

# Postoperative Atrial Fibrillation

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## KEYWORDS

- Atrial fibrillation • Arrhythmia
- Postoperative • Antiarrhythmic • Surgery

The incidence of atrial fibrillation (AF) in the general population is estimated as 0.4% in patients younger than 70 years, and 2% to 4% in older patients.<sup>1</sup> The incidence of AF is higher in patients with cardiovascular disease. The Cardiovascular Health Study demonstrated that the prevalence of AF was 9.1%, 4.6%, and 1.6% in patients with clinical, subclinical and no cardiovascular disease, respectively.<sup>2</sup> Atrial arrhythmias occur frequently after major cardiothoracic surgery and result in increased morbidity and length of hospital stay.<sup>3–6</sup> The prevalence of atrial arrhythmias after cardiac surgery has been reported to vary between 10% and 65%,<sup>4,7–27</sup> depending on type and technique of surgery, patient characteristics, method of arrhythmia surveillance, and definition of arrhythmia. Postoperative AF may occur in up to 40% of patients undergoing coronary artery bypass surgery,<sup>28–31</sup> 35% to 40% after valvular surgery,<sup>13,28,32</sup> 60% after combined coronary artery bypass graft (CABG) and valve surgery, and 11% to 24% after cardiac transplantation.<sup>13,33</sup> In a large, multicenter, international cohort study, the majority of the initial episodes of AF occurred within the first few (2–5) days after CABG surgery (**Fig. 1**).<sup>29</sup>

## PATHOGENESIS

The electrophysiologic mechanisms of AF after cardiac surgery are not yet well understood. However, preexisting atrial substrate, such as atrial fibrosis or dilatation may predispose to atrial fibrillation.<sup>34</sup> Perioperative factors, such as atrial injury or ischemia, inflammation, increase in adrenergic tone, catecholamines, atrial stretch from volume overload, or electrolyte disturbances, may trigger

postoperative AF in patients who are susceptible to AF through dispersion of atrial refractoriness,<sup>35,36</sup> nonuniform atrial conduction,<sup>37</sup> or increased premature atrial complexes.<sup>38</sup>

Expression of proinflammatory cytokines and activation of oxidases with an increase in oxidative stress have also been implicated in the genesis of postoperative AF.<sup>39–46</sup> Oxidative stress may decrease atrial effective refractory period and may also promote progressive fibrosis.<sup>47</sup> Consistent with these mechanisms, steroids and statins have been shown to attenuate profibrillatory effects of oxidative stress.<sup>48,49</sup>

## CLINICAL IMPLICATIONS

Postoperative AF is associated with increased incidence of postoperative complications and longer length of hospital stay.<sup>7,8,13,29,30</sup> Patients with postoperative AF are more likely to develop hypotension, pulmonary edema,<sup>19</sup> and cerebrovascular accident.<sup>7,8,13,50,51</sup> The incidence of stroke is significantly higher in patients who developed AF after cardiac surgery (3.3% versus 1.4%).<sup>13</sup> The incidence of a composite outcome, including encephalopathy, decline in Mini-Mental State Examination score, increase in National Institutes of Health Stroke Scale score, renal dysfunction, renal failure, pneumonia, mediastinitis or deep sternal wound infection, sepsis, harvest site infection, vascular catheter infection, and genitourinary infection is also higher in patients with postoperative AF (22.6% versus 15.4%).<sup>29</sup> The cost of care on patients who developed postoperative AF was increased by approximately \$10,000 per patient.<sup>30</sup>

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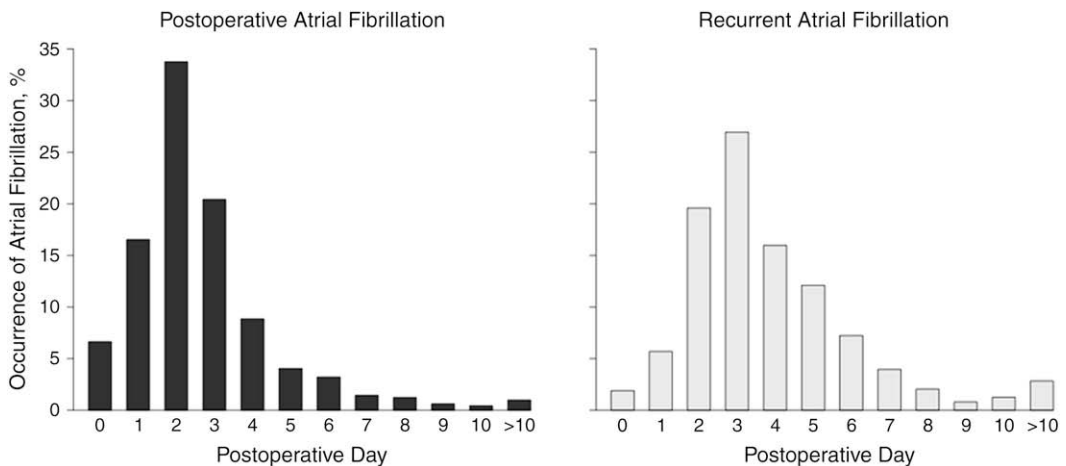
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The denominators are 1503 patients for postoperative atrial fibrillation and 640 for recurrent atrial fibrillation.

**Fig. 1.** Postoperative atrial fibrillation after CABG surgery was most common on postoperative day 2 (*left graph*) and recurrence was most common on postoperative day 3 (*right graph*). More than 60% of initial recurrence occurred within 2 days of first onset. (Reproduced from Mathew JP, Fontes ML, Tudor, IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004;291:1720; with permission.)

Postoperative AF is also associated with lower in-hospital and long-term survival. A retrospective cohort study found that patients who developed AF after CABG surgery had higher in-hospital mortality (odds ratio or OR 1.7,  $P = .0001$ ) and a decrease in survival at 4 to 5 years (74% versus 87%,  $P < .0001$ ).<sup>30</sup>

#### PREDICTORS OF ATRIAL FIBRILLATION AFTER CARDIAC SURGERY

Several clinical factors have been shown to be associated with an increased incidence of AF following cardiac surgery.<sup>28,29</sup> These include age, gender, hypertension, prior history of AF, obesity, chronic obstructive pulmonary disease (COPD), left atrial size, and left ventricular ejection fraction.<sup>52</sup>

Older age has been consistently shown in multiple studies as a predictor for postoperative AF. Every 10-year increase in age is associated with a 75% increase in the odds of developing AF and age greater than 70-years old alone is considered to be high risk.<sup>29</sup> The increase in postoperative AF in older age is likely related to degenerative changes in atrial myocardium, dilatation, and nonuniform anisotropic conduction.<sup>53</sup>

Men are more likely to develop AF after CABG surgery than women.<sup>7-9,21,27</sup> Previous history of AF also increases the risk of postoperative AF.<sup>4,11</sup> Hypertension is a predictor of AF in the general population as well as after cardiac surgery.<sup>7,8</sup> Higher body mass index has been shown to be an independent predictor for new-onset AF after cardiac surgery.<sup>52</sup> There is a strong correlation between body mass index and left atrial

enlargement.<sup>54-56</sup> Patients with COPD have been reported to have a 43% increase in the probability of developing postoperative AF,<sup>29</sup> likely because of an increase in P-wave dispersion and heterogeneity of conduction.<sup>57</sup>

#### PREVENTION

The incidence of AF after cardiac surgery is high, especially in patients with multiple risk factors described above. Although it is often transient, postoperative AF often is associated with increased morbidity and prolonged intensive care unit and hospital stay. Therefore, prophylactic therapy should be considered in all patients, particularly high risk, who are considered for cardiac surgery. Pharmacologic therapy and cardiac pacing have been evaluated in several trials.

#### Pharmacologic Prophylaxis

##### $\beta$ -adrenergic receptor antagonists

$\beta$ -adrenergic receptor antagonists alone or combined with other antiarrhythmic drugs, such as digitalis or calcium channel blockers, have been commonly used to prevent postoperative AF. Beta-blockers attenuate the effects of beta-adrenergic stimulation, which facilitates vulnerability to AF after cardiac surgery. The efficacy of beta-blockers in reducing the incidence of postoperative AF has been demonstrated in several trials. Therefore, beta-blockers should be administered perioperatively in patients without contraindications as the standard therapy to reduce the incidence of AF after CABG.<sup>58</sup>

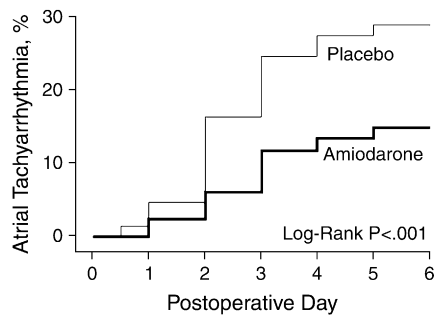
### Sotalol

Sotalol, a combined  $\beta$ -receptor and potassium channel-blocking agent, has been shown to decrease postoperative AF by 41% to 93% in comparison to placebo.<sup>59–66</sup> Although sotalol was well tolerated, ventricular arrhythmias were reported in two patients among the six trials.<sup>60,61,63–66</sup> However, it is not clear whether sotalol provides an incremental antiarrhythmic effect for postoperative AF prophylaxis compared with regular beta-blockers. Sotalol is considered a class IIb indication for postoperative arrhythmia prevention in the American College of Cardiology/American Heart Association (ACC/AHA) 2004 guideline for CABG surgery, and low-dose sotalol should be considered in patients who are not candidates for traditional beta-blockers.<sup>58</sup>

### Amiodarone

Amiodarone is a class III antiarrhythmic agent that inhibits multiple ion channels and  $\alpha$ - and  $\beta$ -adrenergic receptors. The efficacy of amiodarone in preventing postoperative AF has been evaluated in multiple randomized trials using various regimens. Overall, it has been shown that amiodarone significantly reduces the incidence of postoperative AF, whether it is administered orally,<sup>67–71</sup> intravenously,<sup>72–75</sup> or both.<sup>76–79</sup> A meta-analysis of 10 trials confirms that amiodarone therapy is associated with a significant reduction in the incidence of postoperative AF or atrial flutter (relative risk or RR 0.64; 95% confidence interval or CI, 0.55–0.75).<sup>80</sup>

In the largest double-blind, randomized, controlled trial of prophylactic oral amiodarone for the prevention of arrhythmias (PAPABEAR),<sup>70</sup> postoperative atrial tachyarrhythmias were reduced by 48% in patients who received oral amiodarone (10 mg/kg daily) 6 days before surgery through 6 days after surgery, in comparison to placebo, as shown in **Fig. 2**. A reduction in postoperative AF was also observed across subgroups predefined according to age, type of cardiac surgery, and concomitant beta-blocker therapy. Although oral amiodarone has been shown to be effective in postoperative AF prophylaxis, it should be administered several days before the surgery. A single-day loading dose of oral amiodarone given 1 day before the cardiac surgery has been shown to be ineffective in preventing postoperative AF.<sup>81</sup> However, intravenous formulation acts more rapidly than oral preparation. The Amiodarone Reduction in Coronary Heart trial<sup>73</sup> demonstrated that low dose intravenous amiodarone (1 g/day for 2 days) administered immediately after cardiac surgery was safe and effective in reducing the incidence of postoperative AF.



No. at Risk	301	295	284	249	223	199	138
Placebo							
Amiodarone	299	298	291	278	260	238	169

**Fig. 2.** Postoperative atrial tachyarrhythmia occurred in 48 of 299 (16.1%) patients who were on amiodarone and 89 of 302 (29.5%) patients who were on placebo (hazard ratio or HR, 0.52; 95% CI 0.34–0.69;  $P < .001$ ). (Reproduced from Mitchell LB, Exner DV, Wyse DG, et al. Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization valve replacement, or repair; PAPABEAR: A randomized controlled trial. *JAMA* 2005;294:3093; with permission.)

The efficacy of amiodarone to prevent postoperative AF was shown to be similar to that of beta-blockers in the meta-analysis of prophylactic therapies against postoperative AF.<sup>82</sup> Side effects of amiodarone therapy were uncommon in clinical trials. Amiodarone was discontinued mainly because of bradycardia. Amiodarone is considered a class IIa indication in ACC/AHA 2004 guidelines for CABG surgery. Preoperative administration of amiodarone is an appropriate prophylactic therapy for patients at high risk for postoperative AF who have contraindications to therapy with beta-blockers.<sup>58</sup>

### Calcium channel antagonists

Prior studies have demonstrated that verapamil does not have a significant effect on the incidence of postoperative AF.<sup>15,23,24,83</sup> A meta-analysis of randomized, controlled trials also confirmed that verapamil does not reduce the probability of developing supraventricular arrhythmias after CABG (OR 0.91, CI 0.57–1.46).<sup>84</sup> Similar to verapamil, diltiazem was not effective in preventing postoperative AF when compared with placebo.<sup>85</sup> Therefore, nondihydropyridine calcium channel blockers are considered a class IIa indication primarily for ventricular rate control during AF. However, calcium channel blockers have no role in prophylaxis of postoperative AF.<sup>58</sup>

### Digitalis

The efficacy of digitalis for postoperative AF prophylaxis has been previously evaluated in

randomized, controlled trials. However, results have been conflicting about the potential benefits of digitalis for postoperative AF prophylaxis. Two meta-analyses<sup>84,86</sup> showed no significant reduction in the incidence of supraventricular arrhythmias after CABG in patients receiving digitalis in comparison to controls. However, digitalis may be helpful when administered with beta-blockers. Similar to calcium channel blockers, digitalis has a class IIa indication primarily for ventricular rate control. There is no indication to use digitalis for prevention of postoperative AF.

### **Magnesium**

Hypomagnesemia is common after cardiac surgery and may predispose patients to postoperative arrhythmias. The efficacy of prophylactic magnesium administration on postoperative arrhythmias have been evaluated previously. However, the results have been variable. A meta-analysis of randomized, controlled trials suggested that prophylactic treatment with magnesium reduces postoperative supraventricular arrhythmias by 23% (AF by 29%).<sup>87</sup> Because of conflicting results, prophylactic magnesium therapy is not routinely recommended. However, serum magnesium levels should be maintained in patients undergoing cardiac surgery.<sup>88</sup>

### **Statins**

Statin therapy has been shown to reduce the incidence of postoperative AF after noncardiac thoracic<sup>89</sup> and CABG surgery.<sup>90</sup> Statin therapy was associated with a reduction of postoperative AF regardless of the C-reactive protein levels. A recent randomized, controlled trial demonstrated that atorvastatin (40 mg/d) starting 7 days before cardiac surgery significantly reduced the incidence of postoperative AF in comparison to placebo (OR 0.39, 95% CI 0.18–0.85).<sup>91</sup> Because benefits of statins, besides prevention of postoperative AF, have been well established in patients with coronary artery disease, all patients without contraindications for statin therapy should receive it before CABG surgery.

### **Corticosteroids**

Corticosteroid treatment has been shown to reduce the incidence of postoperative AF after cardiac surgery in previous randomized, controlled trials.<sup>92,93</sup> A prospective, double-blind, randomized multicenter study found that intravenous hydrocortisone reduced the relative risk of postoperative AF by 37% compared with placebo. Corticosteroids may decrease the incidence of postoperative AF by reducing inflammatory response after the surgery. No significant adverse

events related to corticosteroid treatment were reported in these trials.<sup>92,94</sup>

### **Atrial Pacing**

The efficacy of temporary atrial overdrive pacing on postoperative AF prevention has been evaluated in a number of studies. Algorithm and site of pacing varied among these studies. Although the results of postoperative AF reduction with right atrial pacing are conflicting,<sup>95–101</sup> most studies showed no significant reduction in postoperative AF.<sup>96–100</sup> In contrast, bi-atrial overdrive pacing has been shown to be effective in preventing postoperative AF.<sup>99,100,102</sup> Postoperative atrial pacing at the Bachmann's bundle was also evaluated in a prior study.<sup>101</sup> Although pacing at the Bachmann's bundle was associated with better pacing thresholds, it did not reduce the incidence of postoperative AF.

### **Therapy**

Although prophylactic therapy can reduce the incidence of postoperative AF, some patients will still develop AF after cardiac surgery. Spontaneous conversion of AF may occur within 2 hours in 15% to 30% and within 24 hours in 25% to 80% of the patients. If AF persists or recurs, two therapeutic strategies of rate and rhythm control may be considered.

### **Rate control**

Rate control is a reasonable option in patients who are asymptomatic and hemodynamically stable. A prior study showed that patients with postoperative AF could be safely discharged home in AF after ventricular rate had been controlled and anticoagulation initiated.<sup>103</sup> Medications that slow atrioventricular nodal conduction, such as beta-blockers, nondihydropyridine calcium-channel blockers (verapamil or diltiazem), or digoxin can be used for rate control. However, beta-blockers seem to be the most effective agent for patients with postoperative AF with rapid ventricular response because of augmented postoperative sympathetic tone. Digoxin alone may control ventricular rate at rest but rarely is adequate when sympathetic tone is high in the postoperative period. Combined therapy may be required to achieve adequate heart rate control. In patients who cannot tolerate beta-blockers or calcium-blockers, intravenous amiodarone is an alternative option for ventricular rate control.<sup>104</sup> Because amiodarone has both sympatholytic and calcium channel blocker action, it is effective in slowing atrioventricular nodal conduction in patients with AF and rapid ventricular response rates.

### Rhythm control

Rhythm control is preferred in patients who are highly symptomatic or hemodynamically unstable or when anticoagulation is contraindicated. Sinus rhythm can be restored by either electrical or pharmacologic cardioversion. Direct-current cardioversion should be considered in patients who are hemodynamically unstable because of hypotension or heart failure. In patients with unsuccessful electrical cardioversion or early recurrence of AF, direct-current cardioversion may be repeated after administration of antiarrhythmic drugs, such as ibutilide<sup>105</sup> or amiodarone. Electrical cardioversion using a rectilinear biphasic waveform is more effective than a monophasic sinusoidal waveform.<sup>106</sup>

Pharmacologic conversion can be achieved by class IA (quinidine, procainamide, and disopyramide), class IC (flecainide and propafenone), and class III (amiodarone, sotalol, ibutilide, and dofetilide) agents. Although intravenous administration of class IA and IC agents in patients with AF after CABG surgery results in conversion to sinus rhythm in 40% to 75% of patients within 1 hour,<sup>107–110</sup> and in 50% to 90% of patients within 12 hours,<sup>16,111–114</sup> class IA agents are not available in the United States and can be proarrhythmic in patients with ischemia or impaired left ventricular systolic function. The efficacy of intravenous class III agents for the acute conversion of postoperative AF appears comparable to class IA and IC drugs. However, amiodarone is preferable over the other antiarrhythmic drugs because it also provides ventricular rate control and is less proarrhythmic, particularly in patients with a reduced ejection fraction.

### ANTICOAGULATION

Atrial fibrillation is associated with a higher risk of thromboembolic events. There are no specific guidelines for antithrombotic therapy in patients postoperative AF. Antithrombotic therapy is recommended for all patients with AF that persists more than 48 hours to prevent thromboembolic events.<sup>34</sup> The type and intensity of antithrombotic therapy is based upon the risk of thromboembolism. Warfarin with a target international normalized ratio of 2 to 3 is recommended for patients with prior thromboembolism or more than 1 moderate risk factor (age >75, hypertension, heart failure, impaired left ventricular systolic function, and diabetes mellitus). Aspirin 81 mg to 325 mg daily is recommended as an alternative to warfarin in low-risk patients or in those with contraindications to warfarin. Routine anticoagulation with heparin to prevent thrombus formation in patients with postoperative AF is generally not advised because of

#### Box 1

#### Current recommendations for management of postoperative AF

##### Class I

Unless contraindicated, treatment with an oral beta-blocker to prevent postoperative AF is recommended for patients undergoing cardiac surgery. (Level of evidence: A)

Administration of AV nodal blocking agents is recommended to achieve rate control in patients who develop postoperative AF. (Level of evidence: B)

##### Class IIa

Preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and represents appropriate prophylactic therapy for patients at high risk for postoperative AF. (Level of evidence: A)

It is reasonable to restore sinus rhythm by pharmacologic cardioversion with ibutilide or direct-current cardioversion in patients who develop postoperative AF as advised for nonsurgical patients. (Level of evidence: B)

It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative AF, as recommended for other patients who develop AF. (Level of evidence: B)

It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as recommended for nonsurgical patients. (Level of evidence: B)

##### Class IIb

Prophylactic administration of sotalol may be considered for patients at risk of developing AF following cardiac surgery. (Level of evidence: B)

*Adapted from Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 2006; 48:854–906; with permission.*

the risk for postoperative bleeding.<sup>28</sup> Although the incidence of large pericardial effusions and cardiac tamponade was found to be higher in patients receiving warfarin,<sup>115,116</sup> it still can be

administered in the immediate after-CABG period with only a minimal risk of bleeding<sup>116</sup> in most patients.

Current recommendations for management of postoperative AF according to the ACC/AHA and European Society of Cardiology 2006 guidelines for the management of patients with atrial fibrillation<sup>34</sup> are summarized in **Box 1**.

## SUMMARY

Atrial fibrillation is a common arrhythmia that occurs after cardiac surgery. It is associated with an increase in morbidity, length of hospital stay, and mortality. Patients who are at higher risk of postoperative atrial fibrillation should receive prophylactic treatment. Atrial fibrillation usually resolves spontaneously after heart rate is controlled; however, if patients are highly symptomatic or hemodynamically unstable, sinus rhythm should be restored by electrical or pharmacologic cardioversion. Patients with atrial fibrillation of more than 48 hours should receive antithrombotic therapy for thromboembolism prevention.

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