

Post-operative Atrial Fibrillation: An overview of Pathogenesis, Complications and Management

Ahmed Samy Alsadeq, Montaser Mostafa Alcekelly, Ahmed Shawky Shereef, Hala Gouda Abomandour
Cardiology Department, Faculty of Medicine, Zagazig University, Egypt.
Corresponding Author: Ahmed Samy Alsadeq
Email: ahmedalsadeq2015@gmail.com

Abstract

Background: Postoperative atrial fibrillation (POAF), is the most important type of secondary AF (AF resulting from an identifiable, primary, acute condition), defined as new-onset atrial fibrillation (AF) in the immediate period after surgery with a peak incidence on the second postoperative day. POAF is a complication in approximately one-third of patients undergoing cardiac surgery, causing substantial rises in hospital costs, intensive care unit (ICU) time and hospital stay. A wide variety of mechanisms has been investigated. Also, many preventive treatments have been suggested. Nevertheless, the prevalence of POAF remains substantial and troublesome. POAF engenders multiple effects on the cardiopulmonary hemodynamics, tachyarrhythmia being the most common presentation. The rapid irregular ventricular rate can result in insufficient coronary flow to compensate myocardial oxygen demand, leading to myocardial ischemia. Furthermore, decreased diastolic filling time and cardiac output are important physiological consequences of tachyarrhythmias.

Background

Post-operative Atrial Fibrillation

Acute and new-onset AF (postoperative atrial fibrillation) is one of the most common postoperative complication that affects approximately 35% of patients undergoing cardiac surgery and is associated with numerous detrimental sequelae (1).

Clinical efforts to prevent and manage POAF is a major challenge and its results have been less than optimal. POAF incidence following cardiac surgery has not changed significantly over the past several decades in spite of numerous trials evaluating its prophylactic and treatment modalities (2).

Pathogenesis of POAF

Systemic Inflammation and Oxidative Stress

Surgical trauma, ischemia due to cardiopulmonary bypass and reperfusion induce oxidative stress and production of pro-inflammatory molecules, resulting in endothelial inflammation, leucocytic activation, the release of NADPH oxidases, nitrous oxide production and reactive oxygen species generation (fig.1). The association between systemic inflammation, oxidative stress and POAF is stated in various studies (3).
Figure (1): Post-operative atrial fibrillation pathogenesis(4).

Local inflammation and oxidative stress
Pericardial disruption induces local inflammation and an increase in pericardial fluid (PCF) production. Postoperative PCF causes high oxidative stress and contains high levels of inflammatory substances that initiate leucocyte and platelet activation.
Cardiomyocyte apoptosis and altered electrical activity, which allows heterogenous action potentials and arrhythmias to form and propagate, is caused by pericardial space inflammation(5).

Electrolytes
Hypomagnesemia (a serum magnesium level below normal [<1.2–2.0 mg/dl]) is common in post-operative patients and is a predictor of POAF according to numerous studies. High levels of intracellular magnesium increase atrioventricular (AV) node conduction time and may reduce oxidative damage, while sinus node automaticity is increased by low magnesium levels.
Hypokalemia (a serum potassium level below 3.5 mmol/l) leads to cellular hyperpolarity, higher resting potential, increased automaticity and excitability, and ventricular arrhythmias(6).

Timing of POAF onset
The risk of developing POAF follows a non-linear trend. The risk is highest on the second day after the surgery (Figure 2). The first phase of risk occurs just after surgery then declines rapidly during the first 18 h. The risk factors for this phase include older age, increased aortic cross-clamp time and mitral valve surgery. The second phase rises to a peak from first hour to two days. The risk factors for this peak include older age, increased weight, Caucasian race and mitral valve surgery(7).
Figure (2): Risk for developing POAF shown as Phase I (red line) and Phase II (blue line) (8).

