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Pharmacological strategies for prevention of postoperative atrial fibrillation

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Summary

Atrial fibrillation (AF) complicating cardiac surgery continues to be a major problem that increases the postoperative risk of stroke, myocardial infarction, heart failure, costs and long-term survival. The incidence of AF after surgery has not significantly changed over the last two decades, despite improvement in medical and surgical techniques. The mechanism and pathophysiology underlying postoperative AF (PoAF) is incompletely understood and results from a combination of acute and chronic factors, superimposed on an underlying abnormal atrial substrate with increased interstitial fibrosis. Several antiarrhythmic and non-antiarrhythmic medications have been used for the prevention of PoAF, but the effectiveness of these strategies has been limited due to a poor understanding of the basis for the increased susceptibility of the atria to AF in the postoperative setting. In this review, we summarize the pathophysiology underlying the development of PoAF and evidence behind pharmacological approaches used for its prevention in the postoperative setting.

Keywords

postoperative atrial fibrillation; prevention; antiarrhythmic agents; beta-blockers; statins; antioxidants; amiodarone; cardiac surgery

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Introduction

Atrial fibrillation (AF) complicating cardiac surgery continues to be a major problem that increases short-term complications, hospital costs and long-term survival [1-4]. The association of postoperative atrial fibrillation (PoAF) with postoperative risk of stroke, myocardial infarction (MI), congestive heart failure and ventricular arrhythmias is well documented and its incidence not significantly altered over the last two decade, despite improvement in medical and surgical techniques [5]. The reported incidence of PoAF varies from 10%-60% depending on the type of cardiac surgery (coronary artery bypass graft [CABG], valvular or combined procedure) and underlying cardiac structural and functional abnormalities [1,2,5-7]. The mechanism and pathophysiology underlying PoAF is incompletely understood and results from a combination of acute and chronic factors, such as inflammation, oxidative stress and sympathetic activation, superimposed on an underlying abnormal atrial electrical or structural substrate with increased extracellular matrix deposition and interstitial fibrosis [8-12]. Several antiarrhythmic and nonantiarrhythmic medications have been used for the prevention and treatment of PoAF, but the effectiveness of these strategies has been limited [5,13] due to a poor understanding of factors that increases susceptibility toward initiation or maintenance of AF in the postoperative setting. Increased insights into the pathophysiology underlying PoAF is required to improve therapeutics for the prevention of PoAF and to reduce its impact on morbidity and mortality in the short- and long-term [1-4]. An improved insight into cellular and molecular processes that increases automaticity and triggered activity within the atria and promote the substrate for reentry that contributes to the initiation, maintenance, and progression of AF has been extensively reviewed in several recent state-of-the-art manuscripts [8,9,14]. In this review, we summarize the evidence for the use of various antiarrhythmic and non-antiarrhythmic pharmacological strategies in the prevention of PoAF.

Pathophysiology of Postoperative Atrial Fibrillation

The underlying mechanisms and signaling pathways involved in the development of PoAF after cardiac surgery are incompletely understood [8-12]. Therefore, strategies to prevent PoAF are only partially effective with no additive effect on the reduction in overall incidence of PoAF over the last two decades [5]. Numerous predisposing factors, such as advanced age, coronary artery disease, heart failure, hypertension, mitral valve disease and a previous history of atrial fibrillation [1,5,15-17], have been shown to alter the structure and function of the atria, remodeling the substrate that promotes atrial fibrillation and its progression. The interaction of acute surgery-related factors such as sympathetic activation, inflammation, renin-angiotensin aldosterone system activation, trauma and oxidative stress [10,12,18-20] with the underlying abnormal atrial substrate precipitates electrical instability and onset of atrial fibrillation in the immediate postoperative period (Figure 1) [17]. Evidence regarding the presence of a pre-existing arrhythmogenic atrial substrate [21] that is destabilized by acute surgery-related factors is suggested by the occurrence of PoAF in a majority of patients with underlying atrial disease [8,21,22]. Strong clinical evidence supports the role of neurohormonal activation in precipitation of PoAF [11,23,24]. Increased heart rate variability and frequent atrial ectopy in the postoperative period representing increased sympathetic activity, as well as increased norepinephrine levels and renin-angiotensin

system activation, have been demonstrated in patients with PoAF [11,19,24,25]. At the cellular level, abnormal Ca^{2+} handling and oxidative stress due to ischemia/reperfusion injury during the operative procedure activates a chain of events causing myocardial injury, cell death and inflammation that contributes to electrophysiological instability and precipitation of PoAF [9,26,27]. Similarly, systemic inflammatory effects of cardiac surgery expressed as increased C-reactive protein and inflammatory cytokine levels, as well as complement activation, coincide with the peak PoAF incidence, advocating a direct immune-mediated effect [10,18,28].

