

# Atrial fibrillation post cardiac bypass surgery

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## Access this article online

Website: [www.avicennajmed.com](http://www.avicennajmed.com)

DOI: 10.4103/2231-0770.102280

## Quick Response Code:



## ABSTRACT

Atrial fibrillation occurs in 5-40% patients after coronary artery bypass graft surgery. Atrial fibrillation increases mortality and morbidity in the post-operative period. We sought to conduct a comprehensive review of literature focusing on pathophysiology, risk factors, prevention and treatment of post coronary artery bypass graft atrial fibrillation.

**Key words:** AF, AF post CABG, atrial fibrillation post open heart, CABG

## DEFINITION

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with subsequent deterioration of mechanical function. Postoperative atrial fibrillation (POAF) is common after both cardiothoracic and noncardiothoracic surgery. AF has been reported in up to 5-40% of patients in the early postoperative period following coronary artery bypass graft (CABG),<sup>[1-3]</sup> in 37-50% after valve surgery,<sup>[4]</sup> 64% undergoing mitral valve replacement plus CABG, 49% undergoing aortic valve replacement (AVR) plus CABG and in 12% after cardiac transplantation.<sup>[5,6]</sup> POAF after cardiac surgery tends to occur within 2-4 days after the procedure with a peak incidence on postoperative day 2.<sup>[1]</sup> In a study by Aranki *et al.* on CABG patients, 70% and 94% patients developed POAF before the end of postoperative day 4 and 6, respectively.<sup>[7]</sup>

AF worsens a patient's hemodynamic status and increases the risk of congestive heart failure (CHF), embolic events and longer ICU stays. AF may also necessitate the use of atrioventricular nodal blocking and antiarrhythmics, which may increase the need for cardiac pacing. Stroke is a major complication seen in 2% of CABG patients, 37% of whom had preceding AF. Apart from a higher risk of stroke (OR 2.02), POAF after CABG was associated with greater in-hospital mortality (OR 1.7) and worse survival (74% vs. 87%) at long-term follow-up (4 - 5 years).<sup>[8]</sup> After controlling for a comprehensive array of risk factors associated with

postcardiac surgery adverse outcomes, risk of long-term mortality in patients who developed new-onset POAF was 29% higher, for patients who underwent CABG.<sup>[9]</sup>

The impact of POAF on hospital resources is substantial and was estimated to lengthen hospital stay by 4.9 days, with an extra cost of \$10,000 to \$11,500 in hospital stay costs in the U.S.<sup>[7]</sup> Knowing that there are at least 640,000 open heart surgeries/ year in the U.S. according to the American Heart Association statistics in 2004 and assuming an incidence of 30% of POAF, the extra cost related to this postoperative complication could be estimated at a staggering \$2 billion/year.<sup>[10]</sup>

## PATHOPHYSIOLOGICAL MECHANISMS

The precise mechanism of post-CABG AF is still being investigated. The following pathophysiological factors play an important role: atrial factors (age-related structural changes such as atrial dilatation, hypertrophy, fibrosis and senile amyloidosis), postoperative inflammation (making the myocardium a tissue mosaic of differing refractory periods and conduction velocities susceptible to aberrant electrical activity, conduction and re-entry - the 'anisotropic' atrium,<sup>[11,12]</sup> pericarditis,<sup>[13]</sup> electrical remodeling (shortening of the effective refractory period),<sup>[14-16]</sup> autonomic imbalance (over activation of the sympathetic nervous system in response to stress, increased vagal tone,<sup>[17-20]</sup> atrial incision, perioperative ischemia,<sup>[21]</sup> alterations in atrial oxidative

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stress<sup>[1,22]</sup> increased expression of the gap-junctional protein connexin 40,<sup>[23]</sup> inflammatory mediators and leucocytosis after extracorporeal circulation.<sup>[24,25]</sup> Some theories proposed for AF in general are ‘Theory of Multiple Wavelets’<sup>[5,26-28]</sup> and ‘Theory of Unifocal/ Multifocal Impulse Formation and Re-entry’<sup>[29-31]</sup> However, it is unclear if these theories hold good for post-CABG AF.

## RISK FACTORS

Many risk factors have been investigated in the past; however, we will focus on those found consistently in multivariate analyses in major trials.

### Preoperative

Advanced age;<sup>[7,32,33]</sup> male gender; genetic predisposition assessed by the interleukin-6 promoter gene variant,<sup>[34]</sup> history of CHF or AF; chronic obstructive pulmonary disease, chronic renal insufficiency, diabetes mellitus, rheumatic heart disease,<sup>[2,5,33,35]</sup> previous cardiac surgery, metabolic syndrome, obesity,<sup>[36-38]</sup> absence or withdrawal of beta-blocker or ACE inhibitor treatment, high pre-op Brain Natriuretic Peptide,<sup>[39]</sup> severe proximal right coronary artery stenosis,<sup>[40]</sup> mitral valve disease,<sup>[41]</sup> increased left atrial size,<sup>[42]</sup> decreased left ventricular ejection fraction, left atrial volume index  $\geq$  75 mL/m,<sup>[43]</sup> preoperative increase in P wave duration on surface ( $>116$  ms) or on signal averaged ( $>140$  ms) EKG<sup>[44-46]</sup> and blood transfusion before surgery.<sup>[44-47]</sup>

Age is consistently the independent factor most strongly associated with POAF. For every decade there is a 75% increase in the odds of developing POAF and based on age alone, anyone older than 70 years is considered to be at high risk for developing AF.<sup>[2]</sup> Age-associated changes in the atria such as dilatation, muscle atrophy, and decreased conduction may explain the strong association.

Concomitant valvular heart disease is also associated with postoperative atrial tachyarrhythmias. It is unclear whether this is because of the additional complexity of the required surgical procedure or the valvular disease itself. Neither the degree of ischemia nor the extent of coronary artery disease is a consistent predictor of postoperative atrial tachyarrhythmias.<sup>[3,48,49]</sup>

When beta-blocker was continued or started postoperatively, POAF risk was significantly reduced by 51–68%.<sup>[2]</sup> The use of adrenergic drugs is an independent risk factor for AF post-CABG.<sup>[50]</sup>

### Intraoperative

Prolonged mechanical ventilation, atrial ischemia, hypokalemia,<sup>[51]</sup> hypomagnesemia.<sup>[52]</sup> There is conflicting

data whether increased aortic cross-clamp and cardiopulmonary bypass time increase POAF.<sup>[7]</sup>

### Postoperative

A substudy of the Atrial Fibrillation Suppression Trial II (AFIST) showed that patients who developed postoperative AF received 1.3 L more fluid than those without postoperative AF over 5 postoperative days.<sup>[53]</sup> Net fluid balance on postoperative day 2 was an independent predictor of post-CTS AF among amiodarone-naïve patients (OR 6.4; 95% CI 1.4 to 29.1) which is noteworthy since most post-CTS AF occurs on this day.<sup>[54]</sup>

Characteristics that have not been identified consistently as independent risk factors include hypertension, left ventricular dysfunction, angina pectoris, and noncardiac illnesses.

## PREVENTION

### Beta-blocker

Since the autonomic nervous system plays a major role in the pathophysiology of post-CABG AF, beta blockers have been widely studied in its prevention. In one study beta-blockers had the greatest magnitude of effect across 28 trials (4,074 patients) with an odds ratio (OR) of 0.35, 95% CI 0.26-0.49.<sup>[55]</sup> In another meta-analysis of 24 trials limited to patients with ejection fraction  $>30\%$  undergoing CABG, prophylactic beta-blockers were associated with protection against supraventricular tachycardia with an OR of 0.28, 95%CI 0.21-0.36.<sup>[56]</sup>

### Sotalol

In a meta-analysis of 14 trials including 2,583 patients that compared beta-blocker or placebo, sotalol was found to be more effective in reducing POAF than beta-blocker or placebo. Therefore, it seems to offer significant additional protection over standard beta-blockers.<sup>[57]</sup>

### Amiodarone

In a randomized trial including 124 patients undergoing a complex cardiac surgery, amiodarone administered orally at least 1 week preoperatively significantly reduced the incidence of POAF, from 53% in the placebo group to 25% in the treated group ( $P = 0.003$ ). In the Amiodarone Reduction in Coronary Heart (ARCH) trial, postoperative intravenous administration of amiodarone was associated with a lower incidence of POAF (35%) compared with the placebo arm (47%) ( $P = 0.01$ ).<sup>[58]</sup>

### Atrial pacing

Prophylactic pacing has been investigated in a number of trials. Meta-analyses of these clinical trials have consistently

shown that single- or dual-site atrial pacing significantly reduces the risk of new-onset POAF.<sup>[59,60]</sup> In a randomized trial, biatrial overdrive pacing in patients undergoing CABG was shown to be more effective in preventing POAF than single-site atrial pacing (12.5% vs. 36%).<sup>[61]</sup> However, this trial included a small number of patients and had significant limitations. Major adverse effect is potential proarrhythmic effect.

### Calcium channel blockers

A recent meta-analysis showed that calcium-channel blockers reduce supra-ventricular tachyarrhythmia risk (OR 0.62; 95% CI 0.41-0.93).<sup>[62]</sup> However, in some studies, the perioperative use of these drugs was associated with an increased incidence of AV block and low output syndrome, due to their negative chronotropic and inotropic effect. In patients undergoing CABG, diltiazem reduced post-CABG AF incidence by 50–74% compared with placebo.<sup>[63]</sup>

### Magnesium

A meta-analysis concluded that magnesium administration was effective for reducing POAF with a similar efficacy to common antiarrhythmic drugs.<sup>[64]</sup> Meta-analyses have shown magnesium to reduce POAF risk by 23–36%.<sup>[64,65]</sup> However, the studies included in these analyses included a small number of patients, and the design varied among the different studies, thus limiting the interpretation of the results.

Statins- The prospective randomized study Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery (ARMYDA-3) has demonstrated that treatment with Atorvastatin 40 mg/day started 7 days before elective cardiac surgery under cardiopulmonary bypass and continued in the postoperative period significantly reduces the occurrence of POAF by 61%.<sup>[66]</sup> Statins have been shown to reduce inflammation in patients with coronary artery disease; and thus the theoretical benefit to decrease postoperative

inflammation as a potential cause of POAF. When the theory examined was found to be useful in the prevention of POAF.

### N-3 polyunsaturated fatty acids

In a randomized controlled trial of 160 patients undergoing elective CABG, PUFAs supplementation significantly reduced the incidence of POAF by 65% versus control, an effect similar to that obtained with beta-blockers, sotalol, or amiodarone (OR 0.35; 95% CI 0.16-0.76).<sup>[67]</sup> The modulation of cardiac connexin was probably the contributing mechanism to the antiarrhythmic effects of fish oil supplementation. Furthermore, in the general population, consumption of fish, inducing high plasma PUFA concentration, has been associated with a lower incidence of AF in a 12-year follow-up study.<sup>[68]</sup>

### Anti-inflammatory agents

In a randomised controlled trial the authors concluded that nonsteroidal anti-inflammatory medications are effective in significantly reducing the incidence of AF after CABG. However, the risk versus benefit ratio of such prophylactic strategy remains uncertain, given their nephrotoxicity.<sup>[69]</sup> In another multicenter trial hydrocortisone proved beneficial in reducing the incidence of POAF in the first 84 hours.<sup>[70]</sup>

## TREATMENT

Before initiating the treatment of AF, underlying medical comorbidities like electrolyte imbalance, hypoxia, COPD should be treated.<sup>[71]</sup> AF has been associated with physiological stress, drugs, pulmonary embolism, chronic lung disease, hyperthyroidism, caffeine, infectious processes, and various metabolic disturbances. AF has also been linked with obesity, and this phenomenon seems to be mediated by left atrial dilation

The treatment of post-CABG AF includes use of drugs and electrical cardioversion. Drugs can target to achieve rate control or rhythm control [Table 1]. According to a study

**Table 1: Dosage, advantages, and side effects of drugs used for treatment of POAF**

Drugs	Adult dosage	Advantages	Side effects
Esmolol	500 µg/kg over 1 min then 0.05–0.2 mg/kg/min	Short-acting effect and short duration	Might worsen congestive heart failure; can cause bronchospasm, hypotension; AVB
Atenolol	1–5 mg IV over 5 min repeat after 10 min then 50–100 mg b.i.d. PO	Rapid onset of rate control (IV)	
Metoprolol	1–5 mg IV over 2 min then 50–100 mg b.i.d. PO	Rapid onset of rate control (IV)	
Digoxin	0.25-1.0 mg IV then 0.125–0.5 mg/day IV/PO	Can be used in heart failure	Nausea, AVB moderate effect in POAF
Verapamil	2.5-10 mg IV over 2 min then 80–120 mg/day b.i.d. PO	Short-acting effect	Might worsen congestive heart failure, AVB
Amiodarone	2.5-5 mg/kg IV over 20 min then 15 mg/kg or 1.2 g over 24 h	Can be used in patients with severe LV dysfunction	Thyroid and hepatic dysfunction, torsades de pointes, pulmonary fibrosis, photosensitivity, bradycardia
Procainamide	10–15 mg/kg IV up to 50 mg/min	Therapeutic levels quickly achieved	Hypotension, fever; accumulates in renal failure, can worsen heart failure, requires drug level monitoring
Ibutilide	1 mg IV over 10 min, can repeat after 10 min if no effect	Easy to use	Torsades de pointes more frequent than amiodarone and procainamide

IV = Intravenous; LV = Left ventricular; AVB = Atrioventricular block, b.i.d. = Twice daily, PO = By mouth

conducted to study rate control versus rhythm control it was found that the latter is more beneficial because of a decreased time to cardioversion, prolonged maintenance of sinus rhythm, and decreased length of overall hospital stay.<sup>[72]</sup>

Short acting beta-blockers are the drug of choice,<sup>[71]</sup> especially in patients with ischemic heart disease. They should be used with care in patients with asthma, COPD, congestive cardiac failure and AV conduction block, in whom they are relatively contraindicated. Among calcium channel blockers, verapamil and diltiazem can be used. Digoxin is less effective when adrenergic tone is high but might be used in patients with congestive heart failure.<sup>[73]</sup> Amiodarone can also be used and is also known to improve hemodynamic status when used intravenously.<sup>[71,74]</sup> the risks and benefits of this treatment option, including the conversion rates.

Electrical Cardioversion- Indications for performing electrical cardioversion in patients with post-CABG AF are hemodynamic instability, myocardial ischemia, acute pump failure and elective restoration of normal sinus rhythm after a failed pharmacological attempt. Cardioversion can be associated with thromboembolism if POAF is present for more than 48 hours. The guidelines for anticoagulation in post surgical patients are not clear.<sup>[71]</sup>

Thromboembolism prevention: AF after CABG poses an increased risk of cerebrovascular accidents in the form of stroke;<sup>[75,76]</sup> however, using anticoagulants in the post operative period can lead to increased risk of bleeding and cardiac tamponade.<sup>[77]</sup> The risks might far outweigh the benefits especially in patients with advanced age, previous history of bleeding and uncontrolled hypertension.<sup>[61]</sup> Anticoagulants can be used for prolonged and/or frequent episodes of AF and is recommended by the American College of Chest Physicians in patients with history of stroke and transient ischemic attacks (30 days after the return of sinus rhythm).<sup>[78]</sup> Anticoagulation should be considered in patients 75 years or older and patients with risk factors for stroke, while antiplatelet agents may prove useful in younger patients, subgroups in whom anticoagulation is contraindicated, and in patients with low risk for stroke.<sup>[79]</sup>

## CONCLUSIONS AND RECOMMENDATIONS

POAF is a burden to our health care system and increases ICU stay. We do have multiple modalities which range from the conservative medical approach to invasive biatrial pacing, so it would be worthwhile to be able to predict the occurrence of POAF. Many recent studies have tried to find predictors of POAF.<sup>[80, 81]</sup> Developing a practical and simple

AF score that can predict POAF is in order, and further research is required as to how to interpret these criteria and use them to utilize the available prevention and treatment modalities.

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**Cite this article as:** Mostafa A, EL Haddad MA, Shenoy M, Tuliani T. Atrial fibrillation post cardiac bypass surgery. *Avicenna J Med* 2012;2:65-70.

**Source of Support:** Nil, **Conflict of Interest:** None declared.

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