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FOCUS ISSUE: ATRIAL FIBRILLATION

# Mechanisms, Prevention, and Treatment of Atrial Fibrillation After Cardiac Surgery

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**Post-operative atrial fibrillation (POAF) is a frequent complication occurring in 30% to 50% of patients after cardiac surgery. It is associated with an increased risk of mortality and morbidity, predisposes patients to a higher risk of stroke, requires additional treatment, and increases the costs of the post-operative care. The aim of this review is to present the current state of knowledge about the risk factors, mechanisms, prevention, and treatment of this complication. In addition to the well known risk factors for the development of POAF such as age, left atrial enlargement, and valvular surgery, new metabolic risk factors related to visceral obesity have been identified. With regard to the prevention of POAF, beta-blocker drugs are effective and safe and can be used in most patients, whereas amiodarone can be added in high-risk patients. Biatrial pacing was shown to be effective; however, its complexity might limit its application. Although there are only few data regarding the usefulness of magnesium, statins, N-3 polyunsaturated fatty acids, and corticosteroids, their addition to beta-blocker drugs might be of benefit for further reducing POAF. Treatment includes the use of an AV nodal blocking agent to achieve the rate control. If AF does not spontaneously convert to sinus rhythm within 24 h, anticoagulation should be initiated and a rhythm control strategy should be attempted. More investigations are warranted to explore mechanisms by which POAF occurs. This new knowledge would undoubtedly translate into a more efficient prevention and treatment of this common post-operative complication that is associated with a major health and economic burden. (J Am Coll Cardiol 2008;51:793–801) © 2008 by the American College of Cardiology Foundation**

Post-operative atrial fibrillation (POAF) is the most common complication encountered after cardiac surgery. The incidence of POAF reported in previous studies varies between 20% and 50%, depending on definitions and methods of detection (1,2). The incidence of POAF has increased continuously over the past decades, and this is believed to be due to the aging of the population undergoing heart surgery. The pathophysiology of POAF after heart surgery is not precisely known, but the mechanisms are thought to be multifactorial. Different risk factors have been reported, and many studies have evaluated the prophylactic effect of different pharmacologic or physical interventions. The purpose of this review article is to discuss the recent discoveries about the potential mechanisms and the strategies of prevention and treatment of POAF.

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## Incidence and Clinical Impact

The incidence of POAF is approximately 30% after isolated coronary artery bypass grafting (CABG) surgery, 40% after valve replacements or repair, and increases to approximately 50% after combined procedures. Furthermore, these figures are expected to rise in the future, given that the population undergoing cardiac surgery is getting older and that the incidence of AF in the general population is strongly age-dependent.

Post-operative AF tends to occur within 2 to 4 days after the procedure, with a peak incidence on post-operative day 2. Seventy percent of patients develop this arrhythmia before the end of post-operative day 4 and 94% before the end of post-operative day 6 (3).

Although generally well tolerated and seen as a temporary problem related to surgery, POAF can be life threatening, particularly in elderly patients and those with left ventricular dysfunction in whom it is associated with significant morbidity (4) and mortality (5). Post-operative AF was reported as a major morbid event (6), associated with increased post-operative thromboembolic risk and stroke (7), hemodynamic compromise (8), ventricular dysrhythmias (1), and iatrogenic complications associated with therapeutic inter-

**Abbreviations and Acronyms**

**AF** = atrial fibrillation
**AV** = atrioventricular
**CABG** = coronary artery bypass graft
**CI** = confidence interval
**HR** = hazard ratio
**OR** = odds ratio
**POAF** = post-operative atrial fibrillation
**PUFAs** = N-3 polyunsaturated fatty acids

ventions. Importantly, the risk for perioperative stroke is approximately 3-fold higher for patients with POAF (1,5). Moreover, in a series of 3,855 patients undergoing cardiac surgery, Almassi et al. (6) found that hospital mortality (6% vs. 3%) and 6-month mortality (9% vs. 4%) were significantly higher in patients in whom POAF occurred.

Furthermore, 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. (3). Knowing that there are at least 640,000 open heart surgeries/year in the U.S. according to the American Heart Association (AHA) statistics in 2004 (9) and assuming an incidence of 30% of POAF, the extra cost related to this post-operative complication could be conservatively estimated at approximately $2 billion/year.

