drug therapy should be reassessed periodically based on both efficacy and side effects. If patients fail to respond to or cannot tolerate a particular drug, an alternative drug may be tried after an appropriate washout period. If a patient fails multiple medications, then alternatives to consider include catheter ablation of AF to maintain sinus rhythm (SR) or abandonment of rhythm control in favour of rate control alone (Fig. 1).

Risks of antiarrhythmic drug therapy

Risks of the various antiarrhythmic drugs are listed in Table 3. All antiarrhythmic drugs carry the potential of proarrhythmia, so that treatment of AF or AFL may increase the risk of other, more malignant arrhythmias (often ventricular in origin).45 The class I agents (flecainide and propafenone) can increase the risk of ventricular arrhythmias in patients with coronary artery disease or left ventricular dysfunction, so these agents should be avoided in these populations.56,57 Class I agents slow the atrial rate in AF by slowing conduction in reentrant rotors or wavelets. The ventricular response to AF is determined by complex interactions between the rate and pattern of activation of the proximal AV node from the atrium on one hand and the refractory properties of the AV node on the other. Because of the decremental conduction properties of AV nodal tissue (involving Ca2+-current–dependent action potentials and zones of poor cell-to-cell coupling), atrial impulses that fail to conduct through the AV node leave the node partially refractory to the next impulse, a phenomenon called concealed conduction. Paradoxically, a slowing in atrial rate can therefore cause an increased ventricular response due to a reduction in the number of concealed activations in the AV node. In the most extreme cases with very slow organized atrial activation, conversion of AF to AFL and subsequent 1:1 conduction of AFL can ensue, causing a very high ventricular rate and risk of ventricular tachyarrhythmia.

Practical tip. Class I agents should be combined with an AV nodal blocking agent (beta-blocker, verapamil, diltiazem, or digoxin) to avoid this risk.

Certain class III agents, such as sotalol, lengthen the QT interval and carry a risk of torsades de pointes polymorphic ventricular tachycardia (VT) (1%-3%). Any additional risk factor that prolongs the QT interval increases the likelihood of torsades de pointes VT. This includes female sex, left ventricular dysfunction, significant left ventricular hypertrophy, bradycardia, or hypokalemia or hypomagnesemia (often resulting from diuretic use). By reducing net repolarizing current,43,55,58 these factors can individually or collectively reduce “repolarization reserve” and increase the risk of drug-induced torsades de pointes. Advanced age reduces the efficiency of drug-eliminating systems (renal function, bio-transforming capacity), as well as the volume of distribution for many drugs, and is therefore also a risk factor for drug-induced torsades de pointes. Since sotalol is cleared via the kidneys, any renal dysfunction also increases the proarrhythmic risk. Periodic ECG monitoring of the QT interval should be performed and the drug should be reassessed if the QT is longer than 500 ms or the QTc exceeds 480 ms. Other drugs that increase the QT interval (erythromycin, clarithromycin, antipsychotics) should be avoided by a patient while on sotalol (a full list is available at www.torsades.org).

Amiodarone and dronedarone both carry a low risk of proarrhythmia because of their multiple class effects. Dronedarone is generally safe and well-tolerated. In patients with decompensated heart failure, however, it has been shown to increase mortality (Table 3).53 Amiodarone rarely causes torsades de pointes VT, but has numerous noncardiac toxicities.44 Patients should avoid direct sun exposure to avoid photosensitivity. A clinical exam, with careful history to elicit symptoms of toxicity (eg, sleep disturbance, tremor, gait instability, constipation), and pulmonary assessment should be performed periodically to check for toxicity. Hepatic enzymes and thyrotropin should be measured every 6 months in all patients on amiodarone, regardless of symptoms.

Bradycardia can be exacerbated by any antiarrhythmic agent, whether because of sinus node or AV node dysfunction. If bradycardia results in symptoms, the drug should be discontinued, or consideration should be given to implantation of a permanent pacemaker.

Generally, class I or class III antiarrhythmic drugs may be initiated as an outpatient, in spite of the risk of proarrhythmia. Particularly in patients with no underlying heart disease, the risk of proarrhythmia is quite low. If a conduction disturbance (such as sinus or AV node dysfunction) is present or if a patient has risk factors for torsades de pointes VT or significant underlying heart disease, then consideration should be given to drug initiation in hospital. Amiodarone is the only medication that has been shown to be safe when initiated as an outpatient in patients with heart failure and left ventricular dysfunction.45

**RECOMMENDATION**

We recommend use of maintenance oral antiarrhythmic therapy as first-line therapy for patients with recurrent AF in whom long-term rhythm control is desired (see Figs. 4 and 5) (Strong Recommendation, Moderate-Quality Evidence).

We recommend that oral antiarrhythmic drug therapy should be avoided in patients with AF or AFL and advanced sinus or AV nodal disease unless the patient has a pacemaker or implantable defibrillator (Strong Recommendation, Low-Quality Evidence).

We recommend that an AV blocking agent should be used in patients with AF or AFL being treated with a class I antiarrhythmic drug (eg, propafenone or flecainide) in the absence of advanced AV node disease (Strong Recommendation, Low-Quality Evidence).

**Values and preferences.** These recommendations place a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL and other clinical outcomes with the potentially greater adverse effects of class I and class III antiarrhythmic drugs compared with rate-control therapy.
Intermittent Antiarrhythmic Drug Therapy (“Pill in the Pocket”)

Some patients with symptomatic AF have relatively long-lasting episodes (eg, >4 hours) but with long intercurrent periods of sinus rhythm between episodes (eg, <2-6/y). In these patients, a strategy of daily maintenance antiarrhythmic drug therapy may be unnecessary. An alternative possibility is to prescribe oral antiarrhythmic drugs that can be taken at the time of an episode for acute termination of AF. Clinical trial data have shown this “pill in the pocket” strategy to be both safe and effective.59 The drugs most commonly used for this purpose are class I agents given as a single dose at the onset of AF. Flecainide is given as a single or cumulative 200 to 300-mg dose, and propafenone is given as a single 450 to 600-mg dose. Both these agents have a 50% to 80% efficacy in acutely terminating AF. Some physicians also prescribe a rapidly acting beta-blocker (eg, metoprolol 50 to 100 mg), to be taken at the same time as the class I antiarrhythmic agent in order to minimize the risk of accelerating the ventricular response. In patients taking daily medication, an additional dose of the drug can be used in this manner.

Practical tip. Because of the risk of 1:1 AV conduction of AFL or the risk of bradycardia, an initial trial of this strategy may be performed in a monitored setting to verify safety and efficacy of this approach in a given patient. Combination with a rapidly acting beta-blocker or calcium blocker is recommended (for patients not already on AV nodal blocking medication or known significant AV nodal dysfunction), particularly in patients in whom this approach has been verified in a monitored setting or in patients with little risk of bradycardia or hypotension associated with this therapy.

Patients should ensure their drugs have not expired if the time between episodes is very long.

Drug conversion of AF

Acute restoration of sinus rhythm from recent onset AF is most commonly performed using electrical cardioversion. Drug conversion may, however, be an effective alternative. While less effective than the electrical method, pharmacologic conversion avoids the need for general anaesthesia and may reduce the risk of early recurrence of AF. Oral antiarrhythmic agents such as flecainide and propafenone may be given as single doses (see discussion of “pill in the pocket,” above).59 Ibutilide is an intravenous class III medication that is typically given as a single dose of 1 mg, which may be repeated once. It is superior to intravenous procainamide, but its use is limited by a 2% to 3% risk of torsades de pointes VT.63,64 Ibutilide is more effective for AFL than for AF. The risk of torsades de pointes VT associated with ibutilide can be reduced by pretreatment with 1 to 2 g magnesium sulphate administered intravenously.65 Intravenous procainamide can also be used as a single dose of 15 to 17 mg/kg over 20 to 30 minutes but is associated with a 5% risk of hypotension and is less effective than ibutilide.63,64 Intravenous and oral amiodarone are not effective for acute conversion (conversion in <6-8 hours) of AF and therefore should not be used routinely for this purpose.59,66

Need for anticoagulation

When considering either electrical or pharmacologic cardioversion of AF, patients should be adequately anticoagulated to prevent postconversion thromboembolic complications.28,68 The risk of thromboembolism is the same whether conversion is achieved electrically or with drugs.28 Although oral antiarrhythmic drug therapy given in maintenance doses is less likely to acutely convert AF to sinus rhythm,
Table 4. Randomized trials of pacing modes and impact on AF occurrence

<table>
<thead>
<tr>
<th></th>
<th>Danish86 AAI vs VVI</th>
<th>CTOPP81</th>
<th>Extended82 CTOPP</th>
<th>MOST83</th>
<th>Danish87 AAI vs DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>225</td>
<td>2568</td>
<td>2568</td>
<td>2050</td>
<td>177</td>
</tr>
<tr>
<td>Age (y)</td>
<td>71 ± 17</td>
<td>73 ± 10</td>
<td>73 ± 10</td>
<td>74 (67-80)</td>
<td>74 ± 9</td>
</tr>
<tr>
<td>Pacing indication</td>
<td>SND</td>
<td>All pacemaker patients</td>
<td>All pacemaker patients</td>
<td>SND</td>
<td>SND</td>
</tr>
<tr>
<td>Follow-up (y)</td>
<td>5.5</td>
<td>3.1</td>
<td>6.4</td>
<td>2.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Pacing modes</td>
<td>AAI vs VVI</td>
<td>AAI/R or DDD/R vs VVIR</td>
<td>AAI/R or DDD/R vs VVIR</td>
<td>DDDIR vs VVIR</td>
<td>AAI vs DDDR-s vs DDDR-l</td>
</tr>
<tr>
<td>AF occurrence (%/y)</td>
<td>4.1 vs 6.6</td>
<td>5.3 vs 6.3</td>
<td>4.5 vs 5.7</td>
<td>7.9 vs 10.0</td>
<td>2.4 vs 8.3 vs 6.2</td>
</tr>
<tr>
<td>Risk reduction (%)</td>
<td>46</td>
<td>18</td>
<td>20</td>
<td>21</td>
<td>73</td>
</tr>
<tr>
<td>P-value</td>
<td>.012</td>
<td>.05</td>
<td>.009</td>
<td>.008</td>
<td>.02</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; AAI, atrial pacing; AAI/R, atrial rate adaptive pacing; CTOPP, Canadian Trial of Physiologic Pacing; DDDR, dual chamber rate adaptive pacing; DDDR-l, long atrioventricular delay; DDDR-s, short atrioventricular delay; SND, sinus node disease; VVI, ventricular pacing; VVIR, ventricular rate adaptive pacing.

Prevention of AF in the pacemaker population

A number of prospective, randomized clinical trials have reported that atrial- or dual-chamber pacing reduces the risk of paroxysmal and permanent AF in patients with symptomatic bradycardia as the primary indication for cardiac pacing.85-86 The data from these trials are summarized in Table 4. In contrast, the United Kingdom Pacing and Cardiovascular Events Trial Investigators did not observe a benefit of dual-chamber pacing over ventricular for prevention of AF in patients with AV block as the indication for pacing.87 Thus, these data suggest that the primary benefit of dual-chamber pacing for reducing the risk of AF is observed in patients with sinus node disease and intact AV node conduction.

The Mode Selection Trial Investigators reported that patients who were more frequently paced in the ventricle were more likely to develop AF.86 The risk of developing AF increased approximately 1% for each 1% increase in ventricular pacing. Nielsen et al87 also reported that patients with sick sinus syndrome randomized to atrial rate adaptive pacing were less likely to develop AF during follow-up (7.4%) compared with patients randomized to dual-chamber rate adaptive pacing with a short (≤150 ms) or long (300 ms) AV intervals (23.3% and 17.5%, respectively). There are no data to support specific recommendations directed at upstream molecular targets as part of the management strategy for AF.

**RECOMMENDATION**

We recommend radiofrequency ablation of AF in patients who remain symptomatic following adequate trials of antiarrhythmic drug therapy and in whom a rhythm-control strategy remains desired (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** This recommendation places a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL with the small but measurable risk of serious complication with catheter ablation.

**Novel therapeutic targets**

Experimental research into the substrates that initiate and maintain AF have identified some molecular targets upstream of the electrophysiologic parameters important for AF which might provide novel therapeutic targets for therapy of AF.71,73,74 Candidates for upstream therapy include statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors), drugs that suppress the renin-angiotensin-aldosterone system, and omega-3 fatty acids. Statins may prevent adverse atrial electrical remodelling associated with AF by anti-inflammatory antioxidant, anti-proliferative, or antiapoptotic effects.77-79 Blocks of the renin-angiotensin system may prevent myocyte hypertrophy, apoptosis, and intercellular fibrosis, as well as exerting indirect effects on atrial myocyte electrophysiology.70,75 Clinical studies have reported that statin therapy may prevent AF, particularly in patients following cardiac surgery.76 However, a consistent benefit has not been observed in all patient groups evaluated.77 Drugs which inhibit the renin-angiotensin system have been reported to be effective for primary and secondary prevention of AF, with the greatest benefit observed in patients with left ventricular hypertrophy and/or heart failure.78 However, valsartan did not prevent AF recurrence in the largest randomized prospective trial to date, testing the hypothesis that angiotensin receptor blockade might be an effective therapy for AF.79 At present, studies are underway evaluating the role of omega-3 fatty acids for prevention of AF.73,74 The evidence to date, however theoretically appealing, does not support specific recommendations directed at upstream molecular targets as part of the management strategy for AF.
suggest that atrial overdrive pacing substantially reduces AF. \(^8\) Recently, algorithms designed to minimize ventricular pacing have been shown to reduce the risk of persistent AF following pacemaker implantation in patients with sinus node disease. \(^8\)

**RECOMMENDATION**

We suggest that patients requiring pacing for the treatment of symptomatic bradycardia secondary to sinus node dysfunction, atrial or dual-chamber pacing be generally used for the prevention of AF (Conditional Recommendation, High-Quality Evidence).

We suggest that, in patients with intact AV conduction, pacemakers be programmed to minimize ventricular pacing for prevention of AF (Conditional Recommendation, Moderate-Quality Evidence).

**Values and preferences.** These recommendations recognize a potential benefit of atrial or dual-chamber pacing programmed to minimize ventricular pacing to reduce the probability of AF development following pacemaker implantation.

**Management of AF: Chronic Disease Management Principles**

Chronic disease management principles dictate that the primary care physician is central to coordination of patient care. Ideally, support for the primary care physician should facilitate delivery of care, with specialty clinics providing care to more complex cases and tertiary care specialists reserved for the most challenging cases. To facilitate management of AF patients, specialty clinics have been formed in some regions, and others are in planning stages. \(^9\) Participation of the referring physicians is essential to the success of AF clinics, in which nurse clinicians or nurse practitioners play a key role in patient education and reassurance about both AF and the treatment plan. Direct contact with an AF physician specialist may not be required in all cases. In some instances, recommendations about urgent intervention to control the ventricular rate and initiate anticoagulation to prevent stroke are provided by the AF physician specialist, with reassessment at a later date. Some data suggest that patient education and continuity of care provided by AF clinics may reduce emergency room visits. \(^9\)

**References**

10. Wyse DG, Simpson CS. Rate control versus rhythm control—decision making. Can J Cardiol 2005;21(suppl B):15B-18B.


Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Catheter Ablation for Atrial Fibrillation/Atrial Flutter

Atul Verma, MD, FRCPC, a Laurent Macle, MD, FRCPC, b Jafna Cox, MD, FRCPC, c Allan C. Skanes, MD, FRCPC, d and the CCS Atrial Fibrillation Guidelines Committee e

a Southlake Regional Health Centre, Newmarket, Ontario, Canada
b Montreal Heart Institute, Montreal, Québec, Canada
c Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada
d London Health Sciences Centre, London, Ontario, Canada

ABSTRACT
Catheter ablation of atrial fibrillation (AF) offers a promising treatment for the maintenance of sinus rhythm in patients for whom a rhythm control strategy is desired. While the precise mechanisms of AF are incompletely understood, there is substantial evidence that in many cases (particularly for paroxysmal AF), ectopic activity most commonly located in and around the pulmonary veins of the left atrium plays a central role in triggering and/or maintaining arrhythmic episodes. Catheter ablation involves electrically disconnecting the pulmonary veins from the rest of the left atrium to prevent AF from being triggered. Further substrate modification may be required in patients with more persistent AF. Successful ablation of AF has never been shown to alter mortality or obviate the need for oral anticoagulation; thus, the primary indication for this procedure should be improvement of symptoms caused by AF. The success rate of catheter ablation for AF is superior to the efficacy of antiarrhythmic drugs, but success is still in the range of 75%-90% after 2 procedures. Ablation is also associated with a significant risk of complications, including stroke and heart failure.