**Type of Surgery**
POAF occurs in 35% of the patients after cardiac surgery; however, there is great variations related to the type of the procedure performed and patient characteristics. Isolated CABG carries a risk of 20–30% and isolated valve surgeries carries a risk of 35–40%. Combination of both CABG and valve surgery has a greater risk for POAF, up to 60% (9).

**Intraoperative and Perioperative Factors:**
POAF has consistently been associated with CPB and aortic cross-clamp duration. Off-pump cardiac surgery (primarily off-pump CABG and transcatheter approaches) decreased the incidence of POAF. Predictors of POAF include using intra-aortic balloon pump, longer ventilation duration, cardiac tamponade and bleeding (10).

**ECG predictors**
Abnormal P-wave morphology which include premature atrial contraction {PAC },abnormal P-wave dispersion ,abnormal P- wave index ,increaasd PR interval and abnormal P-wave frontal axis is apredictor for the development of postoperative AF, the risk being 12 times higher in the patients with P-wave abnormality compared with those with normal P-wave morphology. This could be related to the fact that abnormal P-wave morphology reflects abnormality of LA size, interatrial conduction defect and LA structural abnormalities (11).

**Echo Predictors**
Left atrial size and volume are independent predictors of new-onset AF in general population. Additionally, a new noninvasive echocardiographic method has been identified that predicts new-onset AF. This technique measures the total atrial conduction time (PA-TDI duration) using tissue Doppler imaging of the atria and P wave on surface electrocardiogram. The total atrial conduction time provides more exact evaluation of the atrial remodeling than conventional echocardiography parameters. Also, total atrial conduction time has important value for the prediction of new-onset AF or paroxysmal AF (12).
POAF Score:
The POAF score based on routinely available preoperative data is a simple, accurate bedside tool, allowing for identification of patients at high risk for POAF and in whom preventive antiarrhythmic therapies seem justified. Permitting identification of patients at high risk for AF and related or accompanying complications, the POAF score may also help to develop and update clinical and therapeutic strategies that not only would minimize the occurrence of POAF but also would result in an improvement in the morbidity and mortality rates observed among patients affected by this arrhythmia. In particular, patients with a POAF score ≥3 having the highest AF risk and was strongly associated with higher hospital mortality, postoperative CVA, AKI, and RRT(13).

Table (1) : POAF score (14).

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>Coefficients</th>
<th>Additive Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 to 69</td>
<td>2.04 (1.81 to 2.31)</td>
<td>0.715</td>
<td>1</td>
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<tr>
<td>70 to 79</td>
<td>2.93 (2.60 to 3.30)</td>
<td>1.076</td>
<td>2</td>
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<tr>
<td>≥80</td>
<td>3.94 (3.31 to 4.69)</td>
<td>1.372</td>
<td>3</td>
</tr>
<tr>
<td>COPD</td>
<td>1.33 (1.14 to 1.56)</td>
<td>0.288</td>
<td>1</td>
</tr>
<tr>
<td>eGFR &lt;15 mL/min per 1.73 m² or dialysis</td>
<td>1.90 (1.17 to 3.10)</td>
<td>0.643</td>
<td>1</td>
</tr>
<tr>
<td>Emergency</td>
<td>1.50 (1.19 to 1.98)</td>
<td>0.404</td>
<td>1</td>
</tr>
<tr>
<td>Preoperative VAD</td>
<td>1.90 (1.28 to 2.63)</td>
<td>0.644</td>
<td>1</td>
</tr>
<tr>
<td>LVEF &lt;30%</td>
<td>1.45 (1.18 to 1.77)</td>
<td>0.369</td>
<td>1</td>
</tr>
<tr>
<td>Valve surgery</td>
<td>1.68 (1.35 to 2.03)</td>
<td>0.519</td>
<td>1</td>
</tr>
<tr>
<td>Constant</td>
<td>−2.032</td>
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</tr>
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</table>

AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LVES, left ventricular ejection fraction.
4 Age <60 y was the reference group.
**Table (2)**: POAF score (15)