## Risk Factors

The most consistent predictor for the development of POAF is advanced age (3,5,6) (Fig. 1). In a recent study investigating the effect of age on the incidence of POAF, Mathew et al. (10) have documented that for every decade there is a 75% increase in the odds of developing POAF and concluded that, on the basis of age alone, anyone older than 70 years is considered to be at high risk for developing AF. It is indeed well documented that advanced age is associated with degenerative and inflammatory modifications in atrial anatomy (dilation, fibrosis), which cause alterations in atrial electrophysiological properties (shortness of effective refractory period, dispersion of refractoriness and conduction, abnormal automaticity, and anisotropic conduction) (11). It has been demonstrated that these latter processes act as potential substrates for POAF (12).

In addition to older age, many other risk factors for the development of POAF have been identified, including a previous history of AF, male gender, decreased left-ventricular ejection fraction, left atrial enlargement, valvular heart surgery, chronic obstructive pulmonary disease, chronic renal failure, diabetes mellitus, and rheumatic heart disease (1,5,10,13) (Fig. 1). More recently, obesity has also been shown to be an independent predictor of new-onset AF in the general population (14) and in cardiac surgery patients (15,16). In a recent study (16), we reported that obesity is a powerful risk factor for the occurrence of POAF after isolated CABG surgery in patients older than 50 years. However, in the younger population this association was not

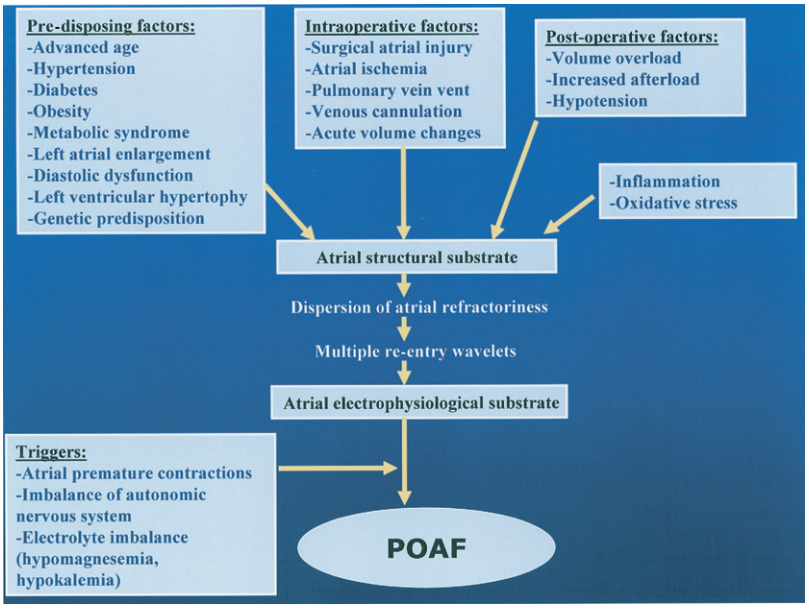


**Figure 1** Pathogenesis of POAF

The occurrence of post-operative atrial fibrillation (POAF) requires the presence of an electrophysiological substrate that is the consequence of multiple re-entry wavelets resulting from the dispersion of atrial refractoriness. The latter requires an atrial structural substrate, which might be the consequence of an association of multiple predisposing factors (advanced age, hypertension, diabetes, obesity, left atrial enlargement, and left ventricular hypertrophy). Alternatively, operative and post-operative factors such as atrial ischemia and surgical atrial injury might also contribute to the development of the structural substrate. Inflammation and oxidative stress also seem to play an important role. Finally, genetic factors likely predispose some patients to the development of POAF. Once these conditions are present, a triggering factor such as an atrial premature contraction, electrolyte imbalance, and/or enhanced adrenergic or vagal stimulation will initiate POAF.

observed, and the metabolic syndrome was the only metabolic risk factor to be independently associated with POAF.