As discussed in detail by Gillis et al., studies have failed to show that a rhythm control strategy improves mortality or reduces the incidence of thromboembolic complications in atrial fibrillation (AF) compared to the use of rate control alone. Thus, the decision to pursue rhythm control should be directed to patients who are symptomatic with their AF despite rate control, specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.
with the aim of improving quality of life. Many of these symptomatic patients, such as younger patients with “lone” AF, were underrepresented in trials comparing rate and rhythm control. Furthermore, in all of these trials, antiarrhythmic drug therapy was used for the rhythm control strategy. Antiarrhythmic drugs remain “first-line” therapy for the maintenance of sinus rhythm, but these medications have only modest efficacy at maintaining sinus rhythm over the long term. They are also associated with side effects, in particular proarrhythmia, which limit their long-term use, especially in younger patients. Catheter ablation offers an alternative to maintaining sinus rhythm when drugs have been ineffective or cannot be tolerated. Data have shown that the success rate of catheter ablation in maintaining sinus rhythm is superior to that of drug therapy and is associated with improved quality of life (see later). While there are clearly upfront risks associated with this invasive procedure, the risks have decreased substantially over time and, if successful, the procedure obviates the long-term risks of antiarrhythmic drugs. Thus, for many highly symptomatic patients who cannot be pharmacologically controlled, catheter ablation offers a promising alternative.

**Mechanism of Action of Catheter Ablation of AF**

Catheter ablation for AF should be distinguished from atrioventricular (AV) junction ablation and pacemaker implantation, which is used for rate control but for not maintenance of sinus rhythm. It should also be distinguished from catheter ablation of typical right atrial flutter, which is a distinct procedure (described later in this article). Catheter ablation of AF aims to eliminate both the triggers of AF and the substrate that maintains AF, to achieve long-term sinus rhythm.

While the mechanism of AF is very complex, rapid ectopic activity from the pulmonary veins (PVs) may be responsible for both triggering and maintaining AF, in particular paroxysmal AF. Scherf and colleagues first described how rapidly firing ectopic foci within the atria could degenerate the atria into a fibrillatory rhythm. It was the seminal report by Haissaguerre and colleagues, however, that first applied this principle in clinical practice. In their report, they described how most of the triggering foci for AF in the human originated in or around the PVs of the left atrium (LA). More than 90% of the foci originate in this region, with 10% originating in other areas such as the LA posterior wall, interatrial septum, coronary sinus, superior vena cava, and crista terminalis in the right atrium (RA). By ablating around the PVs and electrically isolating them from the rest of the atria, the triggering foci can be eliminated and AF prevented (Fig. 1). The procedure is sometimes referred to as a “pulmonary vein isolation” procedure for this reason. Over time, this technique has proved to be widely effective at maintaining sinus rhythm, particularly in patients with paroxysmal AF, and has evolved to become the cornerstone of AF catheter ablation procedures.

In patients with more persistent AF, electrical and structural remodelling of the atria occur, creating an abnormal atrial substrate that tends to perpetuate AF. Changes include a decrease in atrial refractoriness, atrial fibrosis, and atrial stretch. Thus, while PV isolation remains the primary AF ablation approach in persistent AF, it is believed that further ablation of the substrate is required to treat AF in this population. The most common forms of substrate modification are linear ablation and electrogram-guided ablation. Linear ablation involves creating lines of block along the LA roof and the mitral annulus and occasionally in the RA, mimicking the original surgical maze procedure. Electrogram-guided ablation involves targeting specific electrical signals (eg, complex “fractionated” signals) that may represent critical areas of AF perpetuation. The optimal strategy of substrate modification remains an area of active investigation.

**Procedural Considerations**

AF ablation is a complex procedure, requiring a high degree of operator expertise and advanced technological support.

---

**Figure 1.** Ablation lesion set for pulmonary vein isolation. Computed tomography scan of the posterior view of the left atrium including the pulmonary veins. Veins are labelled as follows: LSPV, left superior; LIPV, left inferior; RSPV, right superior; RIPV, right inferior pulmonary vein. The red dots represent point-by-point ablation lesions created by radiofrequency energy in the left atrium surrounding the pulmonary veins, thus electrically disconnecting them from the rest of the atrium. The darker dots represent lesions on the posterior wall of the left atrium, and the lighter dots represent circumferential lesions along the anterior aspect of the left atrium.
While AF ablation is performed as an outpatient, day procedure, the intervention often takes about 3-5 hours or longer to complete. Patients need to be orally anticoagulated with warfarin for at least 1-2 months prior to the procedure and at least 3-6 months postablation to minimize the risk of a thromboembolic complication. Some centres will routinely perform procedural transeosophageal echocardiography to rule out atrial thrombus prior to performing the ablation.10

The procedure itself may be performed under general anaesthesia or heavy conscious sedation using benzodiazepines and/or opiates.11,12 The entire procedure is performed through systemic venous access via the femoral and/or subclavian or internal jugular veins. Access to the LA is achieved by performing a transeptal puncture across the interatrial septum to cross from the RA to the LA. Because the major focus for ablation is in the LA, the patient is systemically anticoagulated to minimize thromboembolic events. In general, the procedure is performed with the patient adequately anticoagulated, either by sustaining the preprocedure warfarin (usually allowing the INR to fall to the lower end of the therapeutic range) or with use of bridging low-molecular-weight heparin both before and after the procedure. In the latter case, unfractionated heparin is administered with access to the LA. Likewise, bridging low-molecular-weight heparin is reinitated within hours of the sheath removal and continued until a therapeutic INR is reestablished with oral anticoagulant therapy. The anatomy and electrical activity of the LA are often reconstructed using a 3-dimensional mapping system that then guides the rest of the procedure. Ablation is most commonly performed with radiofrequency energy delivered from a catheter tip. Technologies are evolving, however, to use different catheter designs and energy sources to maximize energy delivery while minimizing the risks, such as perforation.

Following ablation, patients are evaluated at regular intervals with electrocardiograms and Holter monitoring to determine the success of the procedure. Early recurrences of AF may occur within the first 3 months postablation due to acute inflammation in the LA but do not necessarily indicate long-term failure of the procedure; at least 50% of these recurrences will resolve spontaneously after 3 months.13,14

### Efficacy of Catheter Ablation for AF

Since AF ablation was first described >10 years ago, the technique and technology have evolved such that fairly consistent success rates can be achieved for patients with paroxysmal AF and minimal associated structural heart disease.15 In these patients, the success rate of maintaining sinus rhythm off antiarrhythmic drug therapy is 60%-75% after 1 procedure and 75%-90% after 2 procedures.12 In a recent meta-analysis of 6 clinical trials that compared ablation with antiarrhythmic drug therapy in a total of 693 patients, ablation was associated with a significantly increased odds of freedom from AF at 12 months (odds ratio [OR] 9.74; 95% confidence interval [CI] 3.98-23.87).16 Ablation was also associated with a decreased rate of cardiovascular hospitalization (OR 0.15; 95% CI 0.10-0.23). These results were achieved with a repeat ablation rate of 17%. The results were also quite consistent between trials.17 In a recent multicenter, randomized trial comparing catheter ablation with antiarrhythmic drug therapy, 66% of patients maintained sinus rhythm off drugs after a single ablation of paroxysmal AF compared with only 16% with antiarrhythmic drug therapy alone.18 Ablation also resulted in a significant improvement in quality of life. Another trial has demonstrated similar results.19 Failures most commonly occur as a result of electrical reconnection between the PVs and the LA due to recovery of previous ablation sites.20 Improved outcomes have been demonstrated with repeat procedures to isolate electrically reconnected PVs. Technologies that will help create more permanent lesions during the first ablation may improve long-term success rates and decrease the need for repeat procedures.

In patients with persistent AF, the success rates are 10%-15% lower than those described for paroxysmal AF with a higher need for repeat procedures.21 This lower success rate is predominantly due to the fact that the substrate has to be targeted and ablated in addition to PV isolation, meaning more complex and lengthy procedures. Furthermore, the optimal lesion set to target the substrate has yet to be fully determined, although there are data to suggest that hybrid techniques targeting more than just PV isolation may be required.22 With 2 procedures, the success rate of ablation for persistent AF may approach the success rates for paroxysmal AF.21 Lower success rates (by 5%-10% compared with paroxysmal AF) have also been reported in patients with structural heart disease, such as cardiomyopathy,23 although the benefit in this population may still be significant. The PABA-CHF trial, for example, reported improvements in ejection fraction in patients with congestive heart failure despite the lower overall procedural success rate.24

In patients who do not have a successful outcome postablation, some may become responsive to antiarrhythmic drug therapy that was previously ineffective. While many patients undergoing ablation wish to discontinue antiarrhythmic drugs, those who cannot maintain sinus rhythm postablation may achieve good rhythm control with adjuvant antiarrhythmic drug therapy.

Most studies have looked at 1-year outcomes for AF ablation. Very few longer-term data are available. It appears that after 12-18 months, most patients will continue to do well, but 5%-10% of patients will have late recurrences beyond that time period.25-28 Further data are required to understand better the long-term durability of the results of AF ablation.

### Risks of Catheter Ablation of AF

As with any invasive procedure, catheter ablation of AF is associated with procedural risk. While the risk of any complication was reported to be 6%-8% in early experiences,29 these risks have decreased appreciably in the past 5 years30 and are currently in the range of 2%-3%. The most common risk is a vascular access complication such as hematoma, pseudoneurysm, and AV fistula, occurring in 1%-2% of cases. Less common but more serious risks include those of cardiac perforation (0.5%-1%) and thromboembolism (0.5%-1%). Cardiac perforation can often be managed by percutaneous drainage (pericardiocentesis), although surgical repair is rarely required. Acute thromboembolic stroke results in transient deficits in most affected patients. Pulmonary vein stenosis used to be a more common complication when ablation was initially performed by ablation within the PVs. However, current ablation techniques deliver energy outside of the PVs within the LA, thus avoiding the stenosis hazard and making this complication quite uncommon today (<0.5%).
Fatal complications are quite rare, occurring in approximately 1:1000 cases. However, because of the proximity of the esophagus to the posterior LA wall, the esophagus may be damaged as a result of ablation in the LA. Rarely, this damage can result in a fistula forming between the LA and esophagus, which most often presents 2–4 weeks postablation as an unexplained fever with or without chest pain and unexplained neurologic events. Because this complication often goes unrecognized, it leads to sepsis and death. Use of lower power outputs during ablation, esophageal monitoring, and postprocedural proton pump inhibition may all reduce the already small risk of this complication.

**Candidates for Catheter Ablation of AF**

The decision to pursue a strategy of maintaining sinus rhythm should be aimed at reduction of patient symptoms. To date, there are no clinical trial data available demonstrating a reduction in mortality or stroke through maintenance of sinus rhythm, including through the use of catheter ablation. Thus, the primary indication for catheter ablation is in patients with symptomatic AF for whom the symptoms are adversely affecting quality of life. Patients with totally asymptomatic AF are not candidates for ablation, with the possible exception of patients in whom AF is thought to be adversely affecting left ventricular function (such as with tachycardia-induced cardiomyopathy). Antiarrhythmic drug therapy is still considered first-line therapy for maintenance of sinus rhythm, while catheter ablation should only be considered for patients for whom adequate trials of drug therapy fail. This hierarchy generally means a trial of ≥2 drugs in most patients. More recent clinical trials have demonstrated superiority of ablation in patients for whom ≥1 antiarrhythmic drugs have failed, and these trials form the basis for a conditional recommendation for select patients to be considered for catheter ablation as the initial treatment of AF. Younger patients, for example, may want to avoid long-term amiodarone treatment use given the drug’s accompanying (or cumulative) risks. Patients may also have cardiac or noncardiac absolute or relative contraindications to certain drugs (see Table 3 in Gillis et al in this issue). Also, patients are unlikely to benefit from specific medications if 1 medication in the same class has already failed.

**RECOMMENDATION**

We recommend catheter ablation of AF in patients who remain symptomatic following adequate trials of antiarrhythmic drug therapy and in whom a rhythm control strategy remains desired (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** This recommendation recognizes that failure of multiple antiarrhythmic drugs results in few alternative strategies if maintenance of sinus rhythm is preferred based on symptom burden reduction and quality of life improvement.

We suggest catheter ablation to maintain sinus rhythm in select patients with symptomatic atrial fibrillation and mild-moderate structural heart disease who are refractory or intolerant to ≥1 antiarrhythmic medication (Conditional Recommendation, Moderate-Quality Evidence).

**Table 1. Risk/benefit ratio for ablation in patients with symptomatic AF**

<table>
<thead>
<tr>
<th></th>
<th>Longstanding*</th>
<th>Persistent</th>
<th>Paroxysmal</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Failed first-line drug</td>
<td>—</td>
<td>+</td>
<td>+ +</td>
</tr>
<tr>
<td>Failed second-line drug</td>
<td>+</td>
<td>+ +</td>
<td>+ + + +</td>
</tr>
<tr>
<td>Failed multiple drugs</td>
<td>+ +</td>
<td>+ + + +</td>
<td>+ + + + +</td>
</tr>
</tbody>
</table>

+, Balance of risk and benefit in favour of catheter ablation.

* Ongoing symptomatic AF for ≥1 year.

Because most of the patients included in clinical trials to date have been with paroxysmal AF and because the success rate is higher in this population, these patients are favoured for ablation therapy. However, patients with symptomatic persistent AF are increasingly undergoing ablation. The risk/benefit ratio of performing catheter ablation for AF in various subtypes of AF is detailed in Table 1.

**Practical tip.** There is no formal definition for “adequate trials of antiarrhythmic drug therapy” mentioned in the first recommendation. Early studies assessing AF ablation required that patients have failed therapeutic doses of ≥2 different antiarrhythmics.

This “strong” recommendation stems from both the data and the belief of the consensus committee that AF ablation be reserved for patients who have had trials of therapeutic doses of ≥2 different antiarrhythmics drugs prior to being considered for catheter ablation. Electing to perform ablation after a trial of <2 drugs may be appropriate in carefully selected patients but meets only a “conditional” recommendation based on the more limited availability of data to support this approach.

In highly selected patients, AF ablation may be offered as first-line therapy. Data from 1 small pilot study of 70 patients showed a 63% recurrence rate in the antiarrhythmic arm versus only 13% in the ablation arm (P < .001) with a significant reduction in hospitalization and improvement in quality of life. In addition, although this has not been studied in detail, some patients with tachybrady syndrome are unable to tolerate drug therapy because of bradyarrhythmic complications in the absence of a permanent pacemaker. If the AF can be successfully ablated, then antiarrhythmic therapy and the need for permanent pacing may be avoided, especially in younger patients.

**RECOMMENDATION**

We suggest catheter ablation to maintain sinus rhythm as first-line therapy for relief of symptoms in highly selected patients with symptomatic, paroxysmal atrial fibrillation (Conditional Recommendation, Low-Quality Evidence).
Values and preferences. This recommendation recognizes that individual patients may have a strong intolerance or aversion to antiarrhythmic drugs such that the risk of ablation is deemed warranted.

While there is no absolute age limit for ablation, most clinical experiences have included few patients ≥75 years old and almost no patients ≥80 years old due to concern of increased complication rates.

Finally, if the LA size is too enlarged (typically >55-mm diameter in the parasternal long-axis view on standard echo), the success rate of catheter ablation is poor. Thus, if ablation is to be considered, it should be done prior to severe LA enlargement.

Practical tip. The following represents a typical, but not exclusive, profile of a patient who is referred for consideration of AF ablation today:

- Age <80 years
- Patients who are symptomatic with their AF
- Patients who have tried but failed or are intolerant of antiarrhythmic drug therapy
- Paroxysmal AF or short-standing persistent AF
- Minimal to moderate structural heart disease (eg, LV dysfunction or valvular disease).