Hence, the majority of interventions that reduce the incidence of PoAF target the neurohumoral system (beta-blockers, amiodarone, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker [ARB]), cardiac excitability and conduction through ion channel (sotalol, dofetilide, magnesium), myocardial energy demands (beta-blockers), reduce inflammation (statins, steroids, colchicine, polyunsaturated fatty acids [PUFA]) or oxidative stress (ascorbate, n-acetyl cysteine, n-PUFA) (Figure 2). These interventions are partially effective in reducing the incidence of PoAF by counteracting acute triggering factors but have only limited impact on the underlying substrate that causes progressive structural alterations, atrial enlargement and fibrosis that increases predisposition to AF [8,21,22]..

Pharmacological prevention

Beta-blockers

The rationale for the perioperative use of beta-blockers is to diminish myocardial oxygen demand and overall ischemic events by blunting the chronotropic and inotropic effect of catecholamine surge in the postoperative period [24]. Slowing of the heart rate also improves diastolic filling, which allows better perfusion of the endocardium. Thus, by reducing ischemic events during surgery, beta-blockers have a beneficial effect in reducing adverse events, including the development of PoAF [29,30], as long as care is taken not to cause excessive bradycardia, hypotension or hemodynamic instability in the postoperative period [31,32]. In patients on chronic beta-blockers, its abrupt discontinuation postoperatively results in a two- to fivefold increase in the incidence of PoAF [24,33]. The beneficial effect of beta-blockers has been demonstrated in several clinical studies in patients undergoing CABG or valve surgery alone or in combination (Table) [34-36].

In a large North American observational analysis of 629,877 patients undergoing CABG in the Society of Thoracic Surgeons National Adult Cardiac Surgery Database [37], preoperative beta-blockers were associated with a lower 30-day unadjusted mortality (2.8% vs. 3.4%; odds ratio [OR], 0.80; 95% confidence interval [CI], 0.78-0.82, $p<0.001$) and major procedural complications. In those with mild-to-moderate left ventricular (LV) dysfunction (ejection fraction [EF] >30-50%) there was a trend toward improved mortality, but in those with severely depressed function (left ventricular ejection fraction [LVEF] <30%), a non-significant trend toward increased 30-day mortality (OR, 1.13; 95% CI, 0.96-1.33; p=23) was present. In patients with multiple risk factors in whom a long-term beta-blocker is indicated for prevention of cardiovascular (CV) events [32], this should be continued, and in those not previously treated, a beta-blocker should be started at least 2-7

days before surgery. Initiation of beta-blockers in the immediate perioperative period [32,38-40] is associated with adverse events, as recently demonstrated in the POISE [31] (The PeriOperative Ischemia Study Evaluation) trial. In this randomized, controlled trial (RCT) enrolling 8,351 patients undergoing non-cardiac surgery, a reduction in cardiac events including ischemia and PoAF was demonstrated in the beta-blocker group compared to placebo, but this was associated with an increase in total mortality (3.1 vs. 2.3%; p=0.03) and the incidence of stroke (1.0 vs. 0.5%; p=0.005), possibly due to beta-blocker-induced hypotension (15% vs. 9.7%) and bradycardia (6.6% vs. 2.4%). This is proposed to be due to the use of metoprolol succinate at a high starting dose of 100 mg that was then titrated up to 200 mg daily. This and other studies indicate that the use of beta-blockers should be individualized based on CV risk factors [41], especially in patients who are beta-blockers naïve, and high doses of long-acting formulation without dose titration with the potential for hypotension and bradycardia avoided. Only limited information is available about dose titration before surgery, and the best titration protocol has not been defined by RCT [42]. However, it is prudent to titrate to a dose that will have an anti-ischemic effect and prevent excessive increase in heart rate [43]. Abrupt withdrawal of a beta-blocker after long-term use is detrimental and should be avoided [24,33]. Data about the selection of the most effective beta-blocker in reducing PoAF is limited. Improved efficacy of carvedilol over metoprolol was demonstrated in two studies with 18-20% greater reduction of PoAF in those on carvedilol (44-46); however, the length of hospital stay was not reduced [47].

According to the American College of Cardiology (ACC)/American Heart Association (AHA) and Heart Rhythm Society (HRS) 2014 guidelines; unless contraindicated, perioperative treatment with oral beta-blockers is recommended as a Class IA indication in patients undergoing cardiac surgery [48]. In patients undergoing non-cardiac surgery, caution should be exercised with the use of beta-blockers [32]. In patients already receiving beta-blockers, their use should be continued (Class IA). In patients at high risk for CV events or with known ischemic heart disease or myocardial ischemia, preoperative initiation of beta-blockers may be considered (Class IIB). In patients at low risk for surgery, beta-blockers initiated before surgery are not recommended and high-dose beta-blockers without titration also are not recommended (Class III). Patients on beta-blockers during and after surgery must be carefully monitored if hypotension or bradycardia develops, and the dose reduced or temporarily held.