## Pathophysiology and Mechanisms

The underlying mechanisms involved in POAF development are multifactorial and are for the moment far from being fully elucidated. However, some causative mechanisms have been proposed that include pericardial inflammation, excessive production of catecholamines, autonomic imbalance during the post-operative period, and interstitial mobilization of fluid with resultant changes in volume, pressure, and neurohumoral environment (Fig. 1). These factors might alter the atrial refractoriness and slow atrial conduction. Multiple re-entry wavelets resulting from the dispersion of atrial refractoriness seem to be the electrophysiological mechanism of POAF (17,18). However, one important question remains as to why there is an interindividual susceptibility to POAF. At least one possible answer is that patients with a structural substrate before operation and thus prone to atrial electrical re-entry are more vulnerable to physiological perturbations that are encountered in the post-operative period (1). An alternative explanation is that this substrate is created as a result of the surgical procedure itself. It is indeed possible that the physical alteration of the cardiac structure resulting from incision of the atria or perioperative ischemia might increase cardiac susceptibility to rhythm disturbances (19).

It is well known that neurohormonal activation increases susceptibility to POAF (2,20). Increased sympathetic and parasympathetic activation alter atrial refractoriness (e.g., a shortening of the atrial effective refractory period), thus possibly contributing to the arrhythmia substrate (21). It has been reported by Hogue et al. (22) that patients developing POAF have either higher or lower RR interval variability, suggesting that increased sympathetic or vagal tone occurs before arrhythmia onset. These findings suggest that interventions that would modulate both the sympathetic and parasympathetic nervous systems might be beneficial in suppressing this post-operative arrhythmia.

Also, there is now an increasing body of evidence that inflammation plays an important role in the pathogenesis of POAF. Two recent studies have shown that inflammation can alter atrial conduction, facilitating re-entry and then predisposing to the development of POAF (23,24) (Fig. 1). It is well known that extracorporeal circulation is characterized by a systemic inflammatory response, which might be in part responsible for the occurrence of POAF. Interestingly, it has been reported recently that the leukocytosis, which is usually encountered in the days after cardiopulmonary bypass, is an independent predictor for the occurrence of POAF (25,26).

Obesity is associated with higher cardiac output requirement, higher left ventricular mass, and larger left atrial size (27) (Fig. 1). These factors might predispose to the development of POAF.

In addition to the aforementioned processes, other pathophysiological mechanisms might also intervene as contributing factors in the development of POAF, including volume overload (28), genetic predisposition assessed by the interleukin-6 promoter gene variant (29), alterations in atrial oxidative stress (30), and increased expression of the gap-junctional protein connexin 40 (31) (Fig. 1).

## Prevention

Many studies have evaluated the effectiveness of pharmacologic and nonpharmacologic interventions to prevent or decrease the high incidence of POAF. Recent guidelines for the prevention and management of POAF were published in 2006 jointly by the American College of Cardiology, the AHA, and the European Society of Cardiology (32) (Table 1).

**Beta-blocker drugs.** Because sympathetic activation might facilitate POAF in susceptible patients, and given the increased sympathetic tone in patients undergoing cardiac surgery, beta-blocker drugs have been so far the most studied drugs for the prevention of this post-operative arrhythmia.

**Table 1** Adapted From the ACC/AHA/ESC 2006 Guidelines for the Management of AF After Cardiac Surgery

| | | |
|---|---|---|
| Indication Class I | Unless contraindicated, treatment with an oral beta-blocker drug to prevent POAF 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 POAF | Level of Evidence: B |
| Indication Class IIa | Pre-operative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and represents appropriate prophylactic therapy for patients at high risk for POAF | Level of Evidence: A |
| | It is reasonable to restore sinus rhythm by pharmacologic cardioversion with ibutilide or direct-current cardioversion in patients who develop POAF, 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 POAF, as recommended for other patients who develop AF | Level of Evidence: B |
| | It is reasonable to administer antithrombotic medication in patients who develop POAF, as recommended for nonsurgical patients | Level of Evidence: B |
| Indication Class IIb | Prophylactic administration of sotalol might be considered for patients at risk of developing AF after cardiac surgery | Level of Evidence: B |

Adapted from Fuster et al. (32).
ACC = American College of Cardiology; AF = atrial fibrillation; AHA = American Heart Association; AV = atrioventricular; ESC = European Society of Cardiology; POAF = post-operative AF.

