



Pharmacological and Nonpharmacological Prevention of Atrial Fibrillation after Coronary Artery Bypass Surgery

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Abstract

Atrial fibrillation (AF) is the most common complication of coronary artery bypass graft surgery (CABG). The reported incidence of AF after CABG varies from 20% to 40%. Postoperative AF (POAF) is associated with increased incidence of hemodynamic instability, thromboembolic events, longer hospital stays, and increased health care costs. A variety of pharmacological and nonpharmacological strategies have been employed to prevent AF after CABG. Preoperative and postoperative beta blockers are recommended in all cardiac surgery patients as the first-line medication to prevent POAF. Sotalol and amiodarone are also effective and can be regarded as appropriate alternatives in high-risk patients. Corticosteroids and biatrial pacing may be considered in selected CABG patients but are associated with risk. Magnesium supplementation should be considered in patients with hypomagnesemia. There are no definitive data to support the treatment with nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, procainamide, and propafenone, or anterior fat pad preservation to reduce POAF.

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Introduction

Postoperative atrial fibrillation (POAF) is a common complication of coronary artery bypass graft surgery (CABG), occurring in 20% to 40% of patients.¹⁻⁴ POAF has been associated with increased incidence of acute thromboembolic events, longer hospital stays, and increased health care costs.⁵⁻⁷ POAF may also identify a subset of patients with increased in-hospital and long-term mortality.⁸⁻¹⁰ Therefore, prevention of POAF is of great importance.

A variety of pharmacological and nonpharmacological strategies have been used to prevent atrial fibrillation (AF)

after CABG. Efficacy of beta blockers, amiodarone, sotalol, magnesium, and atrial pacing has been assessed in several randomized and nonrandomized clinical trials. This review tries to present an update on the preventive strategies of AF following CABG.

Pharmacological interventions

Beta blockers

Because patients recovering from cardiac surgery often

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have enhanced sympathetic tone, the risk of postoperative AF is increased. Beta blockers antagonize the effects of catecholamines on the myocardium and are, thus, expected to prevent AF after cardiac surgery. Multiple randomized and nonrandomized clinical trials have evaluated the efficacy of the beta blocker in the prevention of POAF in patients undergoing CABG.¹¹⁻³⁶ Majority of these studies have shown a significant reduction in POAF by beta-blocker prophylaxis in cardiac surgery patients. In addition, three landmark meta-analyses have been conducted to confirm the efficacy of prophylactic beta blockers against post-CABG AF and demonstrated a reduced incidence of post-CABG AF (OR: 0.39, 95% CI: 0.28-0.52).^{2, 37, 38} Following these remarkable results, updated American Heart Association/American College of Cardiology (AHA/ACC) 2006/2011 and recent ESC 2010 guidelines recommended beta-blocker prophylaxis to prevent POAF in cardiac surgery patients in the absence of contraindications.^{39, 40} However, there are still questions not adequately addressed in these guidelines: first, the optimal beta blocker for PAOF prevention is not defined. Second, exact timing of beta-blocker initiation (preoperative vs. postoperative) in cardiac surgery patients for AF prevention is not clear.

Optimal beta blocker for AF prevention after CABG

Different kinds of beta blockers have been used in randomized clinical trials (RCT), including propranolol, atenolol, timolol, nadolol, betaxolol, acebutolol, landiolol, carvedilol, and bisoprolol. Propranolol was the most commonly used beta blocker in earlier clinical trials, and metoprolol was the most commonly used beta blocker in recent studies. There is no head-to-head comparison of propranolol and metoprolol. There are, however, a few recent trials that compared the efficacy of the different types of beta blockers in reducing POAF in patients undergoing surgical revascularization. Two RCTs and one nonrandomized study investigated the efficacy of carvedilol compared with metoprolol in preventing AF following CABG.⁴¹⁻⁴³ A retrospective review of 110 patients who underwent CABG or valvular surgery demonstrated a significant reduction in POAF in the carvedilol group versus the metoprolol or atenolol group.⁴³ Two RCTs clearly confirmed the superiority of carvedilol over metoprolol for AF prevention after CABG;^{41, 42} nonetheless, the number of patients in both of these studies was small. The higher efficacy of carvedilol may be explained by a more comprehensive sympatholytic action (beta-1, beta-2, and alpha-1 adrenergic receptor blockers) than that of the other beta blockers and its antioxidant and anti-inflammatory actions.^{44, 45}