Amiodarone

Amiodarone, an antiarrhythmic agent with multiple ion channel blocking properties as well as an anti-adrenergic effect, has been shown in several RCTs to be effective in reducing the occurrence of PoAF by 12% to 51% when compared to placebo (Table) (49-53). In the Intravenous and Oral Amiodarone for the Prevention of PoAF in Patients Undergoing Off-pump Coronary Artery Bypass Surgery trial, amiodarone infusion (5 mg/kg loading in the first postoperative hour, then 10 mg/kg for the first 24 hours) followed by oral administration (600 mg/day for 7 days and then 200 mg/day for 1 month) significantly reduced the incidence of new-onset AF (11.8% versus 26.5% control; p=0.025), the maximal ventricular rate response during AF and the duration of AF [54]. Similar reduction in PoAF was obtained in the Atrial Fibrillation Supression Trial II (AFIST II), with intravenous and oral

amiodarone compared to the placebo or septal pacing group [55]. The overall risk of PoAF was reduced by 43% (p=0.037) and symptomatic AF by 68% (p=0.019) in amiodarone-treated patients vs. placebo. Intravenous amiodarone given postoperatively immediately after open heart surgery was shown to reduce the incidence of PoAF (35% vs 47%; p=0.01) without significantly altering the length of stay in 300 patients undergoing standard open heart surgery randomized in a double-blind fashion to intravenous amiodarone (1 g/day for 2 days) vs. placebo [53]. Oral amiodarone use starting 6 days prior to surgery and continuing through six days after surgery in the PAPABEAR (Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair) trial, a double-blind, randomized, placebo-controlled trial enrolling 601 patients demonstrated a significant reduction in PoAF (16% vs. 30% in placebo group; p<.001) in both patients younger than 65 years (19% vs. 36%; P = .02) and those 65 years or older (28% vs. 54%; p<.001); in patients who had CABG surgery only (22% vs. 46%; p=0.002), or valve replacement/repair surgery with or without CABG surgery (25% vs. 44%; p=0.008); in patients who were on preoperative beta-blocker therapy (27% vs. 42%; p=0.03); and in those who did not receive preoperative beta-blocker therapy (20% vs. 48%; p<0.001), respectively. There were no differences in serious postoperative complications, in-hospital or 1-year mortality, or hospital readmission within 6 months of discharge [56].

The dose response relationship of amiodarone and its pre- or postoperative use in reducing the incidence of PoAF was assessed in a meta-analysis evaluating 14 RCTs in 2,864 patients, stratified into low (<3 g), medium (3-5 g), or high (>5 g) dosage and preoperative or postoperative timing. The incidence of PoAF was significantly reduced by amiodarone when compared to placebo (p<0.001). However, no difference in PoAF outcomes was observed among the three dosing groups nor was there a difference based on pre- or postoperative administration of amiodarone [57]. This study suggests that total amiodarone doses of 3 grams or higher may be effective in reducing the rate of PoAF and that preoperative administration may not be necessary. However, this needs to be confirmed in a prospective manner. Another recent meta-analysis including 3,950 patients [58] reported that both oral and intravenous administration, as well pre- and postoperative administration, of amiodarone was effective in prevention of PoAF after cardiac surgery. Although superior to placebo in reducing the risk for PoAF, no significant superiority of amiodarone over other antiarrhythmic agents, such as beta-blockers (propranolol, metoprolol and bisoprolol) and sotalol, could be established [49,55,59]. Amiodarone has significant extracardiac (pulmonary, hepatic, visual and thyroid toxicity) and cardiac adverse effects, including significant bradycardia and QT interval prolongation, and caution should be used with its use; particularly, attention should be paid to potential drug-drug interactions with other medications [60]. In a meta-analysis of 18 trials including 3,408 patients, an increase in the incidence of adverse reactions (bradycardia and hypotension), especially with intravenous formulation, was reported, and therefore amiodarone should not be routinely used and should be reserved for patients with a high risk of developing PoAF [60].

In the most recent ACC/AHA/HRS guidelines published in 2014, amiodarone use is recommended as a Class IIa indication for reduction of PoAF in high-risk individuals undergoing cardiac surgery or in patients unable to tolerate beta-blockers [48]. Amiodarone also is recommended as a first-line drug in patients with heart failure who develop PoAF

with rapid ventricular rate response because digoxin is frequently ineffective in controlling ventricular rate with high adrenergic postoperative states and beta-blockers or non-dihydropyridine calcium channel blockers may not be tolerated due to negative inotropic effects in patients with severe ventricular systolic dysfunction.