Several clinical trials have evaluated the effect of various beta-blocker drugs on the incidence of POAF (33–35), showing an overall reduction of this complication. But these studies varied widely in their study design, including the use of different types of beta-blocker drugs, different populations and surgical interventions, and different modalities for defining and detecting POAF. However, most of these studies were consistent in showing a significant reduction in the incidence of POAF. In a recent meta-analysis, Crystal et al. (36) found that beta-blocker drugs had the greatest magnitude of effect across 28 trials (4,074 patients) with an odds ratio (OR) of 0.35, 95% confidence interval (CI) 0.26 to 0.49. In addition, Andrews et al. (2) reported, in another meta-analysis of 24 trials limited to patients with ejection fraction >30% undergoing CABG, that prophylactic administration of beta-blocker drugs was associated with a protection against supraventricular tachycardia with an OR of 0.28, 95% CI 0.21 to 0.36.

In the meta-analysis by Burgess et al. (37), the authors reported that, despite the fact that beta-blocker drugs have shown an overall reduction in AF, there was a significant heterogeneity among the trials for beta-blocker therapy. Differences between the treated and the control groups were much stronger for those trials mandating discontinuation of nonstudy beta-blocker drugs before surgery. The results from this meta-analysis suggested that some but not all of the effect associated with beta-blocker drugs might have been due to beta-blocker withdrawal at the time of surgery. These data strongly suggest that physicians should not discontinue beta-blocker drugs before cardiac surgery.

**Sotalol.** Sotalol is a beta-blocker drug that also has important class III antiarrhythmic drug effects. Numerous studies have evaluated sotalol prophylaxis on the incidence of POAF. In a meta-analysis (37) of 14 trials including 2,583 patients that compared beta-blocker or placebo, Burgess et al. found that sotalol was more effective in reducing POAF than either other beta-blocker medication or placebo. Sotalol therefore seems to offer significant additional protection over standard beta-blocker drugs. However, one trial comparing sotalol with metoprolol in doses considered to provide equivalent beta-blockade reported a higher prevalence of post-operative bradyarrhythmias with sotalol prophylaxis (38). In this trial, more patients withdrew from sotalol treatment, owing to side effects (predominantly hypotension and bradycardia), than placebo (6.0% vs. 1.9%; $p = 0.004$).

**Amiodarone.** Amiodarone is a Vaughan–Williams class III drug, which also has alpha- and beta-adrenergic blocking properties that might attenuate sympathetic overstimulation seen in patients undergoing cardiac surgery (39). In a randomized trial including 124 patients undergoing a complex cardiac surgery, amiodarone administered orally at least 1 week pre-operatively significantly reduced the incidence of POAF, from 53% in the placebo group to 25% in the treated group ($p = 0.003$) (40). In another recent trial, the ARCH (Amiodarone Reduction in Coronary Heart) trial (41), including 300 patients, post-operative intravenous administration of amiodarone was associated with a lower incidence of POAF (35%) compared with the placebo arm (47%) ($p = 0.01$). Although the safety of amiodarone administration in the cardiac surgical patients has been questioned by some authors, a compelling evidence of the efficacy and safety of amiodarone has been demonstrated by the PAPABEAR (Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair) trial (42). In this large-scale study, a 13-day perioperative course of oral amiodarone was well tolerated and effective for the prevention of post-operative atrial tachyarrhythmia after a cardiac surgery. However, there seems to be some heterogeneity among the amiodarone trials, with stronger effects found among patients who were not simultaneously treated with beta-blocker drugs. A recent meta-analysis of 18 randomized controlled trials including 1,736 receiving amiodarone versus 1,672 receiving placebo found that amiodarone was associated with an increased risk of bradycardia and hypotension, particularly when administered intravenously (43). The greatest risk in the occurrence of these adverse events occurred when using regimens containing intravenous amiodarone, initiating prophylaxis during the post-operative period, and using regimens with average daily doses exceeding 1 g. The concomitant use of beta-blocker drugs might also exacerbate these adverse effects.

