Strategies for the Management of Postoperative Atrial Fibrillation

Jennifer G. Bekker, PharmD; Tracy E. Macaulay, PharmD, BCPS

Abstract: Atrial fibrillation is an important complication of non-cardiothoracic surgery and is associated with higher hospital costs and increased morbidity. Strategies of rate versus rhythm control have been compared in several studies and patient populations and generally result in equivalent patient outcomes. Hemodynamically unstable patients should be electrically cardioverted for immediate restoration of sinus rhythm. However, in stable patients, a variety of pharmacologic agents can be selected for either rate or rhythm control. Selection of a particular agent should be based on a patient’s comorbidities and preferences, as well as specific characteristics of each agent.

The incidence of postoperative atrial fibrillation is well described in patients undergoing cardiac surgery. Although fewer data are available in other surgical populations, it is well known that patients who develop postoperative supraventricular arrhythmias experience longer hospital stays, increased morbidity, and higher total health care costs.

This is particularly important in orthopedic populations, as procedures are performed with increased frequency in patients of advanced age who are prone to atrial fibrillation. Given the significant clinical and financial consequences, review of atrial fibrillation treatment is vitally important for those who care for postoperative patients.

Drs Bekker and Macaulay are from the University of Kentucky College of Pharmacy, Lexington, Kentucky.

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Correspondence should be addressed to: Tracy E. Macaulay, PharmD, BCPS, University of Kentucky HealthCare, 800 Rose St, H-112B, Lexington, KY 40536 (temaca2@email.uky.edu).

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Rate vs Rhythm Control

When managing a patient who has developed atrial fibrillation postoperatively, an initial strategy of rate control or rhythm control should be selected. Several studies have evaluated the outcomes of rate vs rhythm control in patients with atrial fibrillation, although none have included postoperative patients and some have specifically excluded patients with recent cardiac surgery.

Most studies have assessed mortality as the primary endpoint or part of a composite primary endpoint. In the largest of these studies, patients older than 65 years or with risk factors for stroke were randomized to evaluate the effect of these strategies on all-cause mortality. With an average follow-up of 3.5 years, no significant difference was found for mortality. Furthermore, no significant difference was found for the composite secondary endpoint of mortality, disabling stroke or anoxic encephalopathy, major bleeding, or cardiac arrest. Results were validated in a similar trial, although both were criticized for the low rates of patients with concomitant heart failure.

Questions remained on the best approach to treating atrial fibrillation in patients with systolic heart failure until a trial in 2008 specifically evaluated rhythm- and rate-control strategies in patients with systolic heart failure. This study included patients with persistent or paroxysmal atrial fibrillation <1 year in duration who had an ejection fraction <35% and a history of congestive heart failure. Like the previous studies, no significant difference was found in cardiovascular mortality between treatment arms. It should be noted that since this was a heart failure population, maximally tolerated beta-blocker therapy was recommended in all patients. While significantly more patients in the rate-control group were on beta blockers (88%), a much higher rate of beta blocker use occurred in the rhythm-control group (80%) than in previous trials.
Several trials also evaluated hospitalization rates between rhythm- and rate-control strategies. In each of these, the rhythm-control group had significantly higher rates of hospitalization vs the rate-control group.\(^3,^5,^7\) This difference was primarily due to hospitalizations for initiation of anti-arrhythmic therapy or repeat cardioversions, but also included hospitalizations for medication-associated side effects.

Given similar rates of morbidity and mortality comparing rate- and rhythm-control strategies, the approach is based on the individual patient and clinical scenario. Unlike randomized trials, patients in clinical practice are often not eligible for both treatment arms and have comorbidities or conditions that limit drug selection. Therefore, the largely equivocal outcomes of rhythm and rate control do not always apply. A rate-control strategy is often appropriate for the management of postoperative atrial fibrillation, especially in patients who are asymptomatic, since postoperative atrial fibrillation is commonly self-limiting. In patients who have signs of hemodynamic instability (hypotension, angina, worsening heart failure), urgent direct-current cardioversion may be necessary. In these patients and others who are refractory to rate control, a rhythm control strategy may be more appropriate.\(^8\) Further discussion of each strategy and individual drug selection follows.