Sotalol

The evidence for the effectiveness of Sotalol, a beta-blocker with Class III antiarrhythmic effects, in prevention of PoAF comes from several small studies with reduction in the incidence of PoAF between 13%-16% [49,61-64]. In a comparative assessment of sotalol vs. conventional beta-blockers, 5 studies showed a significant decrease in the occurrence of PoAF with sotalol when compared to beta-blockers [65]. In another meta-analysis of 14 trials (five trials vs. beta-blockers; seven vs. placebo and two with both beta-blockers and placebo)[66] including 2,583 patients, sotalol when compared to beta-blockers was more effective in reducing PoAF from 25.7% vs. 13.7% (OR 0.42, 95% CI 0.26-0.65). However, the sotalol group had more side effects such as hypotension and bradycardia compared to placebo groups (6% vs. 1.9%, p=0.004). Another study reported a significantly increased risk of adverse events (10.7% vs. 2.9%) with higher sotalol dosing (240 mg) vs. low-dose sotalol (120 mg daily) [67]. Gomes et al. similarly showed that a moderate sotalol dose of 160–240 mg daily significantly reduced PoAF without appreciable side effects [68]. The above data indicate that low-dose sotalol (<240 mg) may be better tolerated, reducing PoAF without significant side effects. Despite its demonstrated effectiveness, sotalol is considered a second-line drug due to its effect on QT interval prolongation and higher incidence of proarrhythmia, including torsades de pointes, as well contraindication to its use in patients with renal insufficiency, congenital long QT syndrome or prolonged repolarization (QTc >460 ms), safety concerns in patients with advanced heart failure and the requirement for monitoring of the QTc interval. In the most recent 2014 ACC/AHA/HRS guidelines, preoperative administration of sotalol is recommended as a Class IIb indication for patients at risk of developing PoAF following cardiac surgery [48].

Dofetilide

Dofetilide, a Class III antiarrhythmic, was reported to be useful in prevention of postoperative atrial tachyarrhythmia following CABG with and without valve surgery [69]. In a double-blind, randomized, placebo-controlled study including 133 patients, dofetilide significantly reduced postoperative atrial tachycardia (18% vs. 36%; p<0.017). Interestingly, the number needed to prevent 1 patient from developing PoAF was only 5.4 patients [69]. There was no incidence of torsades de pointes in this study with a limited number of patients. Dofetilide currently is not recommended as a first-line therapy for prevention of PoAF due to the need for close rhythm monitoring, side effects and increased risk of QT interval prolongation and proarrhythmia.

Ibutilide

Ibutilide fumarate: a Class III antiarrhythmic drug approved for the acute termination of AF and atrial flutter (AFl) was shown to be more effective than placebo (57% 1.0 mg ibutilide vs. 15% on placebo) in converting new onset AF or AFl (occurring 1 to 7 days after surgery) to sinus rhythm in a randomized, controlled study [70]. Ventricular arrhythmias were the

most serious adverse effect (8.3% in ibutilde group vs. 1.2% in the placebo group). Although it has no role in the prevention of PoAF, ibutilide is recommended as a Class IIa indication for pharmacological cardioversion in patients who develop PoAF [48]. The caveat: It require continuous electrocardiographic monitoring for at least 4 hours after infusion or until the prolonged QTc interval returns to baseline.

Non-dihydropyridine calcium channel blockers

There is some evidence regarding the usage of non-dihydropyridine calcium channel blockers (diltiazem and verapamil), which are Class IV antiarrhythmic agents, in the prevention of PoAF following cardiac [71] and non-cardiac [72] surgery. A meta-analysis of 41 studies including 3,327 patients reported that non-dihydropyridine calcium channel blockers significantly reduced MI (OR 0.58; 95% CI: 0.37 to 0.91; p=0.02), ischemia (OR 0.53, 95% CI 0.39 to 0.72; p<0.001) and supraventricular tachycardia (OR 0.62, 95% CI 0.41 to 0.93; p=0.02), which included patients with AF and atrial flutter [72]. The same group in a separate systematic review of 11 studies involving 1,007 patients undergoing non-cardiac surgery reported a reduction in the occurrence of supraventricular tachycardia (SVT) (relative risk: 0.52; 95% CI: 0.37 to 0.72; p<0.0001) with the perioperative use of non-hydropyridine calcium channel blockers [72]. However, other meta-analyses failed to show a significant reduction in the incidence of postoperative SVT with non-dihydropyridine calcium channel blockers following CABG surgery. Currently, routine usage of non-dihydropyridine calcium channel blockers is not recommended by ACC/AHA/European Society of Cardiology (ESC) guidelines for the prevention of PoAF. However, in patients who develop PoAF, a non-dihydropyridine calcium channel blocker, is recommended as a Class I indication when a beta-blocker is inadequate to achieve rate control in both the ACC/AHA [32] and ESC [36] guidelines.