Need for Anticoagulation With Catheter Ablation of AF

To date, there is no clinical evidence to suggest that successful catheter ablation of AF affects long-term stroke risk. One major reason is that some asymptomatic AF may continue to occur postablation undetected by intermittent monitoring. Data show that more intensive or continuous monitoring may detect episodes of asymptomatic AF in patients who have had a “successful” outcome, and this AF may contribute to ongoing thromboembolic risk. Even in patients in whom AF is eliminated, there is a lack of data to support anticoagulation withdrawal in patients with other risk factors for stroke. Trials to evaluate this question are currently under way, including the large-scale CABANA study. At present, if a patient has sufficient risk to warrant oral anticoagulation for their AF preablation (eg, a CHADS₂ [Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack] risk score of ≥2), then it is recommended that oral anticoagulation be continued indefinitely postablation regardless of apparent procedural success. Furthermore, because the very long-term results of ablation have not been fully elucidated beyond 2-5 years, the very late recurrence rate may also warrant ongoing anticoagulation. Avoidance of oral anticoagulation is not an indication for catheter ablation of AF at present.

Practical tip. AF ablation should not be considered as an alternative to oral anticoagulation. If a patient has a high thromboembolic risk profile (eg, CHADS₂ risk score of ≥2), then the patient should continue oral anticoagulation even after successful AF ablation. Studies of long-term monitoring have consistently shown asymptomatic episodes of AF both prior to and following ablation. Initiation of oral anticoagulation should also not be delayed when indicated in patients pending referral for AF ablation.

Catheter Ablation of Atrial Flutter

Typical right atrial flutter is a distinct arrhythmia from AF, although the 2 often coexist, occurring together in up to 40%-50% of patients with atrial flutter. Typical flutter is characterized by the classic “sawtooth” pattern on the electrocardiogram and often conducts 2:1 with a ventricular response of 150 beats per minute. Atrial flutter carries the same thromboembolic risk as AF and should be anticoagulated according to the same guidelines as AF. In contrast to AF, however, typical right atrial flutter involves a single reentrant circuit around the tricuspid annulus. By ablating a line along the isthmus that extends from the tricuspid annulus to the inferior vena cava, flutter can easily be eliminated in a single procedure with a success rate of >85%-90%. Given the simplicity of this procedure (in contrast to AF ablation) with its accompanying low risk and given that atrial flutter is very hard to control pharmacologically, flutter ablation is recommended as an alternative first-line therapy to drugs. This has been supported by a number of clinical trials comparing atrial flutter ablation to drug therapy. However, after elimination of AFL, over the next 5 years, approximately 60%-65% of patients will develop AF as a stand-alone problem.

RECOMMENDATION

We recommend curative catheter ablation for symptomatic patients with typical atrial flutter as first line therapy or as a reasonable alternative to pharmacologic rhythm or rate control therapy (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation recognizes the high efficacy, low complication rate of catheter ablation and low efficacy of pharmacologic therapy, whether rate or rhythm control.

Practical tip. Typical atrial flutter is more challenging to control medically with antiarrhythmic drugs than is AF and adequate rate control is more difficult to achieve. Given the high success rate and low complication rate of atrial flutter ablation, it is a strongly recommended as a first-line therapy in comparison to AF ablation.

Ablation of Accessory Pathways and Other Arrhythmias in AF

The presence of an accessory pathway (eg, Wolff-Parkinson-White syndrome) with evidence of preexcitation (delta wave) during AF presents a rare but potentially life-threatening situation. If the pathway has a short refractory period, it may allow AF to conduct to the ventricles with a very high ventricular rate response. High ventricular rates can occasionally lead to degeneration into ventricular tachycardia or fibrillation, resulting in a cardiac arrest. Administration of an AV nodal blocking agent during preexcited AF can exacerbate this problem and should be avoided. In these cases, especially if the patient has a history of syncope or rapid AF, catheter ablation of the accessory pathway is strongly recommended to avoid any possibility of cardiac arrest.
RECOMMENDATION

In patients with evidence of ventricular preexcitation during AF, we recommend catheter ablation of the accessory pathway, especially if AF is associated with rapid ventricular rates, syncope, or a pathway with a short refractory period (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the prevention of sudden cardiac death in patients at high risk and a low value on the small complication rate of catheter ablation of the accessory pathway.

RECOMMENDATION

In young patients with lone, paroxysmal AF, we suggest an electrophysiological study to exclude a reentrant tachycardia as a cause of AF; if present, we suggest curative ablation of the tachycardia (Conditional Recommendation, Very Low-Quality Evidence).

Values and preferences. This recommendation recognizes that supraventricular tachycardia can initiate AF when the substrate for AF is present and can be ablated with a high success rate and minimal risk.

In younger patients, other reentrant supraventricular tachycardias, such as AV nodal reentry or AV reentrant tachycardia using an accessory pathway, can degenerate into AF. Elimination of the reentrant tachycardia can therefore prevent episodes of AF. Thus, clear onset of AF resulting from another supraventricular tachycardia is an indication for seeking and eliminating the underlying tachycardia by ablation, if possible. If no such onset is clearly demonstrable, in younger patients it may be warranted to perform a general electrophysiological study prior to AF ablation, to look for and eliminate other underlying tachyarrhythmias, and assess the outcome prior to performing AF ablation.

References


Surgery for atrial fibrillation (AF) has been demonstrated as an effective treatment to restore and maintain sinus rhythm in patients for whom a rhythm control strategy is desired. It is usually offered to patients undergoing other types of cardiac surgery (eg, mitral valve repair or replacement, coronary artery bypass grafting, aortic valve surgery, intracardiac defects, ascending aortic surgery). It is also feasible as a stand-alone procedure, bearing a high success rate. In the past few years, less-invasive procedures have been described. AF is a triggered arrhythmia, resulting from ectopic activity most commonly located in and around the pulmonary veins of the left atrium. Therefore, electrical isolation of the pulmonary veins from the rest of the left atrium in order to prevent AF from being triggered is the rationale common to all surgical techniques. Further substrate modification may be required in patients with more persistent AF. This is done by adding ablation of the posterior left atrium with connecting lines of block between pulmonary veins, to the mitral valve annulus, as well as in specific sites in the right atrium. The left atrial appendage is resected or occluded at the same time. Despite patients high rate of freedom from AF after surgery (70%–85% at 1 year), surgical ablation of AF has never been clearly shown to alter long-term mortality. The available literature supports the recommendation to stop oral anticoagulation therapy 6 months after surgery when sinus rhythm can be documented, because a very low rate of thromboembolic events is reported. However, it appears essential to evaluate the surgical approaches to atrial fibrillation (AF) in view of the following clinical objectives: (1) to avoid symptoms associated with rapid and irregular heart beat; (2) to avoid blood stasis in the atrium and the attendant risk of thromboembolic events; and (3) to preserve atrial function, which ensures optimal cardiac performance. There is a need to balance the priority given to each of these objectives in relation to the clinical condition associated with the arrhythmia, as one objective may evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case. This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.
there is no evidence-based data to support the safety of omitting long-term oral anticoagulation. Thus, surgery should be used primarily as a concomitant procedure during cardiac surgery for other diseased states or as a stand-alone procedure after failure of prior attempts of catheter ablation and antiarrhythmic drugs.

dominate, depending on the clinical presentation of AF and the associated cardiac pathology. For instance, symptoms may be the main target in the case of occasional paroxysmal “lone” AF, prevention of thromboembolism may be the major motivation to terminate permanent or persistent AF, and improvement of cardiac performance may be the main objective in treating AF associated with congestive heart failure or valvular disease.

The maze procedure, designed and first reported by Cox et al., was based on the assumption that many electrophysiological mechanisms coexist in the atrium, thus necessitating a standardized procedure that would address each of them. These assumptions were as follows:

1. According to the conceptual notion of Garrey,2 fractionation of the atrial tissue into smaller segments would not allow multiple reentrant wavelets to be maintained.
2. To preserve atrial contraction, mandatory for the transport function and for eliminating the risk of thromboembolic events, all these segments should be linked to each other. Impulse propagation into dead-end pathways would not allow reentry to occur but would allow depolarization of sufficient atrial myocardium to ensure contraction.
3. The numerous atrial incisions required to address the first 2 assumptions would interrupt any possible macroreentrant pathway.

This procedure has been applied clinically since 1987 and has proven extremely effective.3-12 However, despite this success, the maze procedure was perceived as difficult and associated with significant morbidity,13 leading several authors to develop novel strategies aimed at simplifying the procedure without compromising the results. Less-invasive approaches have been designed to avoid sternotomy by accessing the left atrium through minimal incisions and to avoid cardiopulmonary bypass by accessing atrial tissue from the epicardium.14-26 Furthermore, new information regarding the role of the pulmonary vein–left atrial junction, drivers and rotors occurring in the posterior left atrium, and the role of the intrinsic cardiac nervous system has been incorporated into the evolving surgical rationale.27,28 In addition, it has been recognized that the underlying cardiac disorders might alter treatment outcomes. A number of factors, therefore, need to be considered when reengineering the surgical algorithm for AF management.29,30

Elimination of AF

A number of studies have shown that preoperative AF in patients undergoing cardiac surgical interventions is an independent factor for late major adverse cardiac events and poorer survival.31-36 The literature also indicates that once AF appears in patients with mitral valve disease, it is uncommon for mitral valve surgery alone to restore sinus rhythm.31,34,36,37 In this context, the duration of AF is a critical factor in predicting the return of sinus rhythm. When AF has been present for 3 months or less, sinus rhythm may resume in up to 80% of patients, but when the duration of preoperative AF exceeds 6 months, 70% to 80% of patients remain in AF if they do not undergo a specific AF procedure.31,37 Therefore, ablation has been recommended concomitant with a mitral valve procedure in any patient who has had AF for more than 6 months.38 Meta-analyses including prospective randomized trials have documented a high success rate of AF surgery (typically the Cox Maze procedure or several of its later modifications) in terms of restoration of sinus rhythm.38-54 In the Mayo Clinic experience, there was a significant difference in freedom from AF 2 years after a concomitant maze operation (74% ± 8%) compared with 27% ± 7% for a control group with mitral valve surgery alone.55 One of the largest series of patients undergoing the maze surgery associated with other primary cardiac operations was published by Beukema et al in 2008.54 They performed surgery concomitant with a radiofrequency-modified maze procedure in 258 patients (updated to 700 in 2010)56 with permanent AF. Sustained sinus rhythm, including an atrial rhythm or an atrial-based paced rhythm, was present in 69% of their patients at 1 year, in 56% at 3 years, and in 52% at 5 years.54,56 In a recent study by Kim et al including 540 patients undergoing mitral valve repair or replacement, the maze procedure was also performed in 36% of this group.57 After 5 years, the incidence of sinus rhythm was 86% in the patients who had undergone the maze procedure but only 24% in patients who did not undergo the procedure. Therefore, there is moderately high-quality evidence to demonstrate the 1-year efficacy of concomitant AF surgery to eliminate AF in patients undergoing cardiac surgical interventions.

Outcome Benefit: Cardiac Events and Survival

Whether AF surgery affords improved clinical outcome to patients with preoperative AF remains controversial.13,32,54-58 Although it is generally accepted that preoperative AF is predictive of cardiac mortality and morbidity, it is unclear whether direct surgical correction of AF restores the survival curves of AF patients to the same level as those of patients without preoperative AF. Short-term and intermediate-term rates of sinus rhythm after classical maze or its variant procedures differ widely: between 44% and 95%,1-13,60 However, none of the 6 randomized trials comparing outcomes in patients undergoing surgery with and without concomitant maze procedures has shown a clear benefit on mortality or stroke.56 Nevertheless, many observational reports suggest that concomitant AF correction has the potential to improve long-term survival. In the study by Kim et al, a multivariate analysis indicated that the absence of a maze procedure in the presence of AF during mitral valve replacement or repair was an independent predictor of cardiac death and major adverse events.57 Overall, the maze procedure was associated with better event-free survival. Bando et al also reported better survival in mitral valve patients who
underwent the maze procedure in the presence of preoperative AF, compared with patients who underwent mitral valve surgery alone. On the other hand, there was no significant difference in survival data in the Mayo Clinic experience, whereas Bando et al have, in a retrospective study, reported that patients with the adjunct of a maze procedure showed a similar high degree of freedom from cardiovascular-related death (96.9%) and stroke (98.2%), compared with a group of patients without preoperative AF. Although these reports constitute low-quality evidence because of their retrospective design, they suggest that the maze procedure may improve survival when combined with mitral valve repair. In addition, other reports have failed to demonstrate a difference in mortality and morbidity early after surgery, whether the maze procedure is carried out concomitantly with mitral valve surgery or not.41,54,58-61

**RECOMMENDATION**

We recommend that a surgical AF ablation procedure be undertaken in association with mitral valve surgery in patients with AF when there is a strong desire to maintain sinus rhythm, the likelihood of success of the procedure is deemed to be high, and the additional risk is low (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation recognizes that individual institutional experience and patient considerations best determine for whom the surgical procedure is performed.

**RECOMMENDATION**

We recommend that patients with asymptomatic lone AF, in whom AF is not expected to affect cardiac outcome, should not be considered for surgical therapy for AF (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation recognizes that patients with lone AF are at low risk for stroke or other adverse cardiovascular outcomes. Thus, elimination of AF in the absence of a high number of symptoms is unlikely to result in an improvement in quality of life.

**RECOMMENDATION**

In patients with AF who are undergoing aortic valve surgery or coronary artery bypass surgery, we suggest that a surgical AF ablation procedure be undertaken when there is a strong desire to maintain sinus rhythm, the success of the procedure is deemed to be high, and the additional risk is low (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation recognizes that left atrial endocardial access is not routinely required for aortic or coronary surgery. This limits ablation to newer epicardial approaches.

**Stroke**

The risk for late stroke after a maze procedure remains remarkably low throughout the surgical literature.4-7,9,13,36,46,52,54-63 Recent data suggest that restoration of sinus rhythm not only improves survival in this group but also reduces the risks for stroke, other thromboembolism, and anticoagulant-related hemorrhage.58,59,62,63 Furthermore, one study reported that the absence of a maze procedure was the only risk factor for late stroke in patients undergoing mechanical mitral valve replacement.62 This high freedom from late stroke likely is attributable to excision or obliteration of the left atrial appendage—an integral component of the maze procedure—in addition to restoration of sinus rhythm in the majority of patients.

**RECOMMENDATION**

We recommend that closure (excision or obliteration) of the left atrial appendage be undertaken as part of the surgical ablation of AF associated with mitral valve surgery (Strong Recommendation, Low-Quality Evidence).

We suggest that closure of the left atrial appendage be undertaken as part of the surgical ablation of persistent AF in patients undergoing aortic valve surgery or coronary artery bypass surgery if this does not increase the risk of the surgery (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. These recommendations place a high value on stroke reduction and a lower value on any concomitant loss of atrial transport with left atrial appendage closure.

**Lesion Set**

The original cut-and-sew Cox Maze III procedure has been modified in 2 main ways: (1) the use of ablative energy sources deployed with new devices and (2) the elimination of some lines of block. The latter changes consisted of limiting the lesions to electrically isolating the pulmonary veins (PVs) from the rest of the left atrium (Fig. 1), avoiding connecting lines to the base of the left atrial appendage and to the mitral isthmus, and also avoiding ablation in the right atrium. According to the Heart Rhythm Society recommendation document, the term maze should apply only to the lesion sets mimicking that of the Cox Maze III procedure.50 Modifications allowed to this terminology include the replacement of most of the Cox Maze III incisions with bipolar radiofrequency (Fig. 2, often referred to as the “Cox Maze IV procedure”)15,41,44,45,47-50,54,64 or with cryothermic devices.66 Less extensive lesion patterns should not be referred to as a maze. Although new technologies such as bipolar radiofrequency may reliably produce transmural lines of block and can be applied minimally invasively for PVs, they do not allow secure performance of connecting lines in the left atrial isthmus or inside the right atrium.13,25,26 Thus, they cannot allow the complete performance of the original lesion pattern of the Cox Maze III procedure necessary for optimal results in cases of persistent or permanent AF. On the other hand, recent studies have begun to explore the role of isolation of the PVs for paroxysmal AF.14-26 These studies usually report small sample sizes and limited follow-up. In a series of minimally invasive bilateral PVs, Edgerton et al reported that at 6-month follow-up, 86% of patients with paroxysmal AF were in normal sinus rhythm as evaluated by Holter monitor, pacemaker interrogation, or event monitor.15 Unfortunately, the
results of their PV approach have been disappointing in patients with persistent or longstanding AF because freedom from AF off drugs was achieved in only 32% at 6 months.15 Thus, we propose the following algorithm of surgical ablation, which is based on the type of AF and the nature of underlying cardiac abnormalities (Table 1): The recommended lesion set ranges from PVs alone (as shown in Fig. 1) to a bi-atrial complete Cox Maze lesion pattern (as shown in Fig. 2). In between these extremes, PVs in pairs or with a box lesion may be associated with connecting lines to the left atrial appendage and the mitral valve annulus (PVI+ in Table 1, also termed left atrial procedure and Fig. 2, A). The full Cox Maze lesion set (CM in Table 1) should include the left atrial procedure (Fig. 2, A) plus right atrial lines along the sulcus terminalis and a line from the right atrial free wall to the annulus of the tricuspid valve (Fig. 2, B), plus right atrial isthmus ablation (Fig. 2, C). All procedures must include exclusion or resection of the left atrial appendage. Based on our review of the recent literature, we would recommend the full modified Cox Maze III pattern (as shown in Fig. 2, A to Fig. 2, C)64 for patients with persistent or long-standing AF. Alternatively, the left atrial procedure (termed “PVI+” in Table 1 and also shown in Fig. 2, A) may be used in these patients on the surgeon’s judgement to shorten the operative time. The PVI procedure (as shown in Fig. 1) should be confined to patients with lone paroxysmal AF and paroxysmal AF with nonmitral valve disease.