Efficacy of the beta blocker may be influenced by the route of administration in postoperative patients. Two studies specifically investigated the efficacy and safety of intravenous and oral beta blockers: in the pilot study by Balcelyte-Harris

et al.,⁴⁶ intravenous esmolol was compared with the oral beta blocker. This study was terminated prematurely because of significant adverse effect and lack of any reduction in POAF in the intravenous esmolol group. However, a second study, comparing oral and intravenous metoprolol, clearly showed the superiority of intravenous metoprolol with no serious adverse effects.⁴⁷ Similarly, a trend toward more frequent adverse effects was reported in a trial using intravenous propranolol versus placebo.¹³ Considering the higher adverse effects and controversial superiority of the intravenous formulations of the available beta blockers, it appears that oral beta blockers are better tolerated and easier to use than intravenous counterparts.

Preoperative vs. postoperative initiation of beta blockers

Timing of beta-blocker prophylaxis may have an important effect on the development of POAF.⁴⁸ Patients who received both pre- and postoperative propranolol were less likely to develop AF (5%) than those who received only preoperative (40%; p value < 0.001) or postoperative (27%; p value < 0.01) beta blockers.²⁴ Similarly, Ali et al.¹⁴ showed that in patients in whom preoperative beta blockers (metoprolol, atenolol, sotalol, or propranolol) was continued after surgery experienced a lower rate of AF compared with patients in whom beta-blocker therapy was not continued after surgery (17% vs. 38%; p value < 0.02). Two recent meta-analyses have similarly shown a statistically significant difference in protection against post-CABG AF with regard to the timing of the prophylaxis.^{37, 49} These data indicated that beta blockers are more effective in reducing the incidence of POAF when given both before and after CABG.

Amiodarone

Efficacy and safety of both oral and intravenous amiodarone have been investigated in several studies.⁵⁰⁻⁶³ These studies demonstrated that prophylactic amiodarone not only reduced the occurrence of POAF (OR: 0.50, 95% CI: 0.42-0.59) and significantly shortened the hospital stay but also reduced the incidence of cerebrovascular accident and postoperative ventricular tachyarrhythmia; it, however, had no effect on postoperative mortality.⁵⁹ Currently, preoperative administration of amiodarone is deemed class IIa indication for prophylactic therapy in patients at high risk for postoperative AF in the latest AHA/ACC and European Society of Cardiology (ESC) guidelines for AF management.^{39, 40}

Oral amiodarone

The utility of oral amiodarone was described for the first time by Daoud et al.⁵¹ for POAF prevention. In that study, cardiac surgery patients were randomized to placebo or

one week administration of oral amiodarone and followed by postoperative amiodarone. Results of this study showed that oral amiodarone significantly reduced the incidence of postoperative AF compared with the placebo (23% vs. 43%; p value = 0.03). Efficacy and safety of the oral amiodarone were also tested in five randomized trials.^{53, 60-63} The largest trial, the PAPABEAR study (Prophylactic Amiodarone for the Prevention of Arrhythmias That Begin Early After Revascularization, Valvular Repair, or Replacement) randomized 601 patients to either oral amiodarone or placebo.⁶⁴ Oral amiodarone (10 mg/kg qd) or placebo was administered 6 days before surgery and continued 6 days after surgery. The incidence of AF was more significantly lower in the amiodarone group than in the placebo group (16% vs. 29.5%; p value < 0.001). This effect was consistently evident in patients < 65 years or \geq 65 years, patients who received preoperative beta blocker, or those who did not receive beta blocker before surgery, and CABG only or valve surgery or both. However, the amiodarone-treated group experienced more side effects, which required drug discontinuation compared with the placebo group (11.4% vs. 5.3%; p value = 0.02).