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins)

3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins), routinely prescribed to lower LDL cholesterol, have been shown in multiple observational studies to reduce CV events, including PoAF, by improving lipid profile and pleiotropic anti-inflammatory, antioxidative, cardioprotective, neurohumoral modulatory and coronary plaque stabilizing effects [73], reducing perioperative, 30-day and long-term mortality and CV events after cardiac or non-cardiac vascular surgery [10,74-78]. In a recent meta-analysis of 15 RCTs involving 2,292 statin-naive patients undergoing cardiac or non-cardiac surgery, a reduction in the risk of PoAF was reported with the perioperative use of statins (relative risk [RR], 0.56; 95% CI, 0.45 to 0.69) [79] along with the risk of MI (RR, 0.53; 95% CI, 0.38 to 0.74) but not death (RR, 0.62; 95% CI, 0.34 to 1.14). Overall, the duration of hospital stay was reduced in statin-treated patients but length of intensive care unit stay was unaffected. Preoperative initiation of statins (median 37 days before vascular surgery) when compared to placebo have been associated with a reduction in postoperative myocardial ischemia (hazard ratio, 0.55; CI, 0.34 to 0.88; p=0.01), death from CV causes or MI (HR, 0.47; CI, 0.24 to 0.94; p=0.03) without any significant increase in the rate of adverse events [77].

In a recent Cochrane review of 5 RCTs of statin-naive patients undergoing elective or emergency non-cardiac arterial surgery treated with statin therapy (178 patients), started before or on the day of surgery and continuing for at least 48 hours afterward, a non-significant decrease in risk of 30-day all-cause mortality (RR 0.73, CI 0.31 to 1.75), CV mortality (RR 1.05, % CI 0.07 to 16.20) and non-fatal MI (RR 0.47, CI 0.15 to 1.52) compared to placebo was reported [80]. The number of patients (178) included in the meta-analysis was limited. Most studies involving statins in the prevention of PoAF have been promising. Atorvastatin was reported to decrease PoAF following CABG surgery by 14-22% when compared to placebo or usual care [81,82]. The Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery study (ARMYDA-3), including 200 statin-naive patients undergoing elective cardiac surgery with cardiopulmonary bypass, reported that atorvastatin 40 mg daily starting 7 days prior to surgery when compared to placebo significantly reduced the incidence of PoAF (35% versus 57%, p=0.003) and length of stay (6.3±1.2 days vs. 6.9±1.4; p=0.001) [83]. Benefits of statin pretreatment in the prevention of PoAF (24.9 vs. 29.3%; OR 0.67, 95%CI: 0.51-0.88, p<0.001) [84] and reduction in hospital stay (weighted mean difference −0.66 days, 95% CI −1.01 to −0.30 days, p=0.0004) [85] also was demonstrated in 2 other meta-analyses [84,85]. Higher doses of statins had a more protective effect than lower doses in prevention of PoAF [86,87]. One retrospective study including 680 patients reported that higher-dose simvastatin (40 mg) and atorvastatin (40 mg) demonstrated the greatest benefit in reduction of PoAF (15.6% and 21.2%) vs. no statins (ORs, 3.89 [p<0.0001] and 2.76 [p=0.012]) or lower doses [80,88]. Similarly, Mithani et al. reported that patients undergoing cardiac surgery treated with higher-dose simvastatin (>20 mg) daily had a 36% reduction in the risk of PoAF (OR 0.64, 95% CI 0.43 to 0.6; p=0.03) in comparison to those taking lower dosages [87]. Combination of atorvastatin with a beta-blocker appears to be more effective than either drug alone, reducing the risk of PoAF by 90% (OR 0.10; 95% CI 0.02-0.25) in one study [83]. In a recent meta-analysis, statin treatment perioperatively was not associated with a significant reduction of PoAF (OR 0.95; 95% CI 0.88-1.03, p=0.24) beyond 6 months follow-up in CABG patients [88]. Information on PoAF prevention with preoperative statin use in patients undergoing valvular or non-coronary heart surgery are not available [48]. The reduction in PoAF with perioperative use of statins is therefore not universally reported in observational studies that do not provide precise information about the timing of initiation, the duration of statin therapy or the mechanism of benefit. Despite limited data from RCTs that enrolled only a small number of patients, the overall evidence from observational studies points toward a protective effect of perioperative statin use on cardiac complications during cardiac and non-cardiac surgery.

The recent guidelines by ACC/AHA and ESC do recommend perioperative continuation of statins as a Class I indication in patients undergoing non-cardiac vascular surgery [32,40], favoring statins with a long half-life or extended-release formulation and preoperative initiation of statins as a Class IIa indication, ideally at least 2 weeks before surgery. In patients without cardiovascular disease, preoperative initiation of statins is not indicated for primary prevention of AF.