**Atrial pacing.** The utility of prophylactic atrial pacing to prevent AF after heart surgery is based on the fact that pacing is thought to favorably influence intra-atrial conduction and atrial refractoriness (44). There are several mechanisms by which atrial pacing might prevent AF, including the following: 1) reduction of the bradycardia-induced dispersion of atrial repolarization, which contributes to the electrophysiologic substrate for AF (45); 2) atrial overdrive suppression of atrial premature beats and runs of supraventricular premature beats, thus avoiding the trigger for AF (46); and 3) dual-site atrial pacing might change atrial activation patterns, thus preventing the development of intra-atrial re-entry (47).

The effect of prophylactic pacing has been investigated in a number of trials. Meta-analyses of these clinical trials (37,48,49) have consistently shown that single- or dual-site atrial pacing significantly reduces the risk of new-onset POAF. However, the number of enrolled patients was small, and the pacing sites and protocols varied widely among studies. 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%) (50). However, this trial included a small number of patients, and this intervention has significant limitations. Indeed, the major adverse effect of prophylactic atrial pacing is its potential proarrhythmic effect, which might be precipitated by inappropriate sensing or loss of pacing through temporary wires (51). Thus, further studies are needed to deter-

mine the usefulness of this method for the prevention of POAF.

**Other medications.** DIGOXIN. Once widely used, digoxin as a preventive measure of POAF has been abandoned, owing to its inefficacy. Indeed, recent meta-analyses consistently found that the pre-operative use of digoxin was not efficient at reducing POAF incidence (2,52).

CALCIUM-CHANNEL BLOCKER DRUGS. Numerous studies have evaluated nondihydropyridine calcium-channel blocker drugs. A recent meta-analysis of these trials showed that calcium-channel blocker drugs reduce supraventricular tachyarrhythmia risk (OR 0.62; 95% CI 0.41 to 0.93) (53). However, in some studies, the perioperative use of these drugs was associated with an increased incidence of atrioventricular (AV) block and low output syndrome, which might be related to the negative chronotropic and inotropic effect of this class of drug. Hence, although calcium-channel blocker drugs might have a role for POAF prophylaxis, their usage should be considered with caution until more data on their safety profile become available.

MAGNESIUM. Although still controversial, serum hypomagnesemia is common after cardiac surgery (54) and is associated with post-operative atrial tachyarrhythmias (55). Some clinical trials have assessed the efficacy of magnesium administration for the prevention of POAF. A meta-analysis (56) concluded that magnesium administration was effective for reducing POAF with a similar efficacy to common antiarrhythmic drugs. However, the studies included in this analysis included a small number of patients, and the design varied among the different studies, thus limiting the interpretation of the results.

STATINS. Given that observational studies had previously suggested that patients under statin therapy have a lower incidence of POAF after CABG (57) and that statins have been shown to reduce inflammation in patients with coronary artery disease, some investigators examined the usefulness of statins for the prevention of POAF. Recently, the prospective randomized study ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) (58) has demonstrated that treatment with Atorvastatin 40 mg/day started 7 days before elective cardiac surgery under cardiopulmonary bypass and continued in the post-operative period significantly reduces the occurrence of POAF by 61%.

N-3 POLYUNSATURATED FATTY ACIDS (PUFA). Recent experimental studies in rats have shown that PUFAs have significant antiarrhythmic effects on the atrial muscle (59). In another recent experimental study on dogs, a team from our institution (60) reported that oral treatment with fish oils reduces vulnerability to induction of AF. They found that 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 (61). Of particular significance, Calo et al. (62), in a randomized controlled trial of 160 patients undergoing elective CABG, found that PUFAs supplementation significantly reduced the incidence of POAF, with an effect similar to that obtained with beta-blocker drugs, sotalol, or amiodarone.

ANTI-INFLAMMATORY AGENTS. In a recent study, Cheruku et al. (63) randomized 100 patients undergoing CABG to 2 arms: the first arm received 30 mg ketorolac intravenously every 6 h until the patients were able to take oral medications, at which point they were switched to 600 mg ibuprofen orally 3 times/day; the other arm received conventional treatment. Atrial fibrillation occurred in 14 patients (28.6%) in the conventional treatment arm versus 5 patients (9.8%) in the anti-inflammatory medication group ($p < 0.017$). 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 that these agents are potentially associated with nephrotoxicity, which might be exacerbated in the post-operative period, especially in elderly patients.