<table>
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<tr>
<th>Item</th>
<th>Score</th>
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<tr>
<td>Age &gt;60 y</td>
<td>1</td>
</tr>
<tr>
<td>Smoking</td>
<td>1</td>
</tr>
<tr>
<td>COPD</td>
<td>1</td>
</tr>
<tr>
<td>CP bypass time (min) &gt;86.5</td>
<td>2</td>
</tr>
<tr>
<td>Vent. Time &lt;23.5</td>
<td>2</td>
</tr>
<tr>
<td>PLR &gt;113.4</td>
<td>3</td>
</tr>
<tr>
<td>LVEF &lt;53.5</td>
<td>3</td>
</tr>
<tr>
<td>RV function by TAPSE &lt;2.15</td>
<td>3</td>
</tr>
<tr>
<td>Syntax score &gt;34.5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20</strong></td>
</tr>
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</table>

**CHADS2 and CHA2DS2-VASc score**

The patient’s stroke risk could be determined by CHADS2 and CHA2DS2-VASc scores, which combine cardiovascular and non-cardiovascular characteristics. Recent studies have demonstrated a correlation between preoperative CHADS2 and CHA2DS2-VASc scores and POAF, making these tools potentially useful predictors of POAF (16).

**Complication of POAF**

POAF is an independent predictor of several adverse outcomes, including a two to four-fold increase in risk of stroke, bleeding, infection, renal impairment or respiratory failure, cardiac arrest, cerebral complications, permanent pacemaker implantation, and a two-fold rise in all-cause 30-day and 6-month mortality.

POAF may not be directly responsible for these poor outcomes; however, it is certainly an indicator for increased morbidity and mortality in post-operative patients. Additional hospital treatment costs for patients who develop POAF will increase by an average of $10 000 to $20 000 and there ICU time with rise by 12–24 h, and an additional two to five days in overall hospital admission. POAF annual costs in the US only are estimated to be over one billion dollars(6).
Figure (3) : Postoperative complication (hospital mortality, cerebrovascular accident, acute kidney injury, and renal replacement therapy) rates according to the postoperative atrial fibrillation (POAF) score and the occurrence of POAF (17).

Preoperative POAF Prophylaxis

β-Blockers

β-Blockers are Class II antiarrhythmic drugs (AADs) and the most widely used prophylactic medication for patients undergoing cardiac surgery and their likely mechanism is a decrease in sympathetic tone which increases atrial refractoriness and decreases the initiation of arrhythmias. Many studies have previously reported an association between preoperative β-blocker administration and reduced POAF occurrence. It has been reported that oral metoprolol is more effective at reducing POAF than intravenous esmolol, and carvedilol may reduce POAF more effectively than metoprolol, an effect that may be explained by carvedilol’s oxidative stress–reducing properties. In addition to continuing preoperative beta-blockers, the 2011 ACCF/AHA guideline for coronary artery bypass grafting (CABG) offers specific Class I recommendations to administer beta-blockers for at least 24 hours before CABG to all patients without contraindications to beta blockade, to reduce the incidence or clinical sequelae of POAF. Beta-blockers receive a Class I recommendation from multiple societies for AF prophylaxis (18). Once AF has been initiated, multiple beta-blockers have been studied and found to be effective for rate control, although the most commonly used are esmolol and metoprolol. All beta-blockers have some negative inotropic effects, with the ultrashort-acting beta-blocker landiolol potentially having the most limited impact on inotropy. Beta-blockers have a Class I recommendation in multiple guidelines for use in rate control of POAF (19).