Magnesium

The data on magnesium supplementation for the prevention of PoAF is conflicting [89-95]. Therefore, supplementation of magnesium in only those with depleted stores has been recommended. However, most large RCTs failed to demonstrate a beneficial effect of magnesium supplementation on prevention of PoAF [92,94-96]. In a meta-analysis of 20 RCTs (2,490 patients), Miller et al. reported a beneficial effect of magnesium supplementation on PoAF reduction (18% vs. 28%; OR 0.54, 95% CI 0.38 to 0.75) without change in the length of stay or overall mortality [97]. This meta-analysis included a small sample size with variation in study design among various studies, limiting results interpretation. Preoperative administration of magnesium compared to intraoperative or postoperative supplementation appears to be more effective in preventing PoAF [98]. The overall data at this time do not support the routine use of magnesium supplementation as monotherapy for the prevention of PoAF in patients going for cardiac surgery.

Corticosteroids

Prophylactic short-term corticosteroid usage as an anti-inflammatory agent has shown some benefit in the prevention of PoAF following cardiac surgery [10,68,99-101]. Prasonsukarn et al., in a study including 88 patients undergoing CABG, demonstrated that 1 gm of intravenous methylprednisolone before surgery and 4 mg dexamethasone every 6 hours for 1 day after surgery reduced the incidence of PoAF by 30% when compared to placebo. However, there was no significant difference with regard to the length of hospital stay, and the steroid group had a significant 21% increased complication rate [102]. Similar findings were reported by Halonen et al. in a randomized, multicenter trial including 241 patients undergoing CABG and aortic valve replacement. Intravenous administration of hydrocortisone (100 mg) in the evening of the operative day, then every 8 hours for the next 3 days significantly reduced the incidence of PoAF with no increased risk of postoperative complications [101]. Interestingly, both these studies also used beta-blockers in all patients. Three other recent meta-analyses also have reported that corticosteroids significantly reduced the incidence of PoAF following cardiac surgery [99,100,103].

Baker et al. reported that corticosteroids significantly reduced the incidence of PoAF following cardiac surgery by 45% (OR 0.55, 95% CI 0.39-0.78) and also reduced the length of stay by 1.6 days [103]. Similarly, another meta-analysis by Whitlock et al. of 44 trials including 3,205 patients reported that corticosteroids reduced the incidence of PoAF [RR 0.71, 95% CI 0.59 to 0.87], duration of intensive care unit stay and length of stay [100]. Another recent meta-analysis by Ho et al. [99] reported that corticosteroid prophylaxis significantly reduced the incidence of PoAF, length of hospital stay and length of intensive care unit stay without an increased risk of infection, but increased risk of hyperglycemia. In a Cochrane systematic review of randomized studies assessing the effect of corticosteroids in cardiac surgery patients, Dieleman et al. [104] reported that use of corticosteroids reduced PoAF but had no significant impact on stroke, infection or postoperative mortality. This was confirmed in a RCT of 4,482 patients undergoing cardiac surgery randomized to either intraoperative high-dose dexamethasone or placebo with no beneficial effect of dexamethasone on risk reduction of PoAF (OR 0.94; 95% CI 0.87 to 1.02), stroke or postoperative mortality. More than 50% of the study population, however, was taking beta-

blockers or statins. In another systematic review of randomized, double-blind trials using different corticosteroids, a protective effect with reduction in PoAF (OR 0.56; CI 0.44-0.72, p<0.0001), postoperative blood loss, intensive care unit stay and overall hospital stay was demonstrated. However, there was no effect on postoperative mortality, mechanical ventilation duration, re-exploration for bleeding or postoperative infection [105]. Other trials, however, have not shown a significant benefit in reducing the incidence of PoAF compared to placebo or usual care [106]. At this time, specific formulations or dosing of corticosteroids that confer optimal protection against PoAF are not clear; however, intermediate doses (50-120 mg dexamethasone equivalent) [103] or low (<1,000 mg) to intermediate doses of hydrocortisone (1,000-10,000 mg) [99] appear to be most beneficial. Due to their potential adverse effects, corticosteroids at this time are not routinely recommended for prevention of PoAF but may be considered in high-risk patients [75].

Colchicine

Postoperative systemic inflammation and pericarditis may contribute to PoAF, and drugs known to prevent pericarditis or postpericardiotomy syndrome such as colchicine could be effective in preventing inflammation and PoAF. Colchicine for the Prevention of the Post-Pericardiotomy Syndrome (COPPS) was a multicenter, double-blind trial, and its PoAF substudy was performed to test the efficacy and safety of colchicine (1 mg twice daily starting postop day 3 followed by 0.5 or 0.25 mg twice daily for 1 month) in 336 patients for the prevention of PoAF after cardiac surgery [107]. Patients randomized to colchicine had a 45% relative reduction of 30-day incidence of PoAF (12% vs. 22%, p=0.02, NNT 11), and shorter in-hospital (9.4±3.7 vs. 10.3±4.3 days; p=0.04) and rehabilitation stays (12.1±6.1 vs 13.9±6.5 days; p=0.009) when compared to the standard therapy group without any significant increase in adverse effects. Although, the results of the COPPS POAF substudy were promising, the follow-up COPPS 2 study with preoperative administration of colchicine (0.5 mg twice or once a day starting 2-3 days before surgery) was disappointing in that despite the reduction in the incidence of postpericardiotomy syndrome, there was no significant decrease of PoAF on intention to treat analysis [108]. An increased risk of gastrointestinal adverse effects and higher rate of drug discontinuation further reduced enthusiasm for colchicine for prevention of PoAF in this setting.