Interestingly, in a recent multicenter trial (64) 241 consecutive patients undergoing cardiac surgery were randomized to receive either 100 mg hydrocortisone or a placebo. The incidence of POAF during the first 84 h was significantly lower in the hydrocortisone group (36 of 120 [30%]) than in the placebo group (58 of 121 [48%], and the adjusted HR was 0.54; 95% CI 0.35 to 0.83; $p = 0.004$).

These promising results might open new avenues in the prophylactic regimen aiming at the reduction of POAF. However, further studies comparing various doses and administration times are still necessary before firm conclusion can be made with regard to the preventive role and safety of calcium-channel blocker drugs, magnesium, statins, PUFAs, and anti-inflammatory agents.

**Impact of the prevention strategies on post-operative outcomes.** Although several pharmacologic or nonpharmacologic interventions have been shown to significantly reduce the incidence of POAF, it is still controversial whether or not these interventions translate into a significant reduction of stroke or other perioperative complications. Moreover, the effect of these interventions on the length of hospital stay and on economic costs also remains controversial. However, a few studies have reported a minimal but significant reduction in hospital stay with amiodarone, magnesium, or biatrial pacing combined with beta-blocker drugs (48). Hence, it is possible that adverse side effects of some interventions might balance or outweigh the benefits of POAF suppression on post-operative outcomes.

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**Table 2** Dosage, Advantages, and Side Effects of Drugs Used for Rate Control in POAF

| Drugs | Adult Dosage | Advantages | Side Effects |
|---|---|---|---|
| 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 |
| Beta-blocker drugs | | | |
| 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) | |
| Calcium-channel blocker drugs | | | |
| 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 |
| Diltiazem | 0.25 mg/kg IV over 2 min then 5–15 mg/h IV | | |

AVB = atrioventricular block; b.i.d. = twice daily; IV = intravenous; PO = by mouth; POAF = post-operative atrial fibrillation.

## Treatment

As a general rule, the management of medical comorbidities (e.g., hypoxia) and the correction of underlying electrolyte imbalance (especially potassium and magnesium) is part of the management strategy for the prevention and treatment of POAF.

Although POAF can be transient and generally self-limiting, treatment is indicated for patients who remain symptomatic, are hemodynamically unstable, and develop cardiac ischemia or heart failure. Conventional treatment strategies include prevention of thromboembolic events, control of the ventricular rate response, and restoring/maintaining sinus rhythm. Currently the evidence suggests a trend toward a strategy of rhythm control over rate control. The advantages of rhythm control are a decreased time to cardioversion, prolonged maintenance of sinus rhythm, and decreased length of overall hospital stay (65).

**Rate control.** The post-operative period is characterized by increased adrenergic stress, and thus it might be difficult to control the ventricular rate in patients with POAF. Short-acting beta-blocker agents are the therapy of choice, particularly in ischemic heart disease, but they might be poorly tolerated or relatively contraindicated in patients with known asthma or bronchospastic disease, congestive heart failure, or AV conduction block (Table 2). Alternatively, other AV nodal blocking agents, such as the nondihydropyridine calcium-channel blocker agents can be used. Digoxin is less effective when adrenergic tone is high but might be used in patients with congestive heart failure. Amiodarone has also been reported to be effective in controlling heart rate, and its intravenous administration has been associated with improved hemodynamic status (66).

**Rhythm control.** In symptomatic patients or when ventricular response is difficult to control, cardioversion might be preferred, with the same precautions regarding anticoagulation as in nonsurgical patients. Different agents might be effective to convert AF to sinus rhythm (Table 3), including amiodarone (40), procainamide (67), ibutilide, and sotalol (68). In one study (69), ibutilide was more effective than a placebo for the treatment of POAF, but polymorphic ventricular tachycardia has been reported and attributed to electrolyte imbalance. In the post-operative period, sotalol's beta-blocking action is particularly effective at reducing the ventricular rate, and its proarrhythmic toxicity is relatively infrequent, but this agent seems less effective than others for inducing cardioversion of AF.