However, evidence from the guidelines and a series of studies is conflicting. One large-scale retrospective review found that preoperative β-blocker usage was associated with a slight but significant increase in POAF and an unchanged or slightly increased rate of postoperative mortality. Some believe that postoperative β-blocker withdrawal may be responsible for these differences and it is recommended that administration of β-blockers to patients using them chronically should be resumed as soon as possible following surgery (6).
Amiodarone
A lipophilic class III antiarrhythmic drug (K channel blocker) with Na+-channel, Ca2+-channel and β-adrenergic receptor blocking properties, works by prolonging the action potential duration and hence refractory period of atrial, nodal, and ventricular tissues suppressing ectopic triggers as well as re-entrant activity. It therefore has a broad spectrum of activity. An increase in the refractory period of the atrial cells is the major contributing action to the control of atrial tachyarrhythmias (20).

Amiodarone use is associated with adverse events such as bradycardia and hypotension, as well as potential pulmonary, hepatic, and thyroid toxicity, though rarely with short-term use. Its long-term use requires regular monitoring of liver and thyroid function. Amiodarone is also contraindicated in patients with an accessory pathway and can cause bradycardia and QT-interval prolongation (1). Amiodarone reduced the incidence of POAF after cardiac surgery and length of hospital stay, no significant effect of amiodarone was reported on stroke or mortality. For patients undergoing CABG surgery, intravenous versus oral amiodarone administration and preoperative versus postoperative administration were found to be equally effective. High-dose amiodarone (>5,000 mg cumulative dose) was found to be marginally more effective than low-dose amiodarone (<3,000 mg) compared with placebo, but also lower doses could be effectively used while minimizing adverse events. In one meta-analysis of six trials, amiodarone and β-blockers were found to be equally effective for the prevention of POAF. In another small, randomized, placebo-controlled trial, the combination of amiodarone and metoprolol reduced the incidence of POAF more than metoprolol alone, Amiodarone receives a Class IIa recommendation by the ACC/AHA/HRS, ACCF/AHA, ESC guidelines and the SCA/EACTA Practice Advisory for AF prophylaxis (21).

Amiodarone has also been studied as a treatment for POAF once it occurs. It is an effective rhythm control agent that also has rate-control properties. Authors of a 2011 data-base study of dronedarone, amiodarone, sotalol, flecainide, and propafenone in AF patients reported that even though amiodarone was most effective at maintaining sinus rhythm, Some authors caution that ruling out intracardiac thrombi by transesophageal echocardiogram (TEE) should be considered before using amiodarone to treat POAF of 24–48 hrs duration, amiodarone has a Class IIa recommendation from the SCA/EACTA Practice Advisory for use in the treatment of POAF (1).

Other Antiarrhythmic Drugs
Class III AADs such as amiodarone (the most widely used AAD), ibutilide, dofetilide and sotalol (which also has β-blocking effects) have also been widely used prophylactically in the preoperative period. Prophylactic amiodarone and sotalol are currently listed as Class II recommendations for POAF prevention. Preoperative prophylactic administration of Class I AADs, including procainamide and propafenone, are not recommended due to their pro-arrhythmogenic properties (22).

Corticosteroids
Following cardiac surgery, corticosteroids reduce the heterogeneity of atrial conduction and decrease inflammatory reactions, and studies have revealed that preoperative prophylactic corticosteroids reduced POAF incidence without an increased risk of postoperative infection. The most effective dosage and administration route of preoperative corticosteroids remains unclear. Corticosteroids usage is limited as they induce hyperglycemia, suppress patient’s immune response, delay wound healing, and increase the risk of gastrointestinal complications (23).

Statins
Statins also reduce inflammation and oxidative stress following cardiac surgery, and early studies showed that preoperative statins significantly reduced POAF incidence. Dosage varied between these
studies, from 20 to 80 mg, as did the time of administration, from 4 weeks preoperatively to the evening before (24).

**Other Medications**

The 2014 American association of thoracic surgery (AATS) guidelines suggest that administration of preoperative calcium channel blockers (i.e. diltiazem) is reasonable in high-risk patients who are not taking β-blockers, although their effect on POAF remains unclear (25).

Cardiac glycosides (i.e. digoxin) have not been recommended for use in preoperative prophylaxis (26).