Renin-angiotensin-aldosterone system (RAAS) modulators

RAAS has been implicated in atrial remodeling and inflammatory effects, through hemodynamic effects and the release of pro-inflammatory cytokines (i.e. IL-6, IL-8, TNF-α), profibrotic factors, adhesion molecules and selectins, as well as the recruitment of inflammatory cells, but data about potential risks and benefits of drugs modulating RAAS, mainly angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), in the perioperative setting are limited and mainly come from observational studies [19]. Brull et al. reported that ACEI treatment was associated with a significant reduction in IL-6 levels following CABG [109]. Mathew et al. also reported that postoperative administration of ACEI was significantly associated with the reduction of PoAF (OR, 0.62; 95% CI, 0.48-0.79) following CABG [1]. In a smaller prospective study, Ozaydin et al. reported that the treatment with ACEI alone or ACEI plus candesartan (ARB) significantly reduced the incidence of PoAF by 21% and 23%, respectively, when compared to placebo in

128 patients undergoing CABG and valve surgery [110]. However, this beneficial effect was not reproduced in studies enrolling a relatively larger number of patients undergoing cardiac surgery. White et al., in a study enrolling 600 patients, did not find a significant reduction in PoAF (OR; 0.71, 95% CIs 0.42-1.20) with the preoperative use of ACEI or ARB [111]. Similar findings were reported in another retrospective study by Coleman et al. with 1,500 patients [112]. A recent large retrospective study by Miceli et al. [113] including 10,023 patients undergoing CABG also reported no significant reduction in the incidence of PoAF with preoperative use of ACEI. The preoperative use of ACEI doubled the risk of death (OR 2.00, 95% CI 1.17-3.42; p=0.013) and was an independent predictor for the development of new onset PoAF (p<0.0001), mortality and postoperative renal dysfunction. Larger prospective trials are needed to clarify the true effect, if any, of RAAS inhibition on the development of PoAF.

In the current 2014 AHA/ACC/HRS guidelines, treatment with an ACEI or ARB for primary prevention of new-onset AF is recommended as a reasonable choice in patients with heart failure with reduced LVEF (Class IIa) and as a Class IIb indication in the setting of hypertension, but not indicated (Class III) for patients without CV disease [48]. In the perioperative setting, use of ACEIs or ARBs is associated with a risk of hypotension under anesthesia and impaired response to vasopressors, especially when used concomitantly with beta-blockers or other cardioactive drugs [114,115]. Holding ACEIs the day before surgery, if possible, reduces the occurrence of hypotension [115]. In patients with stable LV systolic dysfunction it seems reasonable to continue treatment with ACEIs with close intraoperative and postoperative hemodynamic monitoring. For prevention of PoAF following cardiac surgery, the current guidelines do not recommend initiation of ACEI or ARB [40], but it is reasonable to continue ACEI or ARB perioperatively under close monitoring in patients who are already taking the medicine for LV systolic dysfunction (Class IIa) or to hold transiently before surgery for those taking it for hypertension to avoid hemodynamic instability (Class IIa), and, if held before surgery, to restart as soon as clinically feasible postoperatively [32,40].

N-acetyl cystein

N-acetyl cystein (NAC) is an antioxidant, a free radical scavenger and an anti-inflammatory agent that reduces cellular oxidative damage [116] and therefore could reduce post-cardiac surgery complications including new-onset PoAF. However, the evidence for such a protective effect is conflicting. In a prospective, randomized, double-blind study of 115 patients undergoing CABG with or without valve surgery, NAC treatment decreased the incidence of PoAF by 16% [OR 0.20; 95% CI 0.05 to 0.77; p=0.019] [117]. In another study of 311 patients undergoing cardiac surgery randomized to NAC plus carvedilol, carvedilol or metoprolol, the incidence of PoAF and duration of hospitalization was significantly lower in the NAC plus carvedilol group compared with the metoprolol group (p<0.001) or the carvedilol group (p=0.03) [118]. This was associated with reduced markers of oxidative stress and inflammation [119]. Similar findings were reported in a meta-analysis by Baker et al. including 13 RCTs of 1,300 patients demonstrating a significant 36% [95% CI 2-58%] reduced odds of developing PoAF by NAC [120]. However, this was not confirmed in another prospective, double-blind, placebo-controlled trial of 240 patients randomized to

receive 1.2 gm of NAC twice daily and placebo (n=120) starting 48 hours before and up to 72 hours after cardiac surgery. The study reported no difference in the incidence of PoAF (11.7% vs 15.8%, p=0.34), morbidity, mortality or length of hospital stay between both groups [121]. This also was reported in a meta-analysis of 1,407 patients from 15 RCTs, in which NAC did not reduced the incidence of PoAF following cardiac surgery (OR = 0.67; 95% CI, 0.37-1.22; p=0.19) [122].