**Postoperative Care and Anticoagulation After AF Surgery**

Ad et al developed a strict follow-up program designed to adhere to the Heart Rhythm Society guidelines.30,65 In brief, it consisted of a detailed AF registry that included a statistical platform that interacted with an institutional database. The AF registry tracked all patients’ preoperative, operative, and postoperative characteristics, as well as patients’ health-related quality of life. Clinical information and algorithm-driven protocols served as a basis for recommendations to the referring physicians. The clinical information collected included (1) patients’ self-reported rhythm, (2) current medications, (3) any readmissions and cardiac intervention that had taken place during the interim, and (4) the date of the last visit to the cardiologist. Diagnostic (electrocardiography, Holter monitoring, 1-week monitoring, or pacemaker interrogation) rhythm information and echocardiography were obtained. Then the appropriateness of antiarrhythmic drugs and anticoagulation was decided on, depending on the clinical algorithm.66 Incidentally, the authors recommended discontinuation of warfarin therapy whenever long-term monitoring confirmed rhythm status and atrial contraction assured the absence of intra-atrial stasis for a long period of time after surgery. However, Beukema and Sfe recommend a more conservative approach with respect to anticoagulation.67,68 Since reliable monitoring was not always available and a low flow state could not be ruled out in several patients, most of their patients were still on anticoagulant therapy at long-term follow-up, including patients with bioprosthetic mitral valve replacement. It should also be emphasized that the rate of recurrence of AF is not stable over time and that the moment of AF reappearance is uncertain.54 Therefore, in the absence of strict continuous monitoring capabilities and the lack of a clinical program with algorithm-driven treatment protocols, it is probably best to maintain anticoagulation therapy despite its inherent inconveniences. This conservative approach constitutes the rationale for our recommendation on postoperative anticoagulation therapy. There are new and less troublesome options than warfarin for thromboembolism prophylaxis soon to be available for many of these patients.66

**RECOMMENDATION**

We recommend that oral anticoagulant therapy be continued following surgical AF ablation in patients with a CHADS2 score ≥2 (Strong Recommendation, Moderate-Quality Evidence).

We suggest that oral anticoagulant therapy be continued following surgical AF ablation in patients who have undergone mechanical or bioprosthetic mitral valve replacement (Conditional Recommendation, Low-Quality Evidence).

**Values and preferences.** These recommendations place a high value on minimizing the risk of stroke and a lower value in the utility of long-term monitoring to document the absence of AF.

**Conclusion**

The Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation suggests the following
indications for surgical treatment of AF: (1) symptomatic patients with AF undergoing other cardiac surgical procedures; (2) selected asymptomatic patients with AF undergoing cardiac surgery in whom the ablation can be performed with minimal risk; and (3) symptomatic patients with AF who prefer a surgical approach, have experienced 1 or more failed attempts at catheter ablation, or are not candidates for catheter ablation.30 We modified these recommendations to take into account the recent data on the results of the various surgical options to treat AF. It should also be recognized that all treatment options are not available in all centres dealing with challenging cardiac disorders. There may be significant differences in the experience and skills of the teams in various institutions. The quality of evidence varies significantly with regard to the multiple aspects of surgical care in the field of AF. We therefore developed the recommendations with respect to AF surgery, along with a type-specific surgical algorithm shown in Table 1, to help surgeons select the most appropriate procedure based on the patient’s underlying cardiac status and pattern of AF.

### References


ABSTRACT
The stroke rate in atrial fibrillation is 4.5% per year, with death or permanent disability in over half. The risk of stroke varies from under 1% to over 20% per year, related to the risk factors of congestive heart failure, hypertension, age, diabetes, and prior stroke or transient ischemic attack (TIA). Major bleeding with vitamin K antagonists varies from about 1% to over 12% per year and is related to a number of risk factors. The CHADS2 index and the HAS-BLED score are useful schemata for the prediction of stroke and bleeding risks.

Vitamin K antagonists reduce the risk of stroke by 64%, aspirin reduces it by 19%, and vitamin K antagonists reduce the risk of stroke by 39% when directly compared with aspirin. Dabigatran is superior to warfarin for stroke prevention and causes no increase in major bleeding. We recommend that all patients with atrial fibrillation or atrial flutter, whether paroxysmal, persistent, or permanent, should be stratified for the risk of stroke and for the risk of bleeding and that most should receive antithrombotic therapy. We make detailed recommendations as to the preferred agents in various types of patients and for RÉSUMÉ
L’incidence annuelle de l’accident vasculaire cérébral (AVC) attribuable à la fibrillation auriculaire (FA) est de 4,5 %, causant la mort ou l’invalidité permanente dans plus de la moitié des cas. Cette incidence varie de moins de 1 % à plus de 20 % par année en fonction des facteurs de risque: insuffisance cardiaque, hypertension, âge, diabète et antécédents d’AVC ou d’ischémie cérébrale transitoire. Le risque d’hémorragie majeure sous traitement avec les antagonistes de la vitamine K varie entre 1 % et 12 % par année et s’avère lié à beaucoup d’autres facteurs. L’index de CHADS2 et le score HAS-BLED sont utiles pour la prédiction du risque d’AVC ou d’hémorragie. Le risque d’AVC est réduit de 64 % avec le traitement aux antagonistes de la vitamine K et de 19 % avec l’aspirine. Comparativement à l’aspirine, les antagonistes de la vitamine K réduisent ce risque de 39 %. Le Dabigatran est supérieur à la warfarine pour la prévention du risque d’AVC sans augmentation du risque de saignement majeur. Nous recommandons que le risque d’AVC et de saignement majeur soit déterminé chez tous les patients avec FA ou flutter auriculaire (paroxystique, persistant ou permanent) et que la plupart reçoivent un traitement antithrom-
the management of antithrombotic therapies in the common clinical settings of cardioversion, concomitant coronary artery disease, surgical or diagnostic procedures with a risk of major bleeding, and the occurrence of stroke or major bleeding. Alternatives to antithrombotic therapies are briefly discussed.

Risk of Stroke

Risk factors and risk estimation schemes

In the 5 landmark randomized clinical trials of oral anticoagulants (OACs) among patients with nonvalvular atrial fibrillation (AF),1-6 most of whom had no previous stroke or TIA, control subjects had a mean 4.5% annual incidence of stroke (range, 3%-7%), over half of which resulted in death or permanent disability.7 The mean annual incidence of the composite of stroke or other systemic embolism was 5% (range, 3%-7.4%). These subjects had no contraindications to warfarin and no echocardiographic evidence of rheumatic valvular disease. The observed rates of stroke and other systemic embolism were similar to those reported in earlier cohorts7 and likely are representative of individuals in the general population with AF and not receiving antithrombotic therapy. In the United States, the annual risk of stroke attributable to AF is 1.5% in the age group 50 to 59 years, rises to 23.5% in the age group 80 to 89 years, and overall is 15%.9

An overview of the randomized control trials of warfarin therapy in AF10 determined that previous stroke or TIA, increasing age, history of hypertension, and diabetes were statistically significant multivariate predictors of stroke. Annual stroke risk ranged from 0 (patients younger than 60 years) to 1.3% (patients younger than 80 years with no other risk factors) and to 11.7% (patients with prior stroke or TIA). A recent systematic review10 examined the evidence identifying independent risk factors for stroke as reported in 7 studies selected according to rigorously defined criteria. The absolute annual risk of stroke varied 20 fold among patients grouped by various risk factors. Independent risk factors for stroke were the same as those previously identified: stroke or TIA (relative risk [RR] 2.5), age (RR 1.5/decade), history of hypertension (RR 2.0), and diabetes mellitus (RR 1.7). Female sex was an independent risk factor in 3 of 6 cohorts, but coronary artery disease and clinical congestive heart failure were not found to be independent risk factors in any of these studies. Even though congestive heart failure and reduced ejection fraction have been identified only as univariable risk factors,7,10-12 they are included in current risk classification schemes.13-14 The review10 emphasized a variety of shortcomings of the studies, including inconsistencies in definitions of some of the risk factors, the use of antiplatelet therapies, and the stroke outcomes (ischemic strokes only, all strokes, strokes plus other systemic emboli, and strokes plus TIs).

The CHADS2 index14 (see Table 1 for the components of the acronym) assigns 1 point each for congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and 2 points for a history of stroke or TIA (Table 1). The scheme was validated and compared with 2 other schemes among 1733 Medicare beneficiaries aged 65 to 95 years who had been discharged from hospital with nonrheumatic AF and had not been prescribed warfarin. The CHADS2 index was the most accurate predictor of stroke, with the annual stroke rate increasing by about 2.0% for each 1-point increase in CHADS2 score (from 1.9% with a score of 0 to 18.2% with a score of 6). This scheme was also evaluated in comparison with several others among 2580 patients receiving aspirin in 6 prospective trials.15 The CHADS2 index identified increments in stroke risk similar to those identified in the prior validation and was better than the other schema at discriminating medium- and high-risk patients. Although a recent systematic review16 of 12 risk stratification schemes noted that none has been compared in a single cohort of adequate size and diversity, the CHADS2 index has appropriately become the favored choice for determining risk of stroke and guiding choice of antithrombotic therapy.17

The European Society of Cardiology (ESC) has recently updated its guidelines for the management of AF17 and has incorporated the new Birmingham 2009 schema (known by the acronym CHA2DS2-VASc) for the prediction of stroke risk.18 The schema was validated and compared with standard criteria in a subset of 1577 patients documented in the Euro Heart Survey on AF population. The schema is similar to the CHADS2, but gives 2 points for age of 75 years or older and 1 point for age between 65 and 74 years, 1 point for vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), and 1 point for female sex. The ESC recommends that the widely used and easily remembered CHADS2 be applied first; only if the score is under 2 should the new schema be applied to further grade risk of stroke in patients at low risk. The degree of risk can be refined, and if any of the additional risk factors embodied in the CHA2DS2-VASc are present, the score will be increased and may influence the physician to choose more potent antithrombotic management. Conversely, if the score remains at 0, the patient is clearly at very low risk of stroke and may not require any antithrombotic agent. The ESC recommends that a patient

| Table 1. The CHADS2 score for estimating stroke risk in patients with atrial fibrillation according to the presence of major risk factors |
|-----------------|-----------------|-----------------|
| CHADS2 risk criteria | Score |
| C               | Congestive heart failure | 1 |
| H               | Hypertension        | 1 |
| A               | Age >75 years       | 1 |
| D               | Diabetes mellitus   | 1 |
| S2              | (Prior) stroke or TIA| 2 |

<table>
<thead>
<tr>
<th>CHADS2 score (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

Data from Gage BF, et al.14
with a score of 0 according to the CHA₂DS₂-VASc schema should receive either aspirin or no antithrombotic therapy, with the latter preferred; a patient with a score of 1 should receive either aspirin or OAC, with the latter preferred; and a patient with a score of 2 should receive OAC. This new schema may eventually be useful for patient management, but for the present, the CCS recommends ongoing use of the CHADS₂ schema.

Paroxysmal AF

The Stroke Prevention in Atrial Fibrillation (SPAF) trial found similar annual rates of ischemic stroke in patients with “recurrent” (3.2%) and “chronic” (3.3%) AF. A report from the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-Warfarin (ACTIVE-W), based on 1202 patients with paroxysmal AF and 5495 with persistent or permanent AF, confirmed similar rates of thromboembolic events. However, it is possible that the risk of stroke is less in patients whose episodes of AF are brief (<1 day) and self-terminating. The short-term risk of stroke appears to be higher in patients with recent-onset AF than in those with AF that first occurred more than 1 to 2 years ago. Among AF patients with prior stroke, the annual recurrence rate is about 12% without antithrombotic treatment. Several case series reported recurrence rates of 0.1% to 1.3% per day during the first 2 weeks following a cardioembolic stroke.

Thyrotoxicosis and hypertrophic cardiomyopathy

The risk of stroke in patients with thyrotoxic AF is substantial, although the mechanism and the relative role of congestive heart failure are uncertain. The risk of stroke is also substantial among patients with hypertrophic cardiomyopathy and AF. These risks have not been rigorously evaluated, and antithrombotic therapies for patients with AF and thyrotoxicosis or hypertrophic cardiomyopathy should be based on the presence of validated stroke risk factors.

Atrial flutter

There is a widespread perception that the risk of stroke is less with atrial flutter than with AF. However, a retrospective analysis of a large database of elderly hospitalized patients found little difference in the risk ratios for atrial flutter (1.4) and AF (1.6). By 8 years of follow-up, more than half the patients with atrial flutter had developed AF, and these patients were more likely to experience a stroke. The development of AF was more likely among patients with congestive heart failure, rheumatic heart disease, hypertension, and diabetes mellitus.

Trials of Antithrombotic Therapies

Oral vitamin K antagonists and antiplatelet agents

An overview of the initial 5 randomized trials of oral vitamin K antagonists compared with no treatment found the incidence of ischemic stroke was reduced from 4.5% per year to 1.4% per year (relative risk reduction [RRR] 68%; 95% CI, 50%-79%; \( P < .001 \)). The rate of major hemorrhage with vitamin K antagonists was 1.3% per year vs 1% per year in controls. The most recent meta-analysis of such trials in-
pidogrel might be noninferior to warfarin for the prevention of stroke, while offering the advantages of less bleeding and greater convenience. However, the ACTIVE-W trial\textsuperscript{32} found the RR for the composite outcome of stroke, non–central nervous system embolus, myocardial infarction, and vascular death was 1.44 (95% CI, 1.18-1.76; \(P = .0003\)) for the combination of clopidogrel plus aspirin (75 mg and 75-100 mg/d) vs warfarin (INR 2-3). Somewhat surprisingly, the RR for major bleeding was 1.10 (95% CI, 0.83-1.45) with the combination.

It had also been expected that in patients not suitable for warfarin therapy, the combination of aspirin and clopidogrel might be more effective than aspirin alone. The ACTIVE-A trial\textsuperscript{33} did find that after a mean of 3.6 years, the risk of major vascular events was reduced by the combination (RR 0.89; 95% CI, 0.81-0.98; \(P = .01\)). However, major bleeding was increased by the combination (2.0% vs 1.3% per year; RR 1.57; 95% CI, 1.29-1.92; \(P < .01\)).

### New non–vitamin-K-antagonist anticoagulants

Ximelagatran is an oral direct thrombin inhibitor with predictable and stable pharmacokinetics and relatively low potential for interactions with other drugs and with foods. Coagulation monitoring and dose adjustments are not required. This agent was evaluated in 2 large trials employing noninferiority designs.\textsuperscript{34,35} In both, it was concluded that ximelagatran was noninferior to warfarin. The incidence of major bleeding was similar with the 2 agents, but all bleeding was significantly less with ximelagatran. However, both studies found a 6-fold excess of patients with elevations of alanine aminotransferase to greater than 3 times the upper limit of normal, usually within the first 6 months. The Food and Drug Administration did not approve the new agent, having concluded that the more convenient dose and monitoring regimens and less total bleeding did not outweigh concerns about hepatic toxicity and the inappropriately large noninferiority margins.

Dabigatran is an oral direct thrombin inhibitor that is licensed for use in Canada and the United States. It was compared with warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial,\textsuperscript{36} in which 18,113 patients with AF (mean CHADS\textsubscript{2} = 2.1) were randomized to dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or warfarin (INR 2-3) and followed for a median of 2.0 years. The mean time in the therapeutic range for warfarin was 64%. Rates of discontinuation of therapy by 2 years were 16.6% for warfarin, 20.7% for dabigatran 110 mg, and 21.2% for dabigatran 150 mg. Approximately 20% of subjects were taking aspirin in addition to their study drug. The rates of the principal outcome of all stroke (ischemic or hemorrhagic) or non–central nervous system embolus were 1.69% per year with warfarin, 1.53% per year with dabigatran 110 mg (RR 0.91; 95% CI, 0.74-1.11; \(P < .001\) for noninferiority), and 1.11% per year with dabigatran 150 mg (RR 0.66; 95% CI, 0.53-0.82; \(P < .001\) for superiority; Fig. 4). The RR of stroke or systemic embolus for dabigatran 150 mg vs 110 mg was 0.73 (95% CI, 0.58-0.91; \(P = .005\)). The rates of major bleeding were 3.36% per year with warfarin, 2.71% per year with dabigatran 110 mg (RR vs warfarin 0.8, \(P = .003\)), and 3.11% per year with dabigatran 150 mg (RR vs warfarin 0.93, \(P = .31\) and RR vs dabigatran 110 mg 1.16, \(P = .052\)). The rates of the net clinical benefit outcome (a composite of stroke, systemic em-
did those receiving warfarin. Although there was a trend to a reduction of the composite clinical outcome in the dabigatran groups, there was a trend to more frequent myocardial infarction with dabigatran, which was significant at the 150-mg dose. There was no hint of greater hepatic toxicity with dabigatran than with warfarin, but the total clinical experience extends to only a mean of 2 years, and careful long-term follow-up data are needed. Dabigatran tablets are much more costly than warfarin, but rigorous cost-effectiveness analyses will be needed to assess total costs.

We recommend that when an OAC is indicated for stroke prevention, most patients should receive dabigatran in preference to warfarin. Possible exceptions would include patients with a propensity to dyspepsia, gastrointestinal bleeding, or both and those at substantial risk of coronary events (see more detailed discussion under the heading Coronary Artery Disease). The dose of 150 mg twice a day is preferable to 110 mg twice a day, except in patients of low body weight, decreased renal function, or at increased risk of major bleeding.

Idraparinux is a specific inhibitor of activated factor X, which may be given in a fixed, weekly subcutaneous injection without coagulation monitoring. This agent was compared with vitamin K antagonists (INR 2-3) in the AMADEUS trial of 4576 patients. The trial was stopped early because of excess clinically relevant bleeding with idraparinux (19.7% vs 11.3% per year, P < .001), at which point idraparinux was noninferior for the principal outcome of all stroke or systemic embolism (hazard ratio 0.71; 95% CI, 0.39-1.30; P = .007). Elderly patients and those with renal insufficiency were more at risk of excess bleeding, but clearly at the dose regimen tested, idraparinux would not be a suitable alternative to vitamin K antagonist therapy in AF patients.

There are several available oral, direct-acting factor Xa inhibitor drugs that have proven effective and safe in studies of deep venous thrombosis and offer promise in the setting of AF. In the Apixaban Versus ASA to Reduce the Rate Of Embolic Stroke (AVERROES) trial, apixaban (5 mg twice a day) was compared with aspirin (81-324 mg daily) among patients with AF at more than very low risk of stroke in whom vitamin K antagonist therapy was unsuitable. The trial was terminated for early efficacy in 2010. In the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) trial, apixaban (5 mg twice a day) is being compared with warfarin (INR 2.5) among patients at somewhat higher risk of stroke. The expected enrollment is 15,000 patients, with completion in 2010. In the Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial, which enrolled over 14,000 patients, rivaroxaban (20 mg/d) was compared to warfarin (INR 2.5) among patients with AF at risk of stroke and suitable for warfarin therapy. Rivaroxaban was noninferior to warfarin for the principal outcome of all stroke or systemic embolus.

**Atrial flutter**

Although there are no rigorous prospective data on the incidence of stroke among patients with atrial flutter, nor are there randomized trials of the value of anticoagulation, it is generally recommended that patients with atrial flutter be risk stratified and treated in the same manner as patients with AF.9,13

---

**Figure 4.** Cumulative hazard rates (y-axis) vs time in years (x-axis) for the primary outcome of stroke (ischemic or hemorrhagic) or systemic embolism, according to treatment group (dabigatran 150 mg twice daily, dabigatran 110 mg twice daily, or warfarin [INR 2-3]). RR, relative risk. Reprinted from Connolly SJ et al\(^{36}\) with permission from N Engl J Med, © Massachusetts Medical Society.
EMBARGOED

EMBARGOED

EMBARGOED

tic range, 48% of thromboembolic events took place when INRs were above the therapeutic range. 44% of hemorrhages occurred when INRs were below it, and the mean proportion of events that occurred when the patient’s INR was outside the therapeutic range was higher in the studies of shorter follow-up. Patients with a previous TIA or minor stroke may benefit from a somewhat higher INR of 2.0 to 3.5, with a target of 3.0. Patients at higher risk of cerebral hemorrhage, particularly those older than 75 years, may benefit from a somewhat lower INR range of 1.6 to 2.5, with a target of 2.0. Although protection against ischemic stroke drops off sharply when INRs fall below this target.

The HEMORRHAGES scheme was developed from 3 previously published prediction rules, a recent systematic review, and a formal literature search. The scheme allotted 2 points for a previously documented episode of bleeding and 1 point each for hepatic or renal disease, ethanol abuse, malignancy, age >75 years, reduced platelet count or function, rebleeding risk, hypertension (uncontrolled), anemia, genetic factors (CYP 2C19 SNPs), excessive falls (including neuropsychiatric disease), and stroke. When compared with the 3 earlier prediction rules in a population of elderly patients with AF who were receiving warfarin, aspirin, or no antithrombotic therapy, the new scheme provided good discrimination among patients with an annual risk of hospitalization for hemorrhage while receiving warfarin, which ranged from 1.9% to 12.3%.

The new ESC guidelines for management of AF suggest the use of a new schema for the prediction of bleeding risk (Table 2). It is based on the presence of hypertension, abnormal liver or renal function, history of stroke or bleeding, labile INRs, elderly age (>65 years), and concomitant use of drugs that promote bleeding or excess alcohol use (HAS-BLED is the acronym) and was derived from the Euro Heart Survey on AF. The proposed schema relies on fewer and more readily obtained risk factors than earlier schemata do and performs at least as well as the HEMORRHAGES schema in the prediction of bleeding events. Documentation of a HAS-BLED score allows the clinician to assign the patient a risk of major bleeding ranging from about 1% (score 0-1) to 12.5% (score 5) and can be useful in decisions about the relative risks of stroke vs major bleeding with various antithrombotic therapies. Patients at high risk of major bleeding warrant caution in the use of antithrombotic therapies and closer monitoring and follow-up. We suggest the use of this new schema as a simpler alternative to the HEMORRHAGES schema.

### Risk of Hemorrhage

The efficacy of any antithrombotic therapy for the prevention of ischemic stroke must be balanced against the risk of major hemorrhage, particularly cerebral hemorrhage, which is often fatal. In each of the initial randomized trials of antithrombotic therapies, the principal outcome was the composite of ischemic stroke or systemic embolus. Although hemorrhage and the subsets of intracranial and intracerebral hemorrhage were generally reported, the net benefit for major clinical outcomes was not always clear. More recent trials and overviews have focused on the principal outcome of all stroke (ischemic plus hemorrhagic) or systemic embolus, a more meaningful outcome for patients and treating physicians. The incidence of extracranial major hemorrhage (usually without long-term sequelae among survivors) can be subjectively compared to the reduced incidence of all stroke in order to reach conclusions about the net patient benefits of antithrombotic therapies.

The risk of hemorrhage depends on the specific antithrombotic agent (including dose and monitoring) and on a variety of patient characteristics. The risks of hemorrhage are lowest with either aspirin (75-325 mg/d) or clopidogrel (75 mg/d) alone, higher when they are combined, higher still with dabigatran 110 mg twice a day, and highest with dabigatran 150 mg per day and vitamin K antagonists, which carry similar risks. When vitamin K antagonists are used, the bleeding risk depends on the INR, the quality of monitoring, the duration of therapy (the risk is higher during the initial few weeks of therapy), and the stability of dietary and other factors that may alter the INR at a given dose of the chosen agent. The risk of bleeding is likely to be higher in common clinical practice than in the rigorous setting of a clinical trial or a dedicated, expert anticoagulation service.

For most patients who are candidates for warfarin, an INR range of 2.0 to 3.0 with a target of 2.5 appears optimal. In a large cohort of patients, the risk of ischemic stroke, severity of stroke, and mortality rose sharply when INR fell to 1.5 to 1.9, but the risk of intracranial hemorrhage did not rise until INR values exceeded 3.9. A recent meta-analysis of studies that assigned hemorrhagic and thromboembolic events in patients taking anticoagulants to discrete INR ranges found that 44% of hemorrhages occurred when INRs were above the therapeutic range, 48% of thromboembolic events took place when INRs were below it, and the mean proportion of events that occurred when the patient’s INR was outside the therapeutic range was higher in the studies of shorter follow-up. Patients with a previous TIA or minor stroke may benefit from a somewhat higher INR of 2.0 to 3.5, with a target of 3.0.

### Table 2. The HAS-BLED score for estimating the risk of major bleeding among AF patients

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal or liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (eg, age &gt;65 yr)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Risk factor score Major bleeds (%/y)
0 1.13
1 1.02
2 1.88
3 3.74
4 8.70
5 12.50

Data from Pisters R, et al.

### RECOMMENDATION

We recommend that all patients with AF or AFL (paroxysmal, persistent, or permanent) should be stratified using a predictive index for stroke (eg, CHADS2v2) and for the risk of bleeding (eg, HAS-BLED) and that most patients should receive antithrombotic therapy (Strong Recommendation, High-Quality Evidence).

We recommend that patients at very low risk of stroke (CHADS2v2 = 0) should receive aspirin (75-325 mg/d) (Strong Recommendation, High-Quality Evidence).

We recommend that patients at low risk of stroke (CHADS2v2 = 1) should receive OAC therapy (either warfarin [INR 2 to 3] or Dabigatran) (Strong Recommendation,
Overview of Thromboembolic Management

Figure 5. A summary of our recommendations for thromboembolic management guided by the CHADS2 score. See Tables 1 and 2 for definitions of CHADS2 and HAS-BLED. OAC, oral anticoagulant.

Figure 5 is a flow chart outlining our recommendations for the choice of antithrombotic therapy.

Recent practice guidelines\(^9,13\) stress the importance of appropriate antithrombotic therapy for AF, and yet practice surveys indicate that rates of compliance range from rather low\(^47-51\) to reasonably high.\(^52\)

Selected Clinical Settings

Elderly patients

Advanced age (>75 years) has been consistently noted as a risk factor for both ischemic stroke and major hemorrhage, particularly intracranial. Hylek et al\(^53\) reported a series of 472 patients aged ≥65 years (153 patients aged ≥80 years), with electrocardiogram-verified AF, newly started on warfarin at the study institution, and managed by the on-site anticoagulation clinic. Anticoagulation control was very good, with 56% of person-time within the INR range of 2.0 to 3.0, 29% below 2.0, 11% within 3.0 to <4.0, and only 2% ≥4.0. Even within this optimized setting, the rate of major hemorrhage (100% follow-up) was 7.2 per 100 patient-years (intracranial hemorrhage 2.5 per 100 patient-years). The incidence of major hemorrhage was 13.1% for patients aged ≥80 years vs 4.75% for those <80 years. The risk during the first 90 days of therapy was 3 times that of the remainder of the year. The risk of major hemorrhage was increased 20 times among patients with an INR > 4.0. Most of the intracranial bleeds occurred in patients aged ≥75 years. The rate of major hemorrhage was higher in patients with higher CHADS2 scores. In contrast, the Birmingham Atrial Fibrillation Treatment of the Aged study\(^54\) found that in patients aged >75 years, warfarin was more efficacious than aspirin in preventing all strokes (ischemic plus hemorrhagic) and did not cause more major extracranial hemorrhage (1.4% per year with warfarin vs 1.6% per year with aspirin).

The lower bleeding risk may be attributable to more restrictive patient selection for a clinical trial than for the Hylek survey and to the fact that 40% of them had been taking warfarin safely prior to entering the trial. A more recent cohort study found an annual incidence of major extracranial bleeding of 1.3% with careful INR management.\(^55\) These observations point to the challenges in choosing the optimal antithrombotic therapy for very elderly patients in order to ensure a favourable risk-benefit ratio.\(^56\) For those with no stroke risk factors other than age ≥75 years, some guidelines have recommended consideration of aspirin in preference to warfarin.\(^13\) Nevertheless, ischemic stroke, with its dire consequences, is relatively frequent, and the competing risk of intracranial hemorrhage with warfarin may be acceptable. If warfarin is to be used, great care must be taken to rigorously maintain the selected therapeutic INR with frequent monitoring in the first 3 months and more often than the “standard” monthly interval subsequently.

Cardioversion

Although the randomized trials have shown no improvement in major outcomes, including thromboembolism, with a rhythm control strategy vs rate control, individual patients may gain symptomatic benefit and even long-term freedom from AF after electrical or pharmacologic cardioversion. The strongest predictor of initial and persistent success with cardioversion is short duration of the AF before cardioversion. In general, it may be expected that AF occurring in conjunction with surgery (see accompanying article titled “Prevention and Treatment of Atrial Fibrillation Following Cardiac Surgery\(^57\)”) viral illness, alcohol excess, or in association with thyrotoxicosis or pulmonary embolus has a high likelihood of reversion with persistence of sinus rhythm if there has been resolution of the precipitating cause. Successful and sustained reversion to sinus...
rhythm is associated with relatively young age and freedom from underlying heart disease. Some patients have intolerable symptoms and poor exercise tolerance during AF and may prefer attempted rhythm control to rate control. The rate of initial success in restoring sinus rhythm is high, but in the contemporary Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, vigorous efforts to establish and maintain sinus rhythm resulted in prevalences of only 82.5%, 73.3%, and 62.6% at 1, 3, and 5 years, respectively.58

Stroke risk with cardioversion

Cardioversion is appropriate for selected patients with AF or AFL,57,58 necessitating consideration of the possibility of associated thromboembolism. A well-designed prospective cohort study reported a reduction of postcardioversion systemic embolism of from 5.3% to 0.8% among anticoagulated patients.59 These observations have been supported by several published case series.13 Two more-recent studies reported remarkably similar incidences of cerebral embolization among patients receiving OAC in the setting of electrical cardioversion.60,61 It is generally believed that a newly formed thrombus will become organized and adherent to the left atrial wall within 2 weeks of formation. Transesophageal echocardiography (TEE) reveals that in the majority of patients, thrombus resolves, rather than simply becoming firmly adherent to the wall of the left atrium or left atrial appendage.62 Accordingly, it is generally recommended that documented systemic anticoagulation at therapeutic levels be instituted at least 3 weeks before cardioversion.9,13 An analysis that pooled data from 32 studies found that 98% of thromboembolic events occurred within 10 days of cardioversion of AF or flutter.63 However, evidence exists that even after successful electrical cardioversion, atrial contraction may not normalize for weeks when AF has been present for some time,64,65 and therefore maintenance of anticoagulation for at least 4 weeks after cardioversion seems prudent.9,13 If AF or AFL persists or recurs after attempted cardioversion, or if symptoms suggest that the presenting AF or AFL has been recurrent, antithrombotic therapy should be continued indefinitely with either aspirin or OAC as appropriate. If normal sinus rhythm is achieved and maintained for 4 weeks, the need for ongoing antithrombotic therapy depends on the risk of stroke.66,67 It is generally recommended that anticoagulant management should not differ.13 New-onset AF is generally not thought to warrant anticoagulation if cardioversion is undertaken within 48 hours of its onset, based on case series showing an incidence of thromboembolism <1%.9,13,68,69 Even when the duration of the current episode of AF is <48 hours, if the patient is at particularly high risk of stroke (eg, mechanical valve, rheumatic heart disease, recent stroke, or TIA), it would be appropriate to delay cardioversion to allow the patient to receive OAC for 3 weeks before the procedure and to continue indefinitely. Following attempted cardioversion, if AF persists or recurs or if symptoms suggest the presenting AF or AFL has been recurrent, antithrombotic therapy (OAC or aspirin) should be commenced and continued indefinitely. If normal sinus rhythm is achieved and sustained, the need for ongoing antithrombotic therapy depends on the risk of stroke. (See accompanying article titled “Management of Recent-Onset Atrial Fibrillation and Flutter in the Emergency Department.”)

Atrial flutter

Retrospective studies of patients with atrial flutter undergoing cardioversion suggest that the risk of thromboembolism may not be importantly different from that for patients with AF.68,69 Case series note a very low incidence of thromboembolism when patients with atrial flutter are adequately anticoagulated prior to cardioversion.69-71 It is generally recommended that patients with atrial flutter who are to be cardioverted receive an anticoagulant regimen identical to that for patients with AF.9,13,17

Emergency cardioversion

Emergency cardioversion may be required because of ischemia or hemodynamic compromise in some situations and should not be delayed, even if the AF has been present for more than 48 hours and the patient is not already anticoagulated. In such a situation, concomitant anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) may offer some benefit, but there are no published evaluations. (See accompanying article titled “Management of Recent-Onset Atrial Fibrillation and Flutter in the Emergency Department.”)

**RECOMMENDATION**

We recommend that hemodynamically stable patients with AF or AFL of ≥48 hours or uncertain duration for whom electrical or pharmacologic cardioversion is planned should receive therapeutic OAC therapy (warfarin [INR 2-3] or dabigatran) for 3 weeks before and at least 4 weeks post-cardioversion.

Following attempted cardioversion,

If AF or AFL persists or recurs or if symptoms suggest that the presenting AF or AFL has been recurrent, the patient should have antithrombotic therapy continued indefinitely (using either OAC or aspirin, as appropriate).

If sinus rhythm is achieved and sustained for 4 weeks, the need for ongoing antithrombotic therapy should be determined on the basis of the risk of stroke, and in selected cases expert consultation may be required (Strong Recommendation, Moderate-Quality Evidence).

We recommend that hemodynamically stable patients with AF or AFL of known duration 48 hours may undergo cardioversion without prior or subsequent anticoagulation. However, if the patient is at particularly high risk of stroke (eg, mechanical valve, rheumatic heart disease, recent stroke, or TIA), cardioversion should be delayed, and the patient should receive OAC for 3 weeks before and at least 4 weeks post-cardioversion.

Following attempted cardioversion,

If AF or AFL persists or recurs or if symptoms suggest that the presenting AF or AFL has been recurrent, antithrombotic therapy (OAC or aspirin, as appropriate) should be commenced and continued indefinitely.

If normal sinus rhythm is achieved and sustained for 4 weeks, the need for ongoing antithrombotic therapy should...
Figure 6. A summary of our recommended strategies for antithrombotic therapy in conjunction with cardioversion. CHADS2, please see Table 1; INR, international normalized ratio; NSR, normal sinus rhythm; OAC, oral anticoagulant; TEE, transesophageal echocardiography; TIA, transient ischemic attack.

Figure 6 is a flow chart outlining our recommendations for antithrombotic therapy in conjunction with cardioversion.

Transesophageal echocardiography guidance

The potential role of TEE to rule out the presence of atrial thrombi and the avoidance of anticoagulation was studied in several case series. An overview of these studies\(^5\) reported that patients with no atrial thrombus who then underwent electrical cardioversion had an unacceptably high incidence of embolization by comparison with anticoagulated patients in separate case series. It is generally accepted that the absence of thrombi on TEE does not eliminate the requirement for a period of 4 weeks of anticoagulation following cardioversion.

The Assessment of Cardioversion Utilizing Echocardiography (ACUTE) was a multicentre randomized prospective trial of 1222 patients with AF of more than 2 days’ duration.\(^6\) Patients were assigned to therapy guided by TEE findings or to conventional management. Patients assigned to TEE were anticoagulated at therapeutic levels (typically with UFH intravenously for 24 hours or warfarin [INR = 2-3] for 5 days) prior to attempted cardioversion. If TEE showed no thrombus, the patient underwent cardioversion and continued on anticoagulant therapy for 4 weeks. If thrombus was detected, warfarin was given for 3 weeks, TEE was repeated, and if the thrombus had resolved, cardioversion was performed and warfarin continued for 4 weeks. If thrombus was still detected after 3 weeks of anticoagulation, no cardioversion was attempted, but warfarin was continued for 4 weeks further. The patients randomized to no TEE received warfarin for 3 weeks precardioversion and a further 4 weeks post-cardioversion. There was no significant difference between the TEE and the no-TEE groups in the rate of embolic events or prevalence of sinus rhythm. The TEE group had fewer total hemorrhagic events, most of them...
minor. Right or left heart thrombi were identified in 13.8% of patients who underwent TEE. Of those patients with thrombi detected, 88.2% had a thrombus in the left atrial appendage. Among those patients with atrial thrombi detected, the value of repeat TEE after the initial 3 weeks of anticoagulation is uncertain. The investigators subsequently reported the results of a small randomized controlled trial which found no difference in safety outcomes between UFH and enoxaparin for the acute anticoagulation phase. In centres where TEE is readily available and the interpretations reliable, a TEE-guided management strategy may safely shorten the time to cardioversion by comparison with standard anticoagulant regimens. The cost-effectiveness of such an approach depends very much on local and national patterns of practice and cost structures.

### RECOMMENDATION

We suggest that hemodynamically stable patients with AF or AFL of ≥48 hours or of unknown duration may undergo cardioversion guided by TEE (following the protocol from the Assessment of Cardioversion Utilizing Echocardiography trial as detailed in the text) (Conditional Recommendation, High-Quality Evidence).

### Coronary Artery Disease

The clinician managing a patient with AF must often deal with concomitant coronary artery disease in the settings of primary prevention, stable coronary artery disease, an acute coronary syndrome (ACS), or percutaneous coronary intervention (PCI). There is good evidence for the use of aspirin for primary prevention, for aspirin or clopidogrel for stable coronary artery disease, for aspirin supplemented by clopidogrel for up to 1 year following an ACS (with or without PCI) and for PCI (both elective and post-ACS). Warfarin alone or in combination with aspirin is less effective than aspirin plus clopidogrel for patients post-PCI. There is considerable evidence from randomized controlled trials, that for primary prevention among patients at high risk of coronary events, low-intensity warfarin (INR 1.5) is as effective as aspirin for the prevention of coronary events, and for secondary prevention following myocardial infarction, warfarin alone (INR 2.8-4.8) or warfarin (INR 2-2.5) plus aspirin (75-100 mg) is at least as efficacious as aspirin alone in reducing subsequent coronary events.

There has been no rigorous comparison of warfarin vs the combination of aspirin and clopidogrel.

The benefits of antithrombotic therapies for the primary prevention of coronary events must be balanced against the risks of major bleeding attributable to both aspirin and vitamin K antagonists. Although viewpoints vary, once the annual risk of a coronary event exceeds 1% to 1.5%, antithrombotic therapy is likely to confer more benefit than harm. Among patients with known coronary artery disease, ACS, or recent PCI, the benefits of appropriate antithrombotic therapy strongly outweigh the harms. Both aspirin and warfarin are appropriate for the primary prevention of coronary events in those patients at higher risk and for secondary prevention in most patients with known coronary artery disease. Accordingly, when such patients also have AF or AFL, it seems reasonable to choose the most appropriate antithrombotic therapy for the prevention of stroke with the expectation that the chosen therapy will also be protective against coronary events. For primary prevention of coronary events and for stable coronary artery disease, when the risk of stroke is very low (CHADS2 = 0), aspirin would be appropriate because of its lower bleeding risk and greater ease of administration. When the risk of stroke is higher (CHADS2 ≥1), warfarin would be appropriate, instead of aspirin.

In the setting of elective PCI, aspirin plus clopidogrel are required for optimal prophylaxis against stent thrombosis. If the patient also has AF with a risk of stroke that is very low to low (CHADS2 ≤1), then aspirin plus clopidogrel would be appropriate for a minimum of 1 month for a bare metal stent, 3 months for a sirolimus drug-eluting stent, or 6 months for a paclitaxel drug-eluting stent; subsequently, CHADS2 = 0 patients might continue on aspirin alone, and CHADS2 ≥1 patient might stay on aspirin plus clopidogrel or be switched to warfarin. If the risk of stroke is higher (CHADS2 ≥2), OAC is required for adequate stroke prophylaxis. Hence, for optimal prophylaxis against both stroke and coronary events, a period of therapy with a combination of aspirin, clopidogrel, and OAC (“triple antithrombotic therapy”) may be required, even though the risk of bleeding is considerably increased by this combination. Whereas the optimal duration of dual antiplatelet therapy post-PCI for patients without AF is up to 12 months, the duration of triple therapy in patients with AF is uncertain and should be decided on the basis of balancing the likely risks of a stent-related event vs the risk of bleeding. Those patients at particularly high risk of bleeding should be considered for the use of a bare metal stent rather than a drug-eluting stent, with the triple therapy continued for only 1 month.

Following an episode of ACS, aspirin plus clopidogrel appear optimal for up to 1 year. If the patient also has AF with a risk of stroke that is very low to low (CHADS2 ≤1), then aspirin plus clopidogrel would be appropriate for up to 1 year; subsequently, CHADS2 = 0 patients might continue on aspirin alone, and CHADS2 ≥1 patients might stay on aspirin plus clopidogrel or be switched to warfarin. If the risk of stroke is higher (CHADS2 ≥2), warfarin is required for adequate stroke prophylaxis. Hence, for optimal prophylaxis against both stroke and coronary events, a period of therapy with combination aspirin, clopidogrel, and OAC (“triple antithrombotic therapy”) may be required, as for the patients with elective PCI. Whereas the optimal duration of dual antiplatelet therapy post-ACS for patients without AF is up to 12 months, the duration of triple therapy in patients with AF should be decided based on balancing the likely risks of a stent-related event vs the risk of bleeding. There are no randomized trials to guide the decisions, but it might be reasonable to prescribe 1 month of triple therapy, followed by up to 1 year of a combination of warfarin plus clopidogrel or warfarin plus aspirin, followed by warfarin alone as suggested in other guidelines.

The issues regarding antithrombotic therapies for patients with coronary artery disease plus AF have been extensively evaluated in recent evidence-based guidelines.

In the RE-LY trial, although the net clinical benefit outcome (a composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding) was in favour of dabigatran 150 mg (hazard ratio 0.91; 95% CI, 0.82-1.00; \(P = .04\)), there was a higher incidence of myocardial infarction with dabigatran (hazard
ratio 1.38; 95% CI, 1.00-1.91; \( P = .048 \)). There has not yet been a trial of dabigatran to evaluate the agent for the primary or secondary prevention of coronary events. Given the known benefits of warfarin for the reduction of coronary events, which can be substantial in those patients at higher risk, when OAC is indicated to prevent stroke in those who have AF and are also at high risk of a coronary event (eg, those without evidence of coronary artery disease whose Framingham risk is \( \geq 2\% \) per year, those with stable coronary artery disease with high risk features, and those with or ACS in recent months), it seems prudent to recommend warfarin in preference to dabigatran.

**RECOMMENDATION**

We suggest that patients with AF or AFL who have stable coronary artery disease should receive antithrombotic therapy selected on the basis of their risk of stroke (aspirin for CHADS\(_2\) = 0 and OAC for CHADS\(_2\) \( \geq 1\)). Warfarin is preferred over dabigatran for those at high risk of coronary events (Conditional Recommendation, Moderate-Quality Evidence).

We suggest that patients with AF or AFL who have experienced ACS or who have undergone PCI should receive

**Antithrombotic Management of AF/AFL in CAD**

![Diagram](image)

**Figure 7.** A summary of our recommendations for antithrombotic management in settings of coronary artery disease. ACS, acute coronary syndrome; CAD, coronary artery disease; CHADS\(_2\), see Table 1; OAC, oral anticoagulant; PCI, percutaneous coronary intervention.

**Patient With AF undergoing Surgical or Diagnostic Procedure With Major Bleeding Risk**

![Diagram](image)

**Figure 8.** A summary of our recommendations for management of antithrombotic therapies in patients undergoing surgical or diagnostic procedures with a risk of major bleeding. AF, atrial fibrillation; CHADS\(_2\), see Table 1; INR, international normalized ratio; LMWH, low molecular weight heparin; OAC, oral anticoagulant; TIA, transient ischemic attack; UFH, ultrafractionated heparin.
antithrombotic therapy selected on the basis of a balanced assessment of their risks of stroke, of recurrent coronary artery events, and of hemorrhage associated with the use of combinations of antithrombotic therapies, which in patients at higher risk of stroke may include aspirin plus clopidogrel plus OAC (Conditional Recommendation, Low-Quality Evidence).

Figure 7 is a flow chart outlining our recommendations for the management of antithrombotic therapy in the setting of coronary artery disease.

Invasive Procedures

When a patient receiving an OAC or antiplatelet agent is to undergo a surgical or diagnostic procedure that has a risk of major bleeding, the risk of a thromboembolic event occurring while the antithrombotic agent is reduced or stopped must be weighed against the goal of a reduced risk of major bleeding.34,95 We suggest that such patients be stratified as to their risk of stroke, which can range from <1% to >20% per year. If there is a very low to moderate risk of stroke (CHADS2 ≤ 2), the antithrombotic agent should be discontinued before the procedure (aspirin or clopidogrel for 7-10 days, warfarin for 5 days if the INR was in the range of 2-3, and dabigatran for 2 days). Once postprocedure hemostasis is established (about 24 hours), the antithrombotic therapy should be reinstated. If the risk of bleeding from the procedure is low, the clinician might choose to continue the antithrombotic agent uninterrupted.

On the other hand, if there is a particularly high risk of stroke (eg, prosthetic valve, recent stroke or TIA, rheumatic valve disease, CHADS2 ≥ 3) or of other thromboembolism (eg, Fontan procedure), some form of antithrombotic therapy should be continued until as close to the time of the procedure as is judged to be safe in terms of the risk and consequences of procedural bleeding, and it should be reinstated as soon as hemostasis is established post-procedure. Consideration should be given to the risk of major bleeding from the procedure in determining the antithrombotic regimen. It is likely that most potentially hemorrhagic dental procedures, if undertaken with appropriate surgical skill and the use of hemostatic mouthwash, can be done without discontinuing warfarin, provided the preoperative INR is under 3.0.96 Cataract extraction and minor dermatologic procedures may also be done without interrupting warfarin.95 A randomized controlled trial is currently underway by a group of Canadian investigators who are comparing the strategies of uninterrupted warfarin vs bridging UFH or LMWH in the management of patients having a cardiac rhythm device implanted.97

**RECOMMENDATION**

We suggest that patients with AF or AFL who are receiving aspirin, clopidogrel, or OAC and are scheduled for a surgical or diagnostic procedure carrying a risk of major bleeding be stratified by their risk of stroke:

If there is a very low to moderate risk of stroke (CHADS2 ≤ 2), patients should have their antithrombotic agent discontinued before the procedure (aspirin or clopidogrel for 7-10 days, warfarin for 5 days if the INR was in the range of 2-3, and dabigatran for 2 days). Once postprocedure hemostasis is established (about 24 hours), the antithrombotic therapy should be reinstated (Conditional Recommendation, Low-Quality Evidence).

If there is a particularly high risk of stroke (eg, mechanical valve, recent stroke or TIA, rheumatic valve disease, CHADS2 ≥ 3) or of other thromboembolism (eg, Fontan procedure), further consideration should be given to the risk of major bleeding from the procedure:

If there is an acceptable perioperative bleeding risk (ie, risk of stroke outweighs risk of bleeding), patients should have OAC therapy continued perioperatively or have their OAC discontinued before the procedure and be bridged with LMWH or UFH peroperatively (Conditional Recommendation, Low-Quality Evidence).

If there is a substantial risk of major and potentially problematic bleeding (ie, risk of bleeding and risk of stroke are both substantial), patients should have their OAC discontinued before the procedure, with LMWH or UFH bridging until 12 to 24 hours preprocedure. Once postprocedure hemostasis is established (about 24 hours), the OAC should be reinstated with LMWH or UFH bridging (Conditional Recommendation, Low-Quality Evidence).

Figure 8 is a flow chart outlining our recommendations for the management of antithrombotic therapy in patients undergoing invasive procedures.

**Stroke Management in Patients With AF**

Among AF patients experiencing a stroke, the high rate of recurrence suggested that there was some urgency in initiating anticoagulation after the occurrence of embolic stroke. The International Stroke Trial Collaborative Group randomized 18,451 patients with ischemic stroke within 24 hours of onset to subcutaneous unfractionated heparin (5000 IU twice a day or 12,500 IU twice a day), aspirin 300 mg per day, both, or neither and maintained for 14 days or until prior hospital discharge.24 CT scan was performed to exclude intracranial hemorrhage when possible and was mandatory in comatose patients. Among the 3169 patients with AF, both doses of heparin were significantly more effective for the prevention of recurrent stroke of ischemic or unknown type but resulted in significantly more symptomatic intracranial hemorrhage. There was no significant difference among the regimens in the rate of the composite outcome of recurrent stroke or symptomatic intracranial hemorrhage or in the rate of all-cause mortality. Patients with AF had a higher mortality than did patients without AF (16.9% vs 7.5%), probably because of greater mean age and larger cerebral infarcts. The rate of recurrence, within 14 days, of stroke of ischemic or unknown type was 3.9% among patients with AF, considerably lower than that reported in earlier studies but still higher than in patients with-
out AF in this study. The results indicate that heparin is not indicated in the acute management of embolic stroke among patients with AF. Published guidelines for the management of stroke in a patient with AF are based on extrapolations from clinical trials and include recommendations for the use of intravenous rtPA for selected patients within 3 hours of onset. Patients who receive rtPA should not receive any antiplatelet or anticoagulant therapy for at least 24 hours subsequently. If there is no evidence of hemorrhage on urgent CT scan, and yet the patient is not to receive fibrinolytic therapy, the patient should begin aspirin 325 mg per day immediately thereafter, with conversion to OAC after 14 days, or sooner if the infarct size is small and the patient is normotensive. If the clinical and computed tomography picture are consistent with a TIA, then immediate heparin therapy may be acceptable. If stroke occurs in a patient with AF or AFL who is already receiving anticoagulation, the drug should be stopped and intracranial hemorrhage should be excluded. If intracranial hemorrhage is present, the anticoagulation should be reversed, and subsequent decisions to resume anticoagulation should be made after reassessment of the risks of embolism and the risks of recurrent intracranial hemorrhage. For those without intracranial hemorrhage, it would be reasonable to start aspirin 325 mg per day when the INR falls below 1.5 and to restart the anticoagulant at day 14, or sooner if the infarct is small and the patient is normotensive. If warfarin is chosen as the anticoagulant, meticulous attention should be given to maintenance of the INR in the range of 2 to 3. A double-blind randomized trial of LMWH vs aspirin (160 mg/d) among patients with acute ischemic stroke and AF showed a trend to more recurrent ischemic stroke in the LMWH group (odds ratio 1.13; 95% CI, 0.57-2.24), supporting the strategy of early administration of aspirin to such patients in preference to heparin.

**Hemorrhage on OAC Therapy**

The major determinants of OAC-induced bleeding are the INR, patient characteristics, and the concomitant use of drugs that interfere with hemostasis. The acute management of hemorrhage in a patient receiving OAC requires a graded response according to published guidelines, beginning with the immediate measurement of the INR, stopping the OAC, and assessment of the severity of hemorrhage. If there is major bleeding, vitamin K may be given intravenously, and if the bleeding is life threatening, vitamin K should be accompanied by fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa. If the INR is elevated and no explanatory pathology is found, it may be appropriate to restart the OAC, attempting to maintain the INR in the usual therapeutic range with intensified monitoring and attention to patient factors that can increase the INR in the setting of a given dose of OAC. If the bleeding is not life threatening and occurs with an INR in the therapeutic range, once pathology is ruled out and if the CHADS2 score is ≥2, it may be appropriate to reinstitute the OAC, attempting to maintain a therapeutic INR.

**RECOMMENDATION**

We recommend that patients with AF or AFL who experience a stroke be managed acutely according to the published guidelines of the American Heart and American Stroke Associations (Strong Recommendation, Moderate-Quality Evidence).

**Pharmacogenomics**

Eventually, pharmacogenomic algorithms may allow more rapid and safe determinations of initial warfarin dosage, particularly among patients whose warfarin requirements are particularly low or high. For the present, routine genetic testing is not advised in the management of therapy with a vitamin K antagonist.

**Alternatives to Antithrombotic Therapies**

**Rhythm control and stroke risk**

An overview of the 5 trials that compared the strategies of rhythm vs rate control in AF found a mortality of 13.0% with rate control vs 14.6% with rhythm control (odds ratio 0.87, P = .09). The rates of ischemic stroke and major hemorrhage were similar. The AFFIRM trial is by far the largest, mandated anticoagulation (INR 2.0-3.0) in the rate-control group (85% maintained warfarin) and strongly encouraged in the rhythm-control group, while allowing cessation at the physician’s discretion if sustained sinus rhythm was achieved (70% maintained warfarin). Ischemic stroke occurred at an annual rate of about 1% in each group, and in most instances the patient was either off warfarin or the INR was <2.0. The authors concluded that continuous anticoagulation is warranted in all patients with AF and 1 or more risk factors for stroke, whether or not sinus rhythm appears to be restored and maintained, and this approach is recommended by consensus groups.

Left atrial radiofrequency ablation is increasingly used as a rhythm control approach to treat AF, raising questions about the role of long-term OAC therapy in such patients. The issues are the risk of dislodgement of left atrium thrombus during the ablation procedure, bleeding in association with the invasive procedure, creation of thrombogenic areas of left atrium endothelial damage, and the risk of embolization during long-term follow-up. Recommendations are generally weak and based on evidence of low or very low quality. TEE is advised immediately preprocedure to ensure there is no important left atrium thrombus. In general, the procedure is performed with the patient adequately anticoagulated, either by sustaining the preprocedure warfarin (usually allowing the INR to fall to the lower end of the therapeutic range) or with use of bridging LMWH both before and after the procedure. In the latter case, UFH is given with access to the left atrium. The UFH or LMWH are discontinued at the completion of the procedure, and the sheath is removed when the ACT returns to

---

**RECOMMENDATION**

We suggest that patients with AF or AFL who experience hemorrhage while on OAC therapy be managed according to the practice guidelines of the American College of Chest Physicians (Conditional Recommendation, Low-Quality Evidence).
a safe level. Parenteral anticoagulation is reinitiated within hours of the sheath removal and maintained until therapeutic anticoagulation is reestablished with warfarin or dabigatran, which is continued for at least 3 months. Long-term OAC should continue if AF recurs. In the presence of sustained normal sinus rhythm, OAC should be discontinued only if the long-term risk of stroke is low (CHADS2 score <2). (See further details in the accompanying article titled “Catheter Ablation of Atrial Fibrillation and Flutter.”)\[106\]

**Left atrial appendage-directed interventions**

A range of surgical procedures focused on curing AF have been developed and reported during the past 20 years.\[107\] Left atrial appendage removal or occlusion may be done in an attempt to lower the risk of thromboembolism as part of a Cox Maze procedure or as an adjunct to another cardiac surgical procedure. Only case series are available in the literature, with levels of success very specific to individual centres and the indications uncertain. The long-term risk of stroke after such procedures appears to be low, but the requirement for long-term OAC is unclear, and advice should be provided by the expert centre conducting the arrhythmia surgery. A Canadian collaborative group is currently conducting a pilot study evaluating left atrial appendage occlusion in conjunction with various cardiac surgical procedures (clinicaltrials.gov, NCT00908700). (See detailed discussion in the accompanying article titled “Surgical Therapy for Atrial Fibrillation.”)\[108\]

Percutaneous closure of the left atrial appendage was evaluated in a randomized, noninferiority comparison of conventional warfarin vs the Watchman occluding device and subsequent discontinuation of warfarin.\[109\] The composite primary outcome (any stroke, cardiovascular or unexplained death, or systemic embolism) at a mean of 18 months was nonsignificantly less in the Watchman group (RR = 0.62; 95% CI, 0.35-1.25), and the device was concluded to be noninferior to conventional warfarin therapy. However, there were relatively few events, the follow-up was short, there are substantial learning curve considerations, and the antithrombotic regimen used with the device was complex and changing. Additional, adequately powered studies, particularly in patients at higher risk of stroke, are needed for adequate assessment of this new technique.

**Acknowledgements**

The authors are grateful to Grant Stotts, MD, FRCPC, for advice and liaison with the Canadian Stroke Network and to Marie-Josee Martin and Jody McCombe for final transcription of the manuscript. Administrative and technical support was provided by the Canadian Cardiovascular Society.

**References**


34. Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin for the prevention of thromboembolism in patients with nonvalvular atrial fibrillation (SPORTIF III) [a randomized trial. Lancet 2003;362:1691-98.
EMBARGOED

EMBARGOED

EMBARGOED

Cairns et al

Stoke Prevention in Atrial Fibrillation


Society Guidelines

Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention and Treatment of Atrial Fibrillation Following Cardiac Surgery

L. Brent Mitchell, MD, FRCPC, and the CCS Atrial Fibrillation Guidelines Committee

ABSTRACT

Postoperative atrial fibrillation and atrial flutter (POAF) are the most common complications of cardiac surgery that require intervention or prolong intensive care unit and total hospital stay. For some patients, these tachyarrhythmias have important consequences including patient discomfort/anxiety, hemodynamic deterioration, cognitive impairment, thromboembolic events including stroke, exposure to the risks of antiarrhythmic treatments, longer hospital stay, and increased health care costs. We conclude that prevention of POAF is a worthwhile exercise and recommend that the dominant therapy for this purpose be β-blocker therapy, especially the continuation of β-blocker therapy that is already in place. When β-blocker therapy is contraindicated, amiodarone prophylaxis is recommended. If both of these therapies are contraindicated, therapy with either intravenous magnesium or biatrical pacing is suggested. Patients at high risk of POAF may be considered for first-line amiodarone therapy, first-line sotalol therapy, or combination prophylactic therapy. The treatment of POAF may follow either a rate-control approach (with the dominant therapy being β-blocking drugs) or a rhythm-control approach. Anticoagulation should be considered if persistent POAF lasts >72 hours and at the time of discharge and given that all of these factors are frequently present immediately after cardiac surgical procedures, it is not surprising that AF and atrial flutter are frequent complications of these procedures. Indeed, atrial tachyarrhythmias are the most common postoperative complications of cardiac surgery that require intervention or prolonged intensive care unit and total hospital stay.

Incidence of Postoperative Atrial Tachyarrhythmias

Given that atrial fibrillation (AF) and atrial flutter are facilitated by atrial trauma, atrial stretch, atrial ischemia, epicardial inflammation, hypoxia, acidosis, electrolyte disturbances, and the refractoriness changes that accompany sympathetic nervous system changes that accompany sympathetic nervous system changes, it is not surprising that AF and atrial flutter are frequent complications of these procedures. Indeed, atrial tachyarrhythmias are the most common postoperative complications of cardiac surgery that require intervention or prolonged intensive care unit and total hospital stay.

RÉSUMÉ

La fibrillation auriculaire (FA) et le flutter auriculaire postopératoires sont les complications les plus courantes de la chirurgie cardiaque qui nécessitent une intervention et prolongent la durée de séjour de l’unité des soins intensifs ou hospitalier. Chez certains patients, ces tachyarhythmies ont des conséquences importantes, citons entre autres l’inconfort et l’anxiété, la détérioration hémodynamique, les troubles cognitifs, les thromboembolies, l’accident vasculaire cérébral, l’exposition aux effets secondaires des traitements antiarythmiques, le séjour prolongé à l’hôpital et les coûts additionnels. Nous concluons que la prévention de la FA postopératoire est un exercice qui en vaut la peine et recommandons que le but premier du traitement soit le traitement par β-bloquant, particulièrement la continuation des β-bloquants déjà administrés en préopératoire. Lorsque le traitement par β-bloquants est contre-indiqué, on recommande l’amiodarone en prophylaxie. Si ces deux traitements sont contre-indiqués, on suggère le traitement soit à l’aide de magnésium intraveineux ou la stimulation biauriculaire. Les patients à haut risque de FA postopératoire peuvent être considérés pour le traitement de première intention à l’amiodarone, le traitement de première ligne par sotalol ou la combinaison de...
point of hospital discharge. The ongoing need for any POAF treatment (including anticoagulation) should be reconsidered 6–12 weeks after the surgical procedure.

The incidence of POAF after cardiac surgery ranges from ≈30% for patients undergoing isolated coronary artery bypass graft (CABG) surgery to ≈40% for patients undergoing valve replacement or repair to ≈50% of patients undergoing both procedures. Furthermore, there is evidence that the incidence of POAF is increasing as older individuals with a higher prevalence of atrial tachyarrhythmia risk factors are more commonly undergoing these procedures.

The peak incidence of these atrial tachyarrhythmias is between postoperative days 2 and 4. Of the patients who develop an atrial tachyarrhythmia, 70% do so before the end of the fourth postoperative day and 94% do so before the end of the sixth post hospital day.

**Risk Factors for Postoperative Atrial Tachyarrhythmias**

Independent patient characteristics that predict the occurrence of atrial tachyarrhythmias after cardiac surgery include prior AF episodes, older age, male gender, history of hypertension, requirement for an intraoperative balloon pump, requirement for prolonged ventilation (>24 hours), and withdrawal of β-blocker therapy. As in the general population, age has the highest predictive value. Operative variables reported to be atrial tachyarrhythmia risk factors include the procedure performed (isolated CABG, valve repair/replacement, or both), the number of bypass grafts, the duration of surgery, and the duration of aortic cross-clamp time.

**Consequences of Postoperative Atrial Tachyarrhythmias**

Post cardiac surgery atrial tachyarrhythmias may be transient and cause little morbidity. However, for some patients these tachyarrhythmias have important consequences including patient discomfort/anxiety, hemodynamic deterioration, cognitive impairment, thromboembolic events including stroke, exposure to the risks of arrhythmia treatments, longer hospital stay, and increased health care costs. Linear regression models indicate that postoperative atrial tachyarrhythmias are independently associated with an increase in the duration of hospitalization and in health care costs.

**Prophylaxis of Postoperative Atrial Tachyarrhythmias**

**Standard β-blocker drug therapy**

A recent meta-analysis of randomized controlled clinical trials (RCTs) evaluating standard β-blocker drug therapy (Table 1) for the prevention of postoperative AF after cardiac surgery examined 31 RCTs involving 4452 patients. β-Blocker drug therapy was associated with a reduction in the probability of postoperative AF with an odds ratio (OR) of 0.36, a 95% confidence interval (95% CI) for this point estimate of 0.28–0.47, and a statistical significance level (P-value) of .001. Nevertheless, this meta-analysis also revealed a highly statistically significant heterogeneity assessment P-value of <.001, indicating that differences between the trials preclude meaningful merging of their results. Much of the heterogeneity in the results of these trials was explained by the practice in some trials of permitting preoperative withdrawal of preexisting β-blocker drug therapy in those patients randomized not to receive study β-blocker drug therapy (β-blocker therapy withdrawal–mandated trials) versus the practice in other trials of continuing preexisting β-blocker drug therapy in those patients randomized not to receive study β-blocker drug therapy (β-blocker therapy withdrawal–not mandated trials). In the β-blocker therapy withdrawal–mandated trials, study β-blocker drug therapy was associated with a large reduction in the probability of postoperative AF (OR 0.30, 95% CI 0.22–0.40, P-value for effect <.001, P-value for heterogeneity of .06). In the β-blocker therapy withdrawal–not mandated trials, study β-blocker drug therapy was associated with a smaller reduction in the probability of postoperative AF (OR 0.69, 95% CI 0.54–0.87, P-value for effect of .002, P-value for heterogeneity of .72). This observation may relate to preoperative β-blocker therapy withdrawal increasing the control group probability of postoperative AF.

The largest of the β-blocker therapy withdrawal–not mandated trials, the Beta Blocker Length Of Stay (BLOS) trial, reported a post-hoc analysis indicating that, in patients receiving preoperative nonstudy β-blocker drug therapy, study metoprolol therapy was associated with a decrease in postoperative AF (metoprolol group AF incidence 29.6%, placebo group AF incidence 40.1%, OR 0.63), while in patients not receiving preoperative nonstudy β-blocker drug therapy, study metoprolol therapy was not associated with a decrease in postoperative AF (metoprolol group AF incidence 38.5%, placebo group AF incidence 35.0%, OR 1.16) (unadjusted P-value for interaction of .05). Furthermore, in patients not receiving preoperative nonstudy β-blocker drug therapy, study metoprolol therapy was associated with greater acute reduction in heart rate (unadjusted P-value for interaction of .002), greater acute reduction in cardiac index (unadjusted P-value for interaction of .002), and an increase in total hospital stay (unadjusted P-value for interaction of .002).

Current evidence suggests that the standard β-blocker drugs are equivalent with regard to their efficacy in the prevention of postoperative AF after cardiac surgery. Nevertheless, one small, nonrandomized, retrospective comparison of carvedilol versus other β-blocker drugs (mostly metoprolol or atenolol) suggested that carvedilol prevented postoperative AF better than did the others (relative risk 0.24, 95% CI 0.11–0.51, P < .05). This possibility will need to be assessed in a comparative clinical trial.

Thus, the evidence for continuing preoperative β-blocker drug therapy after cardiac surgery for the prevention of postoperative AF is very strong. However, initiating β-blocker drug therapy just before or after cardiac surgery in patients...
who were not receiving preoperative β-blocker drug therapy for the purpose of preventing postoperative AF has less compelling support.

**RECOMMENDATION**

We recommend that patients who have been receiving a β-blocker before cardiac surgery have that therapy continued through the operative procedure in the absence of the development of a new contraindication (Strong Recommendation, High-Quality Evidence).

We suggest that patients who have not been receiving a β-blocker before cardiac surgery have that therapy initiated just before or immediately after the operative procedure in the absence of a contraindication (Conditional Recommendation, Low-Quality Evidence).

**Values and preferences.** These recommendations place a high value on reducing postoperative AF and a lower value on adverse hemodynamic effects of β-blockade during or after cardiac surgery. It is also noted that inherent to a strategy of prophylaxis, a number of patients will receive β-blocker therapy without personal benefit.

**Amiodarone therapy**

A recent meta-analysis of RCTs evaluating amiodarone therapy (Table 1) for the prevention of postoperative AF after cardiac surgery examined 19 placebo-controlled RCTs involving 3295 patients. Compared to placebo, amiodarone therapy was associated with a reduction in the probability of postoperative AF (OR 0.50; 95% CI 0.43-0.59, P < .0001). This meta-analysis reported that amiodarone therapy for the prevention of postoperative AF was also associated with a reduction in postoperative ventricular tachyarrhythmias (OR 0.39, 95% CI 0.26-0.58, P < .001), a reduction in postoperative neurologic events (OR 0.53, 95% CI 0.30-0.92, P = .02), a reduction in the postsurgery hospital length of stay (0.6 days: 95% CI 0.4-0.8 days, P < .0001), and a reduction in hospital costs (–$2527, 95% CI –$500 to –$5815, P = .1). Another meta-analysis that included adverse events noted that amiodarone therapy in this setting is also associated with an increase in postoperative bradycardia (OR 1.66, 95% CI 1.73-2.47). A meta-analytic comparison of the effects of amiodarone therapy initiated preoperatively (6 studies, OR 0.50, 95% CI 0.30-0.63) versus that initiated intraoperatively or postoperatively (8 studies, OR 0.48, 95% CI 0.37-0.63) showed no statistically significant difference in the prevention of postoperative AF (P = .86). In a small, direct-comparison RCT, amiodarone was reported to be more effective for the prevention of postoperative AF after cardiac surgery than standard β-blockade (propranolol) (RR 0.53, 95% CI 0.37-0.93, P = .05). Similarly, amiodarone therapy was suggested to be more effective than sotalol therapy for this purpose, but the difference was not statistically significant in a small trial of 160 patients (RR 0.77, 95% CI 0.54-1.12, P = .21).

**RECOMMENDATION**

We recommend that patients who have a contraindication to β-blocker therapy before or after cardiac surgery be considered for prophylactic therapy with amiodarone to prevent postoperative AF (Strong Recommendation, High-Quality Evidence).
**Values and preferences.** This recommendation places a high value on minimizing the patient population exposed to the potential adverse effects of amiodarone and a lower value on data suggesting that amiodarone is more effective than β-blocker therapy for this purpose.

**Sotalol therapy**

A recent meta-analysis of RCT evaluating sotalol therapy for the prevention of postoperative AF after cardiac surgery examined 9 placebo-controlled RCTs involving 1382 patients. Compared to placebo, sotalol therapy was associated with a reduction in the probability of postoperative AF (OR 0.34, 95% CI 0.26–0.45, P-value <.001). More patients receiving sotalol had their therapy withdrawn because of adverse effects than did patients receiving placebo (6.0% versus 1.9%, respectively, P = .004).

The same meta-analysis of RCTs evaluating sotalol therapy for the prevention of postoperative AF after cardiac surgery examined 7 RCTs involving 1240 patients comparing sotalol for the prevention of postoperative AF after cardiac surgery.

Sotalol therapy has greater efficacy for this purpose than does standard β-blocker drug therapy but this difference was not statistically significant (7.2% versus 4.8%, respectively, P = .25). Thus, sotalol therapy for the prevention of postoperative AF after cardiac surgery has been less well studied than standard β-blocker drug therapy. Nevertheless, it appears that sotalol therapy has greater efficacy for this purpose than does standard β-blocker drug therapy but may also have a greater adverse effect profile in this setting.

**Intravenous magnesium therapy**

A recent meta-analysis of 7 RCTs involving 1234 patients evaluating intravenous magnesium therapy (Table 1) for the prevention of postoperative AF after cardiac surgery reported that intravenous magnesium therapy was associated with a reduction in the incidence of postoperative AF from 26.7% to 20.0% (OR 0.66, 95% CI 0.51-0.87, P = .003) and with a reduction of the postoperative length of hospital stay in 6 trials involving 1136 patients by 0.29 days (95% CI 0.05-0.54 days, P = .02). However, this meta-analysis also found significant heterogeneity among the intravenous magnesium trials (P = .02) with patients receiving preoperative intravenous magnesium (as opposed to intraoperative or postoperative therapy initiation) and patients receiving lower dosages of intravenous magnesium (as opposed to moderate or higher dosages of magnesium) apparently receiving all of the benefit of therapy with respect to a reduction in the postoperative incidence of AF. Most intravenous magnesium trials report no evident adverse effects of magnesium therapy in properly selected patients. Nevertheless, one trial reported a higher probability of postoperative hypotension with combination intravenous magnesium and propranolol therapy than with propranolol therapy alone.

Intravenous magnesium therapy has been compared to a standard β-blocker (propranolol) in a trial involving 134 patients. Propranolol was more effective for the prevention of postoperative AF than was intravenous magnesium (RR 0.53, 95% CI 0.36-0.80, P = .01). Another small trial of 105 patients found no significant difference in the efficacy of intravenous magnesium therapy versus sotalol therapy for this purpose (RR 0.87, 95% CI 0.48-1.55).

Thus, there is moderate evidence that intravenous magnesium therapy, particularly lower-dose therapy initiated before cardiac surgery, will reduce the postoperative incidence of AF after cardiac surgery. The major advantage of this approach is that the therapy has a very low probability of being associated with adverse effects in patients without renal dysfunction.

**Overdrive atrial pacing**

Trials of overdrive atrial pacing (Table 1) for the prevention of postoperative AF have used multiple pacing configurations: right atrial pacing, left atrial pacing, biatrial pacing, and Bachmann’s bundle pacing. Overall, a meta-analysis of 14 RCTs involving 1885 patients showed that overdrive atrial pacing was associated with a reduction in the incidence of postoperative AF from 35.3% to 17.7% (OR 0.60, 95% CI 0.57-0.77, P < .001). Although the P-value for heterogeneity was not statistically significant, there was a trend to heterogeneity (P = .13) and the majority of the benefit was seen in 10 trials involving 754 patients wherein biatrial pacing was associated with a statistically significant reduction in the incidence of postoperative AF (OR 0.44, 95% CI 0.31-0.64, P < .001). Individual assessment of right atrial and of left atrial or Bachmann’s bundle overdrive atrial pacing did not show a statistically significant result.

The Atrial Fibrillation Suppression Trial II (AFIST-II) compared overdrive atrial septal pacing to amiodarone therapy for the prevention of postoperative AF and reported that amiodarone therapy prevented AF better than did overdrive atrial pacing (RR 0.50, 95% CI 0.30-0.82, P < .05). Accordingly, the quality of evidence to recommend overdrive atrial pacing, in the absence of other prophylactic therapy, for the prevention of postoperative AF after cardiac surgery is low but, when used, the evidence favours biatrial overdrive pacing.

**RECOMMENDATION**

We suggest that patients who have a contraindication to β-blocker therapy and to amiodarone therapy before or after cardiac surgery be considered for prophylactic therapy to prevent postoperative AF with intravenous magnesium (Conditional Recommendation, Moderate-Quality Evidence) or with biatrial pacing (Conditional Recommendation, Low-Quality Evidence).

**Values and preferences.** This recommendation places a high value on preventing postoperative AF using more novel therapies that are supported by lower quality data. A high value is placed on the low probability of adverse effects from magnesium. The use of biatrial pacing needs to be individualized by patient and institution, as the potential for adverse effects may outweigh potential benefit based on local expertise.

**Other interventions**

Meta-analyses have not shown a potential role for the use of digoxin (OR 0.97, 0.62-1.49, P = .88), calcium channel blocker drugs (OR 0.73, 95% CI 0.48-1.12, P = .15),
propafenone (OR 0.73, 0.39-1.38, P = .97), or procainamide (OR 0.51, 95% CI 0.25-1.04, P = .07) for the prevention of postoperative AF after cardiac surgery.25

Newer interventions with promising preliminary results not yet tested in larger patient populations include glucose/insulin/potassium, preservation of the anterior cardiac fat pad, N-3 fatty acids, HMG CoA reductase inhibitors, and systemic steroids.

**Combination therapy**

Two small trials36,37 directly compared 2 apparently effective treatments for the prevention of POAF after cardiac surgery using a 2 × 2 factorial trial design to evaluate the utility of combination prophylactic therapy.

Forlani et al36 randomized 207 patients to receive prophylactic sotalol, prophylactic intravenous magnesium, both therapies, or neither therapy. The incidence of postoperative AF was statistically significantly reduced from 38.0% in the neither-therapy group to 14.8% in the magnesium therapy–alone group and to 11.8% in the sotalol therapy–alone group. The incidence of postoperative AF was statistically significantly reduced even further by combined magnesium and sotalol to an astonishing 1.9%.

The AFIST-II37 randomized 160 patients to receive prophylactic atrial septal pacing, prophylactic amiodarone, both therapies, or neither therapy. The incidence of postoperative AF was 37.5% in the neither-therapy group. The incidence of postoperative AF was not reduced by atrial septal pacing (40.0%). The incidence of postoperative AF was reduced to 28.5% in the amiodarone-treated group but this difference was not statistically significant (RR 0.79, 95% CI 0.48-1.29). Although the incidence of postoperative AF was further reduced by combined amiodarone and atrial septal pacing to 15.8%, this difference was not statistically significant relative to that achieved with amiodarone therapy alone (RR 0.77, 95% CI, 0.49-1.22). These suggestions of no difference are, of course, power-limited.

**RECOMMENDATION**

We suggest that patients at high risk of postoperative AF receive prophylactic therapy to prevent postoperative AF such as sotalol or combination therapy including ≥2 of a β-blocker, amiodarone, intravenous magnesium, or biatrial pacing (Conditional Recommendation, Low- to Moderate-Quality Evidence).

**Values and preferences.** This recommendation recognizes that data confirming the superiority of combinations of prophylactic therapies are sparse.

**Treatment of postoperative atrial fibrillation**

The treatment goals for AF and flutter that occur after cardiac surgery are identical to those of AF and atrial flutter that occur in other settings. These goals include prevention of thromboembolic events, slowing of the ventricular response rate, and consideration of conversion to and maintenance of sinus rhythm. Nevertheless, postoperative physiology does have features that favour some therapeutic strategies over others. The natural history of POAF after cardiac surgery is dominated by self-terminating but frequently recurrent atrial tachyarrhythmia episodes and resolution of this propensity in 6-12 weeks regardless of the therapy used.38-40 Furthermore, the adrenergic discharge state after cardiac surgery lessens the effectiveness of therapies that do not include β-blockade.

There is an association between POAF and postoperative cerebrovascular events2,3,8,20,21 and cognitive impairment19 after cardiac surgery. On the other hand, early anticoagulation therapy in this setting may predispose the postoperative patient to delayed pericardial bleeding and cardiac tamponade.41 In recognition of this risk and in the absence of controlled trials of the optimum timing for the initiation of anticoagulation therapy for patients with AF after cardiac surgery, anticoagulation is recommended for patients with prolonged (>72 hours) AF. Once initiated, anticoagulation is usually continued for ≥6 weeks.

**RECOMMENDATION**

We suggest that consideration be given to anticoagulation therapy if postoperative continuous AF persists for >72 hours. This consideration will include individualized assessment of the risks of a thromboembolic event and the risk of postoperative bleeding (Conditional Recommendation, Low-Quality Evidence).

**Values and preferences.** This recommendation places a higher value on minimizing the risk of thromboembolic events and a lower value on the potential for postoperative bleeding. Because the risk of postoperative bleeding decreases with time, the benefit-to-risk ratio favours a longer period without anticoagulation in the postoperative setting than that suggested in other settings.

Therapy for ventricular rate control for atrial tachyarrhythmias is usually required for patients who experience AF after cardiac surgery. Nevertheless, cardiac surgery may also predispose such patients to bradyarrhythmias after conversion of AF or atrial flutter secondary to sinus nodal, AV nodal, or His-Purkinje system dysfunction. Accordingly, the availability of back-up ventricular pacing is important.

As the postsurgical state includes adrenergic discharge, β-blocker therapy is often very effective for slowing of the ventricular response rate to AF and flutter. Other therapeutic alternatives, used when β-blocker therapy is ineffective, poorly-tolerated, or contra-indicated, include a non-dihydropyridine calcium antagonist (diltiazem, verapamil) or amiodarone. In this setting, therapy with digoxin is usually insufficient.

**RECOMMENDATION**

We recommend that temporary ventricular epicardial pacing electrode wires be placed at the time of cardiac surgery to allow for backup ventricular pacing as necessary (Strong Recommendation, Low-Quality Evidence).
**RECOMMENDATION**

We recommend that postoperative AF with a rapid ventricular response be treated with a β-blocker, a non–dihydropyridine calcium antagonist, or amiodarone to establish ventricular rate control. In the absence of a specific contraindication, the order of choice is as listed (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** This recommendation places a high value on the randomized controlled trials investigating rate control as an alternative to rhythm control for AF, recognizing that these trials did not specifically address the postoperative period.

Considerations related to the advantages, disadvantages, and risks of conversion to and maintenance of sinus rhythm for patients with sustained atrial tachyarrhythmias after cardiac surgery are similar to those in other settings. Nevertheless, because early recurrence of the atrial tachyarrhythmia is common, ongoing antiarrhythmic drug therapy to prevent atrial tachyarrhythmia recurrences is preferred over isolated DC cardioversion provided that the patient is sufficiently stable to proceed. Although intravenous ibutilide has been proposed as a rapid-acting approach to pharmacologic cardioversion of atrial tachyarrhythmias after cardiac surgery, this intervention was effective in <50% of patients (with the highest success rates in patients with atrial flutter) and was associated with the precipitation of Torsades de pointes ventricular tachycardia in ≈2%-5% of postoperative patients. In addition, the short half-life of this agent also translates into the absence of ongoing therapy to prevent atrial tachyarrhythmia recurrences.

The overwhelming majority of patients with postoperative atrial tachyarrhythmias will no longer be susceptible to atrial tachyarrhythmia recurrences within 6-12 weeks after cardiac surgery. Accordingly, a rate-control strategy, as opposed to a rhythm-control strategy, has the advantage of not exposing the patient, who by definition has structural heart disease, to the risks of Class I or Class III antiarrhythmic drugs. No large randomized clinical trial has evaluated the advantages, disadvantages, and risks of the rate-control strategy versus the rhythm-control strategy for POAF. One small randomized pilot study reported a statistically significant reduction in the duration of the postsurgical hospital stay in patients developing postoperative AF who were assigned to a rhythm-control approach versus a rate-control approach to treatment. Nevertheless, a retrospective evaluation suggested a statistically significant reduction in the duration of postsurgical hospital stay in patients discharged in AF (after ventricular response rate control and anticoagulation) compared to patients discharged in sinus rhythm. Accordingly, the preferred approach remains unknown. Regardless of the approach chosen, therapy provided for POAF can usually be withdrawn 6-12 weeks later.

**Values and preferences.** This recommendation reflects the high probability that postoperative AF will be a self-limiting process that does not require long-term therapy.

**References**