**Electrical cardioversion.** Electrical cardioversion should be urgently performed when POAF results in hemodynamic instability, acute heart failure, or myocardial ischemia and electively used to restore sinus rhythm after the first onset of AF when a pharmacologic attempt has failed to resume a sinus rhythm. Anterior-posterior placement of the paddles is preferred, and the patient is sedated with a short-acting anesthetic. A biphasic waveform shock is generally used and is associated with the lowest energy, highest rates of

**Table 3** Dosage, Advantages, and Side Effects of Drugs Used for Rhythm Control in POAF

| Drugs | Adult Dosage | Advantages | Side Effects |
|---|---|---|---|
| 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 |
| Ibitulide | 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; POAF = post-operative atrial fibrillation.

cardioversion, and least dermal injury (70). A major concern of cardioversion, either electrically or pharmacologically, is thromboembolism, particularly when POAF has been present for more than 48 h. Whether guidelines for anticoagulation before cardioversion in nonsurgical patients apply to the post-surgical condition is not clear. In the general population, anticoagulation for 3 to 4 weeks before cardioversion is recommended for AF that has lasted for over 48 h. An acceptable approach in the post-operative period would be to perform a transesophageal echocardiographic examination to exclude mural thrombus, particularly in the left atrial appendage before cardioversion. Because atrial "stunning" persists after cardioversion, anticoagulation is recommended for 3 to 4 weeks after conversion of AF to sinus rhythm.

**Thromboembolism prevention.** Post-operative AF is associated with an increased risk of perioperative strokes (71–72) that might be reduced by therapeutic anticoagulation. In contrast, anticoagulation in the post-operative period might increase the risk of bleeding or cardiac tamponade (73). In this context, the clinician must weigh the usually transient and self-limited duration of new-onset POAF against the potential for post-operative bleeding if anticoagulation therapy is started. The increased risk of bleeding might indeed outweigh the benefits in reducing the risk of stroke in some patients, especially those with the following risk factors: advanced age, uncontrolled hypertension, and history of bleeding.

No controlled trials have specifically evaluated the efficacy and safety of anticoagulation therapy for new-onset POAF, which often resolves spontaneously after 4 to 6 weeks. As a general rule, anticoagulation is instituted for prolonged (>48 h) and/or frequent POAF episode. The American College of Chest Physicians recommends the use of anticoagulation therapy particularly for high-risk patients, such as those with a history of stroke or transient ischemic attack in whom atrial fibrillation develops after surgery. In these patients, it is also recommended to pursue the anticoagulation therapy for another 30 days after the return of a normal sinus rhythm (74).

## Conclusions

Post-operative AF after cardiac surgery is a highly frequent complication that leads to an increased risk of mortality and morbidity, predisposes patients to a significantly higher risk of thromboembolism and stroke, often requires additional treatment, and substantially increases the costs of the post-operative care.

Currently, there is significant variation in the preventive strategy of POAF. However, current evidence suggests that beta-blocker drugs are effective and safe and can be used in most patients. Therefore, unless contraindicated, beta-blocker drugs should be continued perioperatively or initiated in all patients. Amiodarone can be safely added in patients at high-risk for AF. Biatrial pacing was shown to be effective; however, its complexity limits its application on a wide-scale basis. Although there are only few data regarding the usefulness of magnesium, statins, N-3 polyunsaturated fatty acids, and corticosteroids, their addition to a beta-blocker–based therapy might be of benefit for further reducing this post-operative arrhythmia.

When POAF occurs, an immediate electrical cardioversion has to be performed for hemodynamically unstable patients. For those who are hemodynamically stable, an AV nodal blocking agent should be used to achieve the ventricular response control. If AF does not spontaneously convert to sinus rhythm within 24 h, then a rhythm control strategy should be attempted with class III or Ic antiarrhythmic drugs, associated with an early anticoagulation.

A better knowledge of the mechanisms implicated in POAF would undoubtedly translate into a better prevention of this common post-operative complication. In particular, the recent demonstration of an independent association between POAF and metabolic conditions such as obesity, metabolic syndrome, and diabetes certainly deserves further mechanistic studies to identify new druggable targets.

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