Intravenous amiodarone

Early studies using intravenous amiodarone yielded conflicting results.^{54, 56} The Amiodarone Reduction in Coronary Heart (ARCH) trial in 300 CABG patients demonstrated that the postoperative intravenous administration of amiodarone (1 g/d for 2 days) significantly reduced the incidence of POAF (47% vs. 35; p value = 0.01).⁵⁴ Nevertheless, these results were not confirmed in other studies. In addition, the perioperative administration of intravenous amiodarone has been associated with bradycardia and hypotension. More recent studies using postoperative intravenous (2 days) followed by oral amiodarone (up to 30 days) have provided better results in terms of AF prevention and side effect profile.^{64, 65}

Concomitant administration of beta blockers and amiodarone was reported in 20-80% of the patients. In the Budeus et al. study,⁶² the reasons for beta-blocker withdrawal did not differ between the placebo and the amiodarone groups (39% vs. 33%, p value = 0.53). Therefore, the concomitant administration of beta blockers and amiodarone for POAF prevention is not associated with a higher incidence of bradycardia and hypotension compared with amiodarone alone.

In summary, it would be logical to consider either oral amiodarone before and after cardiac surgery or a short course (48 hrs.) of intravenous amiodarone initiated after surgery and followed by oral therapy as an effective strategy to reduce the incidence of postoperative AF.

Sotalol

Sotalol is a class III antiarrhythmic agent with potent beta-blocking activity. As a result, it would be a suitable drug for POAF prevention after cardiac surgeries. Sotalol has been proven to be an effective agent across all the clinical trials using this drug.⁶⁶⁻⁷² In a study on 255 CABG patients with and without valvular surgery, sotalol administration 2 hours before anesthesia induction resulted in a significant reduction in POAF by 43% compared with placebo.⁶⁶ This agent is even more effective when started before surgery and maintained in the postoperative period. Gomes et al.¹² demonstrated that oral sotalol prevented POAF by 67% when initiated 48 hours before surgery and continued for four days postoperatively.

Although sotalol is an effective drug for post-CABG AF, this drug has been associated with significant adverse effects, including bradycardia and hypotension especially in high doses. In the study of Suttrop and colleagues, high-dose sotalol (240 mg daily) was associated with a higher incidence of adverse drug events necessitating cessation of therapy than low-dose (120 mg daily) sotalol (10.7% vs. 2.9%; p value < 0.02).⁶⁷ Gomes et al.¹² similarly showed that sotalol with a daily dose of 160-240 mg significantly reduced POAF without appreciable side effects (5% significant bradycardia and no torsades de pointes). In another study, a high-dose sotalol regimen (320 mg daily) was associated with significant bradycardia in 22% of the patients.⁶⁸ These data indicated that low-dose sotalol (< 240 mg daily) is well tolerated by cardiac surgery patients. However, significant adverse effects are still an important issue, not least in patients with electrolyte disturbance.

Procainamide

Two studies evaluated the efficacy and safety of prophylactic procainamide in preventing AF after CABG.^{73, 74} In the first study, oral procainamide for 4 days after operation did not significantly reduce the incidence of POAF in patients who underwent CABG.⁷³ No serious cardiac or noncardiac adverse events were noted during procainamide therapy. In the study of Laub et al.,⁷⁴ the oral or intravenous administration of procainamide within 1 hr of the patient's arrival in the intensive care unit and continued for 5 days marginally reduced the episodes of POAF after CABG compared with the placebo.

Propafenone

Effect of prophylactic propafenone was evaluated in two studies. Kowey et al.⁷⁵ tested the efficacy and safety of two doses (675 mg or 450 mg daily) of oral propafenone in a group of 293 patients who underwent CABG. Oral propafenone 675 mg/day did not significantly reduce the incidence of AF and had no impact on the length of hospital stay. The



second study similarly showed no benefit for propafenone administration in reducing POAF.⁷⁶

Magnesium

Hypomagnesemia has been suggested as a cause of both supraventricular and ventricular tachycardias, and it is an independent risk factor for the development of POAF in cardiac surgery patients. Therefore, it has been hypothesized that magnesium supplementation may reduce the incidence of POAF after heart surgery. Several clinical trials have examined the use of intravenous magnesium sulfate for the prevention of AF after CABG.⁷⁷⁻⁸⁰ Some studies reported a dramatic reduction in POAF in patients who received magnesium supplement,^{77, 78} whereas other studies failed to show any benefit for intravenous magnesium administration.^{79, 80} A meta-analysis of eight identified RCTs revealed that the use of intravenous magnesium supplementation was associated with a significant reduction in the AF incidence after CABG (OR: 0.64, 95% CI: 0.47-0.87; p value = 0.004).⁸¹ The additive effect of the intravenous magnesium to other antiarrhythmic agents has also been investigated in a few studies. In the study of Bert et al.,⁸² magnesium did not offer additional significant benefit to that provided by beta blockers. Solomon et al.⁸³ randomized 167 CABG patients to receive propranolol alone or propranolol plus magnesium. Similarly, the results of this study failed to show any advantages for the propranolol-treated patients compared with the propranolol plus magnesium-treated patients (19.5% vs. 22.4%; p value = 0.65). Considering these data, the routine administration of magnesium supplement is not recommended in all patients undergoing surgical revascularization except for patients with hypomagnesemia.

Anti-inflammatory agents

POAF may be in part related to the systemic inflammatory response induced by extracorporeal circulation in on-pump cardiac surgery patients. Consequently, it is expected that anti-inflammatory agents, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) prevent AF after open heart operations.

In a randomized clinical trial on 90 CABG patients, the postoperative administration of NSAIDs (IV ketorolac for 24 hours followed by oral ibuprofen) significantly decreased the incidence of POAF compared to those receiving pain medications other than NSAIDs (4.3% vs. 25.5%, p value = 0.01).⁸⁴ On the other hand, the NAFARM (Naproxen as Prophylaxis against Atrial Fibrillation after Coronary Artery Bypass Graft Surgery) randomized trial failed to show the effect of naproxen on the prevention of POAF after CABG.⁸⁵ Additionally, there was a significant increase in acute renal failure in patients receiving naproxen 275 mg twice daily.

Halonen et al.⁸⁶ investigated the role of corticosteroid

therapy for the prevention of POAF after cardiac surgery. In this double-blind randomized study, 241 patients were randomized to receive either 100-mg hydrocortisone (the first dose in the evening of the operative day, followed by one dose every 8 hours during the next 3 days) or placebo. Incidence of POAF was significantly lower in the hydrocortisone group (30%) than in the placebo group (48%, p value = 0.004) without increasing superficial or deep wound infection or other major complications. Meta-analysis of corticosteroid therapy showed a 26-45% reduction in POAF and shorter hospital stay.⁸⁷ However, due to potential detrimental effects on glucose metabolism, wound healing, and infection, their use for AF prevention is limited. In the recent ESC 2010 guidelines, corticosteroids are considered as a class IIB recommendation to reduce the incidence of AF after cardiac surgery.⁴⁰

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

It has been demonstrated that angiotensin II has an important role in the development of AF in nonsurgical patients. Accordingly, it has been hypothesized that antagonizing the effects of angiotensin II with drug therapy may help to prevent AF. However, the role of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) has never been investigated in a randomized clinical trial in post-CABG patients. In addition, there are safety issues about the potential risk of renal failure in patients receiving ACEIs and ARBs early after surgery.⁴⁰

Statins

Inflammation has been claimed to be involved in the pathogenesis of the AF after cardiac surgery. On the other hand, a potent anti-inflammatory action has been suggested for statins in cardiac surgery patients. Similar to the other anti-inflammatory agents, statins are expected to reduce the incidence of POAF after CABG. Interestingly, a meta-analysis of eight RCTs showed a significant benefit for the preoperative statin administration in reducing the incidence of AF (RR: 0.57, 95% CI: 0.45-0.72, p value < 0.0001) and total hospital stay (weighted mean difference 0.66 days, 95% CI: 0.3-1.01 days, p value = 0.0004) after cardiac surgery.⁸⁸ In addition, there was an association between length of preoperative statin therapy and POAF risk reduction (3% reduction per day, p value = 0.008). However, there was no dose-response relationship between statins and POAF (p value = 0.47). It appears that preoperative statin prophylaxis is effective in preventing POAF after cardiac surgery and earlier treatment produces greater benefit. In the latest ESC guidelines for AF management, statins are considered for the prophylaxis of new-onset AF after isolated CABG, combined with valvular surgery.⁴⁰

Nonpharmacological interventions

Atrial pacing

Overdrive atrial pacing may exert its preventive effect on post-CABG AF by suppressing bradycardia-induced irregular heart rate, overdrive suppression of atrial premature beats, suppressing compensatory pauses after atrial premature beats, and resynchronizing atrial activation.⁸⁹ Efficacy of right atrial (RA), left atrial (LA), and biatrial (BiA) pacing has been studied in several randomized studies. Fan et al.⁹⁰ evaluated the efficacy of BiA pacing in preventing post-CABG AF compared with single site atrial pacing in 132 patients. BiA pacing (12.5%) was more effective than the other three groups (LA, 36.4%; RA, 33.3%; no pacing, 41.9%; p value < 0.05) in reducing the incidence of POAF. Hospital stay was also significantly decreased in the BiA pacing group. Similarly, Daoud et al.⁹¹ reported a lower rate of AF in patients treated by BiA pacing (10%) compared with those treated by RA pacing at 45 bpm (28%, p value = 0.03) and RA-triggered pacing at a rate of ≥ 85 bpm (32%, p value = 0.01). Still, there was no difference between the three groups in terms of the duration of hospital stay, morbidity, and mortality. These encouraging results with BiA pacing were not confirmed in the AFIST II (The Atrial Fibrillation Suppression Trial II), using atrial septal pacing⁶⁵ and the Hakala study, using RA pacing.⁹² In a review of 10 RCTs, AF incidence was reduced by overdrive pacing regardless of the atrial pacing site or pacing protocol (fixed rate vs. flexible algorithm).⁹³ It appears that BiA pacing is more effective than single-site pacing; be that as it may, available data do not permit a firm recommendation on the application of this intervention in a post-CABG setting. Recently, the ESC 2010 guidelines on AF management considered BiA pacing as a class IIB recommendation for AF prevention after cardiac surgery.⁴⁰

Anterior fat pad excision (ventral cardiac denervation)

An anterior fat pad (AFP) is located on the anterior surface of the atria between the aorta and right pulmonary artery.⁹⁴ Canine data suggest that AFP excision during cardiothoracic surgery would reduce the risk of developing POAF.^{95,96} Melo et al. confirmed these data in a prospective nonrandomized study.⁹⁷ They showed a lower incidence of post-CABG AF in patients with AFP excision (7%) compared with a control group (27%). However, another human study on 55 patients undergoing CABG paradoxically showed that the preservation of the human AFP during CABG decreased the incidence of POAF.⁹⁸ This paradoxical result was, similarly, repeated in an RCT on 220 patients undergoing CABG (21% vs. 10%, p value = 0.025).⁹⁹ In a pilot study, 131 patients were

randomized to on-pump CABG or off-pump CABG.¹⁰⁰ The patients who had AFP removal (on-pump) had a significantly higher incidence of POAF (OR: 3.49, 95% CI: 1.09-11.18; p value = 0.035). Nonetheless, nonrandomized extension of this study ($n = 320$) failed to show any benefit for the preservation or excision of AFP in relation to post-CABG AF.¹⁰¹ Alex et al.¹⁰² evaluated the effectiveness of AFP excision in reducing the incidence of POAF in 140 CABG patients. They also failed to show any benefit for AFP excision (p value = 0.3). The AFIST-III (Atrial Fibrillation Suppression Trial-III), the largest and latest RCT to date, randomized 180 CABG patients to either AFP preservation or AFP excision.¹⁰³ The result of this trial revealed no benefit for AFP maintenance in reducing the incidence of POAF. Taken together, available data indicated that there is no benefit for AFP preservation or removal in preventing post-CABG AF.

Conclusions

Beta blockers represent the most cost-effective prophylaxis for POAF in the setting of CABG. Preoperative and postoperative beta blockers are recommended in all cardiac surgery patients as the first-line medication to prevent POAF. Sotalol and amiodarone are also effective and can be considered appropriate alternatives in high-risk patients. Patients who need urgent CABG may benefit from a combination of intravenous and oral amiodarone in addition to beta blockers. Corticosteroids and BiA pacing may be considered in selected CABG patients but are associated with risk. Magnesium supplementation should be considered in patients with hypomagnesemia. There are currently no definitive data to support the notion that treatment with NSAIDs, ACEI, ARB, procainamide, and propafenone, or AFP retention could reduce POAF.

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