The overall quality of studies and the number of patients included does not provide strong evidence for the routine use of NAC for prevention of PoAF and further adequately powered randomized, controlled trials with PoAF incidence as a primary outcome measure are needed. Currently, NAC is not routinely recommended by ESC or AHA/ACC guidelines for the prevention of PoAF following cardiac surgery.

Omega-3 polyunsaturated fatty acids

Long chain omega-3 polyunsaturated fatty acids (n-3 PUFA) have been proposed to reduce arrhythmogenicity due to their membrane stabilizing effect on ion channels and anti-inflammatory and antioxidant properties favorably altering atrial electrical remodeling and reducing susceptibility to atrial arrhythmias in animal models [122-126]. The initial clinical trial demonstrating the benefit of PUFA in PoAF was performed by Calo et al. in 160 patients undergoing CABG. PUFA administration during hospitalization substantially reduced the incidence of PoAF (17%, p=0.013) and length of hospital stay [125]. Another study reported that n-3 LC-PUFA supplements could prevent PoAF in patients with low baseline levels of plasma fatty acids undergoing CABG, but may be harmful in those with high levels [127]. However, two other trials have shown no substantial benefit of PUFA supplementation in the prevention of PoAF following cardiac surgery [128,129].

Recently, Mozaffarian et al. in Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA), a double-blind, placebo-controlled multinational trial randomized 1,516 patients undergoing cardiac surgery to fish oil (1g capsules containing ≥840 mg n-3-PUFAs as ethyl esters) vs. placebo, and demonstrated no significant difference between PoAF outcomes [30% vs. 30.7% in placebo group; OR 0.96 (95% CI, 0.77-1.20); p=0.74) [128]. A further analysis of the OPERA trial by Wu et al. reported that neither individual nor total circulating n-3 PUFA levels nor short-term change with fish oil supplementation was associated with a decreased risk of PoAF [130]. Published data from various meta-analyses have been conflicting. A recent meta-analysis including 8 RCTs and 2,687 patients by Costanzo et al. reported that preoperative supplementation of n-3 PUFA significantly reduces the incidence of PoAF by 16% in patients undergoing cardiac surgery, and this effect was more pronounced with a 34% reduction in PoAF (OR, 0.66; 95% CI, 0.50-0.87; p=0.003) in patients undergoing CABG [126,131]. Another metanalysis by Mariani et al., however, reported no significant benefit (OR 0.86; 95% CI, 0.71 to 1.04) with supplementing n-3 PUFA in preventing PoAF [132]. In a systematic review and meta-analysis of omega-3 fatty acids and cardiovascular outcomes including 20 studies with 63,030 participants, no overall effect was found of omega-3 FA on total mortality (RR=0.95; 95% CI, 0.86–1.04; p=0.28), composite CV events (RR=0.96; 95% CI, 0.90–1.03; p=0.24), cerebrovascular events (RR=1.03; 95% CI, 0.92–1.16; p=0.59), coronary events (RR=0.86;

95% CI, 0.67–1.11; p=0.24) and arrhythmias (RR=0.99; 95% CI, 0.85–1.16; p=0.92) [131]. Thus, the bulk of evidence does not support a beneficial role for omega-3 fatty acid supplementation in preventing PoAF or other CV outcomes.

Ascorbic acid

Ascorbic acid has been proposed as a modulator of oxidative stress with direct electrophysiological effects on the atrial tissue in animal models [133,134]. However, the clinical data largely based on small trials has reported conflicting results. Eslami et al. in a small trial consisting of 50 patients undergoing CABG surgery reported that patients who received 2 g of ascorbic acid the night before surgery and 1 g twice daily for 5 days after surgery had a 22% reduction in the incidence of PoAF (OR 0.119; 95% CI, 0.025-0.558, p=0.002) when compared to placebo [135]. Similar reduction in PoAF was demonstrated by another small study including 85 patients undergoing CABG surgery. The group treated with ascorbic acid had a 16% reduction in the incidence of PoAF (p=0.041) and also a reduced length of hospital stay [6.7±1.9 days vs. 9.5±2.8, p=0.034] when compared to placebