Management of Atrial Fibrillation

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia that requires treatment, with an estimated prevalence in the United States of 2.3 million persons in 2001. Its prevalence increases with age, hypertension, and heart failure: 10% of patients aged 80 years or older have AF; 4% of patients with heart failure (HF) functional class I and 50% of patients with functional class IV have AF. On the other hand, HF is present in 34% of AF patients. AF is typically initiated by one or more premature atrial complexes, often originating around the pulmonary veins, or by atrial tachycardia or atrial flutter.

PREDISPOISING FACTORS (TABLE 1)

Hypertension is the most common causal factor associated with AF on a population basis; coronary artery disease (CAD) and HF are the most common associated features in hospital series. Thirty to 45% of cases of paroxysmal AF, and 20%-25% of cases of persistent AF occur in patients younger than 60 years without underlying heart disease, ie, lone AF. Even in the case of lone AF there are structural atrial abnormalities and some degree of atrial dilatation and dysfunction, as well as an increased prevalence of high-normal blood pressure (ie, systolic pressure 130 to 140 mmHg), that contribute to AF.

The most frequent histopathological feature of AF is atrial fibrosis, which may precede the onset of AF. Atrial dilatation is present in over 50% of patients with AF, with a mean left atrial diameter of ~ 40 +/- 8mm in the Canadian Registry of Nonvalvular AF, with a lower prevalence of dilatation in patients with nonrecurrent AF and lone AF. Atrial dilatation may not only be a cause, but also a consequence of AF, as evidenced by the fact that the left atrial size further increases with time in patients with persistent AF. On the other hand, left atrial size decreases after cardioversion of AF. Atrial electrical remodeling, ie, progressive shortening of the effective refractory period, explains how prolonged AF makes restoring and maintaining sinus rhythm less likely.

TYPES OF AF

There are three types of AF: paroxysmal, persistent, and permanent. Paroxysmal AF is defined as AF that reverses spontaneously in less than seven days (often < 24 hours); newly diagnosed AF is most often paroxysmal. Persistent AF is AF that persists more than seven days and requires cardioversion. AF is considered permanent or chronic in cases of failure of cardioversion attempts, early recurrences after cardioversion, or decision not to cardiovert when the patient is asymptomatic after rate control and has a high likelihood of recurrence (eg, AF present for over a year or severe left atrial enlargement).

GENERAL THERAPY OF AF

There are three main consequences of AF: thrombus formation in the left atrial appendage and embolization of this clot, fast and irregular heart rate leading to compromised ventricular filling, and loss of the atrial kick that contributes to up to 40% of the cardiac output in HF patients. Also, AF that has a rapid ventricular response of 120 beats per minute or more and persists for more than two weeks could be a cause of tachycardia-mediated cardiomyopathy and HF.

<table>
<thead>
<tr>
<th>Table 1. Factors predisposing to atrial fibrillation.</th>
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<tbody>
<tr>
<td>- Systemic arterial hypertension</td>
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<tr>
<td>- Coronary arterial disease</td>
</tr>
<tr>
<td>- Heart failure</td>
</tr>
<tr>
<td>- Any acute or chronic structural heart disease</td>
</tr>
<tr>
<td>- Atrial inflammation: pericarditis, myocarditis</td>
</tr>
<tr>
<td>- Metabolic disorders: hyperthyroidism, hypokalemia</td>
</tr>
<tr>
<td>- Pulmonary disorders: pulmonary embolism, sleep apnea</td>
</tr>
<tr>
<td>- Postoperative state (cardiac, pulmonary, or esophageal surgeries)</td>
</tr>
</tbody>
</table>
Table 2. Cases in which a rhythm control strategy should be considered.

- Intolerable symptoms despite rate control
- Difficulty in achieving adequate rate control
- Newly diagnosed AF, especially if symptomatic*
- Decompensated HF or advanced class III-IV HF (This population is not well represented in the AF-CHF trial.)
- HF due to LV diastolic dysfunction is a potential indication for rhythm control
- Right ventricular failure
- Age < 65 years
- AF secondary to a treated precipitant

*21% of patients in whom AF is newly diagnosed are asymptomatic; these patients are unlikely to benefit from a rhythm control strategy. AF: atrial fibrillation; CHF: congestive heart failure; HF: heart failure; LV: left ventricular

Anticoagulation

Administer warfarin (or aspirin in some subgroups), regardless of whether AF is paroxysmal or permanent. AF often recurs, and asymptomatic recurrences are 12 times more common than symptomatic recurrences. In the AF-FIRM study, the risk of ischemic stroke was strongly related to absent or suboptimal anticoagulation.

Rate control

Beta-blockers or nondihydropyridine-type calcium channel blockers (CCB), ie, diltiazem or verapamil, are first-line agents. β-blockers are the most effective drugs chronically, are effective as monotherapy in up to 60% of patients with AF, and are first-line therapy in compensated systolic HF. They also have an anti-arrhythmic effect and may convert adrenergically-mediated AF into sinus rhythm. Digoxin is less effective as monotherapy and is poorly effective for rate control during exertion. In addition, digoxin monotherapy may increase mortality and should be avoided, except in cases of decompensated systolic HF when the acute initiation of β-blockers is not possible. If the rate is inadequately controlled with maximal tolerated
doses of one agent, digoxin is added as a second-line agent; the combination of β-blockers and CCB may also be tried but is not superior to the digoxin combinations.\textsuperscript{14} Triple combination is required in \~15\%-20\% of the cases. Pharmacological therapy can achieve rate control in 80\% of patients. The remaining patients cannot be rate controlled with drugs and require rhythm control or, failing that, atrioventricular nodal ablation with ventricular pacing. Patients with AF, including AF with fast ventricular rates, may also have periods of sinus bradycardia or may have AF-related pauses that limit the use of rate-controlling agents; these patients may require pacemaker placement.

The goal of therapy is to reduce the heart rate to less than 80 beats per minute (bpm) at rest, to less than 110 bpm with moderate activity, and to an average heart rate of less than 100 bpm on 24-hour Holter monitoring.

**Rhythm control**

Rhythm control is generally the least important goal. Long-term rhythm control, as compared with rate control, has not been shown to improve mortality, stroke rate, or HF hospitalizations in patients at high risk of stroke or AF recurrences\textsuperscript{16,17} or in stable HF patients with left ventricular ejection fractions <35\%.\textsuperscript{18} This is at least partly related to the marginal efficacy of antiarrhythmic drugs and to their toxicity: only 62\% of patients in the rhythm-control arm of AFFIRM study, as compared to 34\% of patients in the rate-control arm, were in sinus rhythm at the end of follow-up.\textsuperscript{16} A secondary analysis of the data from the RACE trial showed that patients with symptoms related to atrial fibrillation who were assigned a rhythm-control strategy, and patients who were in sinus rhythm at the end of the follow-up period regardless of the treatment randomly assigned, had an improved quality of life.\textsuperscript{19} A secondary analysis of the AFFIRM trial showed that the presence of sinus rhythm, with or without the use of antiarrhythmic drugs, was associated with a significant reduction in the risk of death, but antiarrhythmic drug use per se was associated with an increased mortality.\textsuperscript{20} Also, atrial dysfunction may persist despite conversion to sinus rhythm and may contribute to the worsened outcomes. Rhythm control is still a valid strategy in patients who are symptomatic despite rate control (Table 2).
MANAGEMENT OF A PATIENT WHO ACUTELY PRESENTS WITH AF (TABLES 3 AND 4)

The management of such patients is presented in tables 3 and 4.

LONG-TERM MANAGEMENT AFTER THE ACUTE PRESENTATION

Anticoagulation is required at least for four weeks after spontaneous or active cardioversion of an AF episode that lasted 48 hours or more, regardless of whether the patient's risk factors dictate long term warfarin therapy. AF conversion to sinus rhythm is followed by a few weeks of atrial hypocontractility during which time a thrombus may form then embolize distally once the atria fully recover their contractility. If the patient does not have an indication for chronic warfarin therapy, administer warfarin for four weeks, then resume chronic aspirin therapy.

Even when anti-arrhythmic agents are used, the recurrence rate of AF is ~35%-60% at one year. An alternative to anti-arrhythmic therapy is catheter radiofrequency isolation of the pulmonary veins, which successfully prevents AF in 80% of the treated cases over one year of follow-up. It is indicated for the treatment and prevention of recurrent paroxysmal or persistent symptomatic AF, especially when the left atrial diameter is less than 4 cm. It

Table 3. Management of the patient presenting acutely with atrial fibrillation (AF).

1. DCCV is indicated emergently in cases of hypotension, acute severe HF, or myocardial ischemia attributed to AF.*

2. Acute rate control which β-blockers or CCBs as first-line agents in the absence of decompensated HF or hypotension, given intravenously if AF is severely symptomatic. Digoxin is a first-time option in cases of decompensated systolic HF or of low BP, and amiodarone may also be used for rate control in these critically ill patients. The onset of action of IV β-blockers or CCBs is fast (minutes), whereas IV amiodarone or digoxin take longer (an hour or more).

3. AF often (~60%) spontaneously resolves by 24 hours. If it persists beyond 24 hours:
   i-Perform DCCV or attempt acute cardioversion with anti-arrhythmic drugs if there is certainty that AF duration<48 hours and if a rhythm control strategy is selected. The patient needs to receive acute anticoagulation with heparin or enoxaparin.
   ii-If unsure of AF duration, give three weeks of warfarin then perform DCCV, or perform DCCV at 24 hours if TEE rules out LAA thrombus.
   iii-May allow the progression to a rate-controlled permanent AF. This decision depends on the severity of AF-related symptoms and on the likelihood of AF recurrence.

4. Hospitalize the patient with severe symptoms, when MI or PE is suspected, or if DCCV is planned.

5. Perform an echocardiogram and look for underlying cardiac, systemic, or metabolic diseases: acute HF, MI, acute PE, acute hypoxia, sepsis, acute anemia, thyrotoxicosis, electrolyte abnormalities, and coronary artery disease. Correcting these factors (eg, diuresis and vasodilators for HF) may control the rate and eventually convert AF to sinus rhythm.

*Typically, to attribute hemodynamic compromise to AF and to justify urgent cardioversion, the heart rate must be over 130-150 bpm. Also, in these cases, look for potential causes of shock that might have triggered both hypotension and AF. BP: blood pressure; CCB: calcium channel blocker; DCCV: direct-current cardioversion; HF: heart failure; LAA: left atrial appendage; MI: myocardial infarction, PE: pulmonary embolism; TEE: transesophageal echocardiography.

can be used as a first-line therapy or as second-line therapy after failure of anti-arrhythmic drugs.

In 25% of patients, DCCV fails or AF recurs after a few seconds or minutes of sinus rhythm; in another 25%, AF recurs within two weeks (Table 5). Cases of late recurrence may benefit from a second attempt of DCCV after preparation with anti-arrhythmic drugs. If DCCV fails or if AF recurs within two weeks despite anti-arrhythmic drugs, a decision may be made to accept the progression to permanent AF. Also, at this point, catheter RF isolation of the pulmonary veins or surgical ablation (maze procedure) may be attempted if AF is symptomatic.
Decision About Long-Term Anticoagulation and the Role of Clopidogrel

The annual risk of stroke in patients with AF not receiving any antithrombotic therapy ranges from 1.9 to 18%. This risk is similar in those with paroxysmal or with permanent AF. Several risk factors help predict this risk; one validated clinical scheme is the CHADS2 score (Table 6). Two points are assigned for a history of stroke or transient ischemic attack (TIA), and one point is assigned for each one of the other four features. Patients with two or more points or with mitral stenosis or a mechanical heart valve require warfarin therapy. Aspirin 81-325 mg is the appropriate therapy for patients with a score of zero. When the CHADS2 score is one, warfarin seems to be slightly superior to aspirin, but long-term therapy with either warfarin or aspirin is reasonable depending on the patient’s preference and bleeding risk. Patients with less validated risk factors (age 65 to 74 years, female gender, CAD, or thyrotoxicosis) may

<table>
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<th>Table 4. Dosage of the drugs used for acute rate control in patients with atrial fibrillation (AF).</th>
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<tbody>
<tr>
<td>1. Metoprolol 5 mg IV, to be repeated Q5 min up to 15 mg total. Then start oral metoprolol 25-50 mg Q6 hours if the IV doses have proven effective and are tolerated. The IV metoprolol effect lasts a few hours. Alternatively, may give esmolol IV drip (short acting; effect lasts 10-20 mins after the drip is off); it is the preferred agent when unsure if the patient will hemodynamically tolerate β-blockers.</td>
</tr>
<tr>
<td>2. Diltiazem 0.25 mg/kg (~20 mg) bolus IV; may rebolus with 0.35 mg/kg (~25 mg) in 15 mins if no response to 20 mg; then start 5-15 mg/hr IV drip in resonders. The IV diltiazem effect lasts a few hours. Diltiazem has more hypotensive effects than β-blockers because of vasodilatory effects, but it has less negative inotropic effects than verapamil or β-blockers*.</td>
</tr>
<tr>
<td>3. Digoxin needs to be given as a load (0.5 mg, then 0.25 mg Q6-8 hrs x 2=1-mg load, oral or IV), followed by 0.125-0.25 mg Q day.</td>
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*Acute monotherapy with β-blockers or CCBs is acutely effective in the majority of the cases. In case of total nonresponse to one agent, switch to another; in case of partial response to one, combine two agents, then try to wean off the first one. β-Blockers are more effective in cases of hyperadrenergic states (eg, postoperatively). Avoid digoxin as a sole agent to control the heart rate, except with decompensated heart failure or a low blood pressure.

IV: intravenous; mins: minutes
Table 5. Risk factors associated with failure of direct-current cardioversion and with recurrence of atrial fibrillation (AF) after cardioversion.24

- AF duration of more than one year
- Severe left atrial enlargement, i.e., antero-posterior diameter >4.5 cm on echocardiogram
- Underlying medical cause that has not been treated, e.g., acute HF or hyperthyroidism
- Underlying HF or structural heart disease
- Age > 70 years
- Previous recurrences of AF, especially early recurrences

be treated with either aspirin or warfarin (Table 7).22

If in addition to AF, the patient has CAD, one may use the combination of warfarin (INR goal 2 to 3) and aspirin, or may use warfarin monotherapy with a higher INR goal (2.5-3.5). The higher INR goal is protective against coronary ischemic events.25 The addition of aspirin to warfarin may increase the yearly bleeding risk by up to 1%, from an average bleeding risk of 2.5% per year to 3.5% per year.29

Role of Clopidogrel

The Active W study has shown that in patients with AF and moderate to high thromboembolic risk warfarin sodium monotherapy is clearly superior to the combination of aspirin and clopidogrel for the reduction of cardiovascular events (yearly rate of 3.93% vs. 5.6%, p<0.001) and stroke (1.4% vs. 2.39%, p<0.001), with a similar major bleeding risk (~2% per year). The number needed to treat to prevent one stroke per year is 100 patients.30 However, the majority of the patients in ACTIVE W were receiving warfarin-like drugs at the time of study entry. Patients not receiving warfarin-like therapy at entry had less major bleeding with the combination of clopidogrel and aspirin than with the warfarin-like therapy, whereas those already receiving warfarin-like therapy at entry had more major bleeding with clopidogrel and aspirin. Recently, the ACTIVE A study has shown that the combination of aspirin and clopidogrel is superior to aspirin monotherapy for the prevention of strokes in patients with AF (2.4% per year vs. 3.3% per year, p<0.001), at the cost of a higher risk of major bleeding (2% per year vs. 1.3% per year, p<0.001).31 Thus, the combination of aspirin and clopidogrel appears to be an option superior to aspirin but inferior to warfarin. It seems reasonable to use the combination of aspirin and clopidogrel in patients who are not deemed good candidates for warfarin therapy and who have not been on warfarin therapy.

Anti-Arrhythmic Drug Therapy
(Indications and Examples)

Anti-arrhythmic drugs (AAD) have three main uses. First, they are used to prevent recurrences of the arrhythmia if a rhythm control strategy is selected, this being the most important use of AADs; these drugs are usually given as long-term therapy after a second episode of AF. Second, AADs are used as an adjunctive therapy to DCCV to increase the effectiveness of DCCV and to sustain sinus rhythm. For that purpose, these drugs are mainly given when AF has been persistent for >3 months, when a prior DCCV has failed, or when there has been an early recurrence after DCCV. Third, AADs may be used to cardiovert acutely (this is their least important use).

Examples of Some AADs and Their Use in Special Conditions (Figure)

Beta-Blockers have shown moderate but consistent efficacy, comparable to conventional antiarrhythmic drugs, in preventing AF recurrence and in reducing the frequency of paroxysmal AF.32 33 This makes them an appropriate first-line therapy in many instances. These agents, however, may aggravate vagally-mediated AF.

Class III Agents: Amiodarone is a class III antiarrhythmic drug that can be used in any cardiac condition, including HF or any cardiomyopathy, without an increase in mortality. It is the only drug that can be used in patients with substantial LVH. It is also the most effective drug for long-term prevention of AF. It has a fast-onset rate-controlling effect (one to several hours), but a slow atrial antiarrhythmic effect (several days). Sotalol is an oral class III antiarrhythmic
drug with a β-blocker effect. Sotalol is inferior to amiodarone, but is particularly effective for chronic AF prevention in patients with CAD.34 Dronedarone is a drug similar to amiodarone without the iodine moiety. It lacks the pulmonary and thyroid toxicity of amiodarone and has a shorter half-life (1-2 days compared to two months). It is the only AAD that has shown a reduction in hospitalization related to cardiovascular events and a reduction in cardiovascular death in patients without HF; however, it increases mortality in patients with HF.35, 36 Oral dofetilide for acute or chronic rhythm control and intravenous ibutilide for acute rhythm control are other useful class III agents.

Class Ic Agents (propafenone, flecainide) may be used for acute cardioversion and for chronic rhythm control, but should be avoided in patients with any structural heart disease, in which case they are proarrhythmic and may increase mortality.37

### SIDE EFFECTS

All AADs can lead to bradyarrhythmias, ventricular arrhythmias, or torsades de pointe (ventricular arrhythmias are related to an increase in QRS duration with class I agents, and to an increase in QTc interval with class III agents). Thus, heart rate, QRS duration, and QTc interval are monitored with these agents. Avoid class Ic drugs if QRS >120 ms at baseline or increases more than 50% with treatment. Avoid class III drugs if QTc >460 ms at baseline, or increases to 520 ms or more or 15% or more with treatment.

Amiodarone has the lowest risk of proarrhythmia (<1%) despite QTc prolongation. It is the safest from the

### Table 6. Stroke risk in patients with nonvalvular atrial fibrillation not treated with anticoagulation.

<table>
<thead>
<tr>
<th>CHADS2 Risk Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke or TIA</td>
<td>2</td>
</tr>
<tr>
<td>Age &gt; 75 y</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients (N=1733)*</th>
<th>Adjusted Stroke Rate (%/y)* (95% CI)</th>
<th>CHADS2 Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>1.9 (1.2 to 3.0)</td>
<td>0</td>
</tr>
<tr>
<td>463</td>
<td>2.8 (2.0 to 3.8)</td>
<td>1</td>
</tr>
<tr>
<td>523</td>
<td>4.0 (3.1 to 5.1)</td>
<td>2</td>
</tr>
<tr>
<td>337</td>
<td>5.9 (4.6 to 7.3)</td>
<td>3</td>
</tr>
<tr>
<td>220</td>
<td>8.5 (6.3 to 11.1)</td>
<td>4</td>
</tr>
<tr>
<td>65</td>
<td>12.5 (8.2 to 17.5)</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>18.2 (10.5 to 27.4)</td>
<td>6</td>
</tr>
</tbody>
</table>

*Data are from reference 27. AF indicates atrial fibrillation; CHADS2: Cardiac Failure, Hypertension, Age, Diabetes, and Stroke (Doubled); CI, confidence interval; and TIA, transient ischemic attack. Reproduced from reference #2, with permission.

### Table 7. Antithrombotic therapy for patients with atrial fibrillation.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommended Therapy</th>
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<tbody>
<tr>
<td>No risk factors</td>
<td>Aspirin, 81 to 325 mg daily</td>
</tr>
<tr>
<td>One moderate-risk factor</td>
<td>Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)*</td>
</tr>
<tr>
<td>Any high-risk factor or more than 1 moderate-risk factor</td>
<td>Warfarin (INR 2.0 to 3.0, target 2.5)*</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Less Validated or Weaker Risk Factors</th>
<th>Moderate-Risk Factors</th>
<th>High Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>Age greater than or equal to 75 y</td>
<td>Previous stroke, TIA or embolism</td>
</tr>
<tr>
<td>Age 65 to 74 y</td>
<td>Hypertension</td>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Heart failure</td>
<td>Prosthetic heart valve*</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>LV ejection fraction 35% or less</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<td></td>
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</tbody>
</table>

*If mechanical valve, target international normalized ratio (INR) greater than 2.5. NR indicates international normalized ratio; LV, left ventricular; and TIA, transient ischemic attack. Reproduced from reference #2, with permission.
cardiac standpoint, but it can lead to noncardiac side effects: pulmonary fibrosis in <3% of patients (it is reversible if detected early); hyper- or hypothyroidism; hepatitis; photosensitivity; neurologic side effects (ataxia, tremor, neuropathy, rarely optic neuropathy). Pulmonary function testing and a chest radiograph should be performed yearly; thyroid and liver profiles, every six months; and eye exams, as needed for symptoms.

In general, AADs should be initiated in the hospital to monitor QRS duration and QT interval and arrhythmia occurrence over three days. Class Ic agents and amiodarone can be initiated in the outpatient setting if the patient has normal electrolytes, creatinine, QRS durations, and QT interval, and does not have any structural heart disease.²

REFERENCES

12. Morgan DE, Tomlinson CW, Qayumi AK, et al. Evaluation of ventricular contractility indexes in the dog with left ventricular
dysfunction induced by rapid atrial pacing. J Am Coll Cardiol 1989; 14:489-495; discussion 496-498.


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