The effects of prophylactic anticoagulants are also unclear; at least one institution has reported that preoperative warfarin reduced POAF incidence, but these results may have been confounded by other medications. Interruption of anticoagulation for surgery in patients using chronic anticoagulants is acceptable for those with low stroke risk, based upon the patient’s CHA₂DS₂-VASc score. Bridging with heparin, low molecular weight heparin or new oral anticoagulants (NOACs) including dabigatran, apixaban and rivaroxaban in patients without valvular disease may provide an alternative when complete interruption is not feasible (27).

While the administration of prophylactic angiotensin converting enzyme (ACE) inhibitors has increased drastically during the past several decades, preoperative ACE inhibitor usage has not been shown to decrease the incidence of POAF, although ACE inhibitor withdrawal has been linked with the development of POAF by some studies (28).

**Intraoperative POAF Prophylaxis**

Intraoperative interventions aimed at preventing POAF include posterior pericardiotomy, anterior fat pad (AFP) preservation (in which the AFP, which contains parasympathetic ganglia, is not excised), and left atrial appendage (LAA) exclusion from circulation. Early evidence showed that posterior pericardiotomy significantly decreased the incidence of POAF, but additional trials have not corroborated these positive findings. AFP preservation likely has no reductive effect on POAF (29).

LAA exclusion has emerged as a target for prophylactic stroke prevention and an alternative to long-term anticoagulation therapy. Interest in this procedure has grown due to the low rates of stroke in patients who have had left atrial exclusion with the Cox-Maze procedure. Data from the Watchman device, which allows for percutaneous LAA exclusion, has provided some evidence that long-term stroke risk may be reduced with LAA exclusion alone. However, recent findings have shown that most elimination procedures fail to fully exclude the LAA from circulation, that percutaneous exclusion is associated with high rates of procedure-related harm. It is therefore unclear whether cardiac surgery patients should undergo concomitant LAA exclusion, or whether anticoagulants may be safely discontinued in patients who do (30).

**Postoperative POAF Prophylaxis**

**Medications**

β-Blockers are the most common medication given for POAF prevention following surgery. While some studies have found that postoperative β-blockers significantly decreased the incidence of POAF and other postoperative complications, other analyses have attributed some β-blockers to excess deaths and disabling strokes. Despite such conflicting evidence, prescription of β-blockers following cardiac surgery remains a Class I recommendation and is performed in nearly 82% of cases (31).

When the use of β-blockers is contraindicated, such as in patients with poorly controlled asthma or heart failure, postoperative administration of amiodarone is considered the second choice for POAF prevention. A recent Cochrane review of 118 studies reported that postoperative administration of amiodarone significantly reduced the incidence of POAF compared to control (32).
The efficacy of postoperative ACE inhibitors in POAF prevention is questionable; some studies have shown that postoperative ACE inhibitors decreased POAF incidence, while others showed no difference or an increase in comorbidities such as recurrent angina (6).

**Electrolyte Supplementation and Repletion**

Current clinical practice often includes intraoperative and postoperative repletion of magnesium and potassium, although its effects remain controversial. Additionally, intraoperative and postoperative electrolyte supplementation has been proposed as a means of POAF prophylaxis, but this has also not been definitively shown to prevent POAF(6).

**MANAGEMENT OF POAF**

Episodes of POAF may resolve without intervention within minutes or hours, but persistent episodes of AF and those occurring in haemodynamically unstable patients require clinical intervention. Primary POAF management includes the use of one or more of the three mainstay medications: β-blockers, amiodarone and calcium channel blockers. Clinical practice typically involves using a single agent and addition of a second medication as needed. Concurrent use of all three may lead to bradycardia and hypotension, and should therefore be performed with caution. Special attention must also be given to prevent thromboembolic events (33).

Two general approaches for treatment of POAF exist: heart rate control and rhythm control. Rate control focuses on slowing the heart rate and includes the use of β-blockers or calcium channel blockers. Rhythm control focuses on converting the arrhythmia into sinus rhythm by using Class I or III AADs or direct-current cardioversion for unstable patients or those with persistent episodes POAF. A recent prospective clinical study comparing rate versus rhythm control found that neither treatment strategy offered a significant clinical benefit over the other (6).