### RATE CONTROL STRATEGIES

The goal of rate control is to control the rate of ventricular response to atrial fibrillation. This is primarily achieved through pharmacologic agents that increase the refractory period of atrioventricular-nodal cells. Rate control methods include the use of beta blockers, nondihydropyridine calcium channel blockers, digoxin, or a combination of these agents (Table 1).

Beta blockers can be used for both acute atrial fibrillation control and long-term maintenance. These agents are first-line for acute atrial fibrillation management in hemodynamically stable patients, especially those with preserved ejection fraction and in states of high adrenergic tone, including postoperative stress.\(^3\) In 1 trial, beta blockers alone were more effective at achieving goal heart rate in patients than digoxin or calcium channel blockers alone.\(^6\) Patients initiated on beta blockers also switched drug classes less frequently than patients taking calcium channel blockers or digoxin. This trend was

<table>
<thead>
<tr>
<th>Drug</th>
<th>VW Class; MOA</th>
<th>Dose</th>
<th>Additional Information</th>
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<tbody>
<tr>
<td>Atenolol</td>
<td>Class II; (\beta_1)-adrenergic receptor antagonism</td>
<td>IV: 2.5 mg over 5 min, repeat Q 10 min, max 10 mg; oral: 25-100 mg daily</td>
<td>Decrease dose if CrCl &lt;35</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Class II; (\beta_1)-adrenergic receptor antagonism</td>
<td>IV: 2.5-5 mg over 2 min, repeat Q 2 min, max 20 mg; oral: 12.5-100 mg BID</td>
<td>Good choice in heart failure</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Class II; (\beta_1)-adrenergic receptor antagonism</td>
<td>LD: 500 mcg/kg IV over 1 min; MD: 25-300 mcg/kg/min IV, titrate by 50 mcg/kg/min Q 4 min</td>
<td>Only available IV; higher rate of hypotension; easy to titrate</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Class II; (\beta_1, \beta_2, \alpha_1)-adrenergic receptor antagonism</td>
<td>IV: bolus: 20 mg over 2 min, repeat 20-80 mg Q 10 min to effect, max 300 mg; IVI: 50-300 mg total at 2 mg/min; oral: 100-400 mg BID</td>
<td>Sympathomimetic activity; used for hypertension, not best choice for rate control; caution in asthma</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Class II; (\beta_1, \beta_2, \alpha_1)-adrenergic receptor antagonism</td>
<td>Oral: 3.125-50 mg BID</td>
<td>Good choice in heart failure; caution in asthma</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Class IV; L-type slow (Ca^{2+}) channel antagonism</td>
<td>IV: LD: 0.25 mg/kg over 2 min; MD: 5-15 mg/hr; oral: 120-360 mg/day in divided doses</td>
<td>Do not use in heart failure; risk of hypotension; drug interactions via CYP3A4, including warfarin; interacts with digoxin</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Class IV; L-type slow (Ca^{2+}) channel antagonism</td>
<td>IV: 0.075-0.15 mg/kg over 2 min; oral: 120-360 mg/day in divided doses</td>
<td>Narrow therapeutic window: 0.8-2 ng/mL; toxicity: visual changes, psychiatric disturbances, gastrointestinal; drug interactions via alterations in Mg(^2+) or K(^+), p-glycoprotein, and inhibition of renal excretion</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Other; vagal nerve stimulation, (Na^+/K^+) ATPase antagonism</td>
<td>IV: LD: 0.25 mg every 2 hrs, max 1.5 mg; MD: 0.125-0.375 mg daily; oral: LD: 0.5 mg; MD: 0.125-0.375 mg daily</td>
<td>Good choice in heart failure; caution in heart failure; use with caution in heart failure; p-glycoprotein, and inhibition of renal excretion</td>
</tr>
</tbody>
</table>

**Abbreviations:** BID, twice daily; CI, continuous infusion; CrCl, creatinine clearance in mL/min; IV, intravenous; IVI, intravenous infusion; LD, loading dose; MD, maintenance dose; MOA, mechanism of action; Q, every; VW, Vaughan-Williams.
also observed in patients with systolic heart failure.

Several beta-blocking agents can be administered intravenously for acute heart rate control. Metoprolol and atenolol have both been shown to significantly decrease heart rate at rest and with exertion vs placebo.\textsuperscript{10,11} Esmolol is another attractive option in acute management of atrial fibrillation and is as effective as verapamil for acute heart rate control.\textsuperscript{12} Its quick onset and short duration of action make it easily titratable as a drip, although it is associated with a greater incidence of hypotension than atenolol or metoprolol. All 3 of these agents are selective for β1-adrenergic receptors, but may lose their selectivity with high doses.

Long-term use of certain beta blockers is associated with decreased mortality in systolic heart failure; however, because beta blockers have negative inotropic activity in addition to negative chronotropic activity, caution should be used in these patients during acute administration. Titration in patients with a low ejection fraction should be executed slowly and with close hemodynamic monitoring. Metoprolol, atenolol, and esmolol are β1-selective; thus, they are generally safe to use in asthmatic patients, although caution should be used at higher doses due to loss of β1-receptor selectivity.

Digoxin exerts its main effects on heart rate through vagal stimulation, decreasing sympathetic tone and atrioventricular-nodal conduction. Consequently, digoxin is effective at controlling heart rate at rest, but is less effective in states of increased sympathet ic activity. This agent may be particularly useful in patients with concomitant systolic heart failure due to its ability to enhance muscle contractility through inotropic effects on the cardiac muscle. However, it is generally not recommended first-line for acute rate control due to its longer onset of action. Digoxin has been shown to enhance rate control in combination with beta blockers or calcium channel blockers vs either agent alone, so it may be useful as an adjunctive therapy.\textsuperscript{9} It should also be noted that digoxin has a narrow therapeutic window; therefore, monitoring of drug concentrations, often in coordination with a pharmacist, is recommended.

The nondihydropyridine calcium channel blockers, diltiazem and verapamil, can be used for acute and long-term heart rate control and are effective for heart rate control both at rest and with exertion.\textsuperscript{13,14} Diltiazem and verapamil are both negative inotropes and are generally not recommended in patients with severe systolic heart failure. Due to their vasodilatory properties, they can cause hypotension, especially after acute intravenous administration, although this is more often reported with verapamil than diltiazem. Both agents interact with a significant number of drugs, including digoxin; serum levels of digoxin should be monitored when used concomitantly to prevent toxicity.

**Rhythm Control Strategies**

Rhythm control is useful for patients who are hemodynamically unstable or are refractory to rate control. As previously mentioned, direct-current cardioversion is considered first-line in hemodynamically unstable patients. If a patient is refractory to the first attempt at direct-current cardioversion, administration of an antiarrhythmic drug prior to the second attempt is warranted. Cardioversion may also be attempted pharmacologically in patients who are refractory to rate control or who have symptomatic atrial fibrillation.

A summary of the agents commonly used for rhythm control is found in Table 2. Of note, thromboembolic events are well described in patients undergoing cardioversion when atrial fibrillation is present >48 hours; therefore, anticoagulation according to the American College of Cardiology/American Heart Association guidelines should be considered prior to chemical or electrical cardioversion.

Flecainide and propafenone are both effective for cardioversion of recent-onset atrial fibrillation. A significantly faster response is seen with intravenous vs oral administration of either agent. Both agents are contraindicated in systolic heart failure due to negative inotropic effects and risk of cardiac decompensation. Evidence also indicates that flecainide increases mortality due to arrhythmias, cardiac arrest, or other cardiac deaths in patients with a history of myocardial infarction.\textsuperscript{15} Therefore, flecainide is contraindicated in patients with coronary artery disease, and this contraindication has been extended to all other class IC antiarrhythmics, including propafenone.

Amiodarone, a class III antiarrhythmic medication, is effective for acute rhythm conversion, but has a slower onset of action than flecainide and propafenone.\textsuperscript{16,17} This delay is likely due to the extensive distribution of amiodarone into the tissues and its long pharmacologic half-life. Thus, a loading dose strategy must be used when initiating amiodarone (Table 2).

Amiodarone is also an effective rate control agent, since it possesses both beta-adrenergic and calcium channel-blocking activity.\textsuperscript{18} Consequently, patients who experience episodes of atrial fibrillation while on amiodarone may continue to be effectively rate controlled. Another potential advantage includes its established safety in patients with a history of systolic heart failure or coronary artery disease. Potential long-term side effects require monitoring and often preclude amiodarone from being the drug of choice in younger patients requiring long-term therapy (Table 2).

Other class III antiarrhythmics include the recently Food and Drug Administration-approved dronedarone, sotalol, dofetilide, and ibutilide. Dronedarone is pharmacodynamically similar to amiodarone, and while it has not been studied for cardio-
version of patients with acute atrial fibrillation, it prolongs the time to recurrence of atrial fibrillation in patients recently cardioverted.\textsuperscript{18} It is important to consider that unlike other medications in this class, it is contraindicated in patients with severe heart failure due to increased mortality.\textsuperscript{19} Recent concerns have also been raised over hepatotoxicity risk.

Sotalol and dofetilide have important niches in therapy; however, both carry a relatively high risk of torsades de pointes and should be initiated in the hospital under the direction of a trained electrophysiologist. In other comparator trials, sotalol was less effective for cardioversion than flecainide, propafenone, or ibutilide, but was an effective agent for rhythm maintenance after cardioversion.\textsuperscript{20} Dofetilide has been shown effective for cardioversion and maintenance of sinus rhythm vs placebo and sotalol.\textsuperscript{17,21} Both agents can be used in patients with coronary artery disease and systolic heart failure.\textsuperscript{22}

Ibutilide is indicated only for cardioversion vs maintenance of sinus rhythm. In trials, it was more effective than placebo and outperformed both intravenous procainamide and intravenous sotalol for cardioversion within 30 to 90 minutes.\textsuperscript{23} Ibutilide is indicated only for cardioversion and is most efficacious for terminating arrhythmias of shorter duration.\textsuperscript{24,25} Like sotalol, ibutilide is associated with high rates of torsades de pointes and must be administered under supervision.\textsuperscript{26} Patients should be supervised for at least 4 hours following ibutilide infusion for potential electrocardiogram changes. Magnesium and potassium levels should be within the upper limits of normal, and patients are often supplemented prophylactically to minimize the potential for arrhythmias. Use should be avoided in patients with coronary artery disease or systolic heart failure due to higher risk of arrhythmias.

<table>
<thead>
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<th>Dose</th>
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<tbody>
<tr>
<td>Procainamide</td>
<td>Class IA; moderate Na\textsuperscript{+} channel antagonism</td>
<td>LD: bolus: 100 mg IV over 2 min; repeat Q 5 min as needed up to 500 mg IV; IVI: 20 mg/min for 25-30 min to total 500-600 mg as needed, max 1 g; MD: 2-6 mg/min IV</td>
<td>Drug of choice for Wolf-Parkinson-White; may cause hypotension, myopathies, blood dyscrasias, and SLE; only available IV</td>
</tr>
<tr>
<td>Flecainide</td>
<td>Class IC; strong Na\textsuperscript{+} channel antagonism</td>
<td>IV: 1.5-3 mg/kg over 10-20 min; oral: LD: 200 mg if &lt;70 kg, 300 mg if &gt;70 kg; MD: 50-150 mg BID</td>
<td>Contraindicated in heart failure and CAD; decrease dose if CrCl &lt;35; may cause ophthalmic problems</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Class IC; strong Na\textsuperscript{+} channel antagonism</td>
<td>IV: 1.5-2 mg/kg over 10-20 min; oral: LD: 450 mg if &lt;70 kg, 600 mg if &gt;70 kg; MD: 450-900 mg/day divided Q 8 h (IR) or 12 h (XR)</td>
<td>Contraindicated in heart failure and CAD; decrease dose in hepatic dysfunction; may cause dysgeusia</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Class III; K\textsuperscript{+} channel antagonism, Na\textsuperscript{+} channel antagonism</td>
<td>1 mg IV over 10 min (use 0.1 mg/kg if &lt;60 kg), repeat in 10 min if needed</td>
<td>Avoid in CAD or heart failure; high risk of torsades de pointes-monitor K\textsuperscript{+} and Mg\textsuperscript{2+}</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Class III; rapid K\textsuperscript{+} channel antagonism</td>
<td>Oral: 500 mcg BID if CrCl &gt;60, 250 mcg BID if CrCl 40-60, 125 mcg BID if CrCl 20-40; decrease MD if QTc increases &gt;15% or &gt;500 msec 2-3 h after dose</td>
<td>Contraindicated if CrCl &lt;20; safe in CAD and heart failure; initiation requires extensive monitoring of QTc, K\textsuperscript{+}, Mg\textsuperscript{2+}; drug interactions via CYP3A4</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Class III; K\textsuperscript{+} channel and β-adrenergic antagonism</td>
<td>IV: bolus: 5-10 mg slowly; MD: 75-150 mg over 5 h BID; oral: 80-160 mg BID</td>
<td>Contraindicated if CrCl &lt;40; dose decrease if CrCl &lt;60; risk of torsades de pointes</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Class III; K\textsuperscript{+}, Na\textsuperscript{+}, Ca\textsuperscript{2+} channel and β-adrenergic receptor antagonism</td>
<td>LD: 5 to 7 mg/kg IV over 30-60 min, then 1.2-1.8 g/day via IV or or divided oral doses to 10 g total; MD: 200-400 mg oral daily; dose can be titrated up Q 3 days if QTc &lt;520 msec</td>
<td>Safe in CAD and heart failure; drug interactions via CYP3A4, including warfarin; interacts with digoxin; long-term hepatic, pulmonary, thyroid, and ocular toxicities</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Class III; K\textsuperscript{+}, Na\textsuperscript{+}, Ca\textsuperscript{2+} channel and β-adrenergic receptor antagonism</td>
<td>Oral: 400 mg BID with food</td>
<td>Contraindicated in NYHA class IV heart failure or class II-III with decompensation in last 6-8 wk; drug interactions via CYP3A4; interacts with digoxin</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; CAD, coronary artery disease; CrCl, creatinine clearance in mL/min; IR, immediate release; IV, intravenous; IVI, intravenous infusion; LD, loading dose; MD, maintenance dose; MOA, mechanism of action; NYHA, New York Heart Association; Q, every; SLE, systemic lupus erythematosus; VW, Vaughan-Williams; XR, extended release.
Orthopedic surgery patients are often at risk for developing postoperative atrial fibrillation due to stress, comorbidities, and increased age. In the presence of hemodynamic instability, direct-current cardioversion is indicated for immediate restoration of sinus rhythm. Strategies of rate control and rhythm control exhibit similar outcomes in most studies; pharmacologic therapy should be based on specific characteristics of each agent, the acuity of the situation, patient comorbidities, and patient preference. Aspirin is recommended for stroke prevention in patients with minimal additional risk factors, while long-term anticoagulation is recommended in patients at moderate to high risk of stroke. Management of atrial fibrillation should be executed in coordination with a cardiologist, electrophysiologist, and/or clinical pharmacy specialist.

**THE BOTTOM LINE**

- Orthopedic surgery patients are often at risk for developing postoperative atrial fibrillation due to stress, comorbidities, and increased age.
- In the presence of hemodynamic instability, direct-current cardioversion is indicated for immediate restoration of sinus rhythm.
- Strategies of rate control and rhythm control exhibit similar outcomes in most studies; pharmacologic therapy should be based on specific characteristics of each agent, the acuity of the situation, patient comorbidities, and patient preference.
- Aspirin is recommended for stroke prevention in patients with minimal additional risk factors, while long-term anticoagulation is recommended in patients at moderate to high risk of stroke.
- Management of atrial fibrillation should be executed in coordination with a cardiologist, electrophysiologist, and/or clinical pharmacy specialist.

**REFERENCES**


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