**Antiarrhythmic Drugs (AADs)**

β-Blockers (Class II AADs) have rate control and antiarrhythmic effects and are listed as a Class I recommendation for treatment of POAF. Due to the negative inotropic effects and heart rate depression caused by many traditional β-blockers, they should be used with caution in patients with hypotension, LV dysfunction, or heart failure. In haemodynamically unstable patients, ultrashort-acting β-blockers such as esmolol and landiolol may provide better relief (6).

Class III AADs (potassium channel blockers) such as amiodarone may also be used to convert patients to sinus rhythm, but are associated with bradycardia, hypotension and QT interval prolongation(6).

These agents are a Class II recommendation for POAF management and may be used independently or in conjunction with β-blockers, or as a first-line treatment in patients with hypotension, heart failure, or LV dysfunction(6).

Discharge on any Class III AAD has been associated with a reduction in all-cause postoperative mortality, but long-term Class III AAD use has been linked with prolongation of atrial and ventricular refractory periods (21).

The 2014 AATS guidelines state as a Class II recommendation that AAD usage for patients discharged in sinus rhythm should be continued for 4 weeks after the last episode of POAF or until the first postoperative visit (2–6 weeks after discharge), while patients discharged in AF should continue AAD usage for 4 weeks following the first postoperative visit without POAF recurrence (34).

The 2010 Canadian Cardiovascular Society guidelines state that treatment may be discontinued between 6 and 12 weeks after restoration of sinus rhythm (6).
The effectiveness of Class I AADs (sodium channel blockers) such as procainamide, flecainide and propafenone in POAF treatment is unclear, but these medications carry a significant risk of pro-arrhythmic side effects and are therefore not recommended for treatment of POAF(6).

**Calcium Channel Blockers**
Calcium channel blockers slow ventricular response by slowing the propagation of action potentials at the AV node. Calcium channel blockers are considered as a Class I recommendation for treatment of POAF when use of β-blockers is contraindicated or ineffective (6).

**Direct-Current Cardioversion**
Direct-current cardioversion to sinus rhythm may be necessary in haemodynamically unstable patients or in patients with rapid ventricular response which could not be control by pharmacological treatment. Cardioversion is considered a Class I recommendation by the AATS and a Class II recommendation by the 2014 AHA/ACC/HRS task force (35).

The need for anticoagulation prior to cardioversion should be based upon the patient’s bleeding risk, CHA2DS2-VASc score and confirmation of the absence of intracardiac thrombus, particularly within the LAA, by TEE. When warranted, anticoagulation should be administered 3 weeks prior to cardioversion and continued for at least 4 weeks. In patients with a high bleeding risk, cardioversion without anticoagulation is listed as a Class II recommendation by the AATS (32).

**Anticoagulants and Antithrombotics**
Within the first two days of POAF, anticoagulation to prevent thromboembolism is a Class I recommendation when the patient’s CHA2DS2-VASc score is higher than zero. However, in some patients, bleeding risk may outweigh the benefits of anticoagulation (6).

Administration of anticoagulants and anti-thrombotics to patients without contraindications is a Class I recommendation for episodes lasting longer than 48 h (6).

NOACs may be used. NOACs are likely more effective than traditional warfarin at preventing stroke and major postoperative bleeding events, have fewer drug–drug interactions, and have a predictive effect and shorter duration of action (33).

Low molecular weight heparin can be used instead of warfarin in patients with high bleeding risk and those who may need invasive procedures. Anticoagulants and antithrombotics should be prescribed for a minimum of four weeks after restoring sinus rhythm but may be continued for longer durations depending on the patient’s CHA2DS2 VASc2 score. Due to the self-limiting nature of POAF, long-term usage is often not needed (35).

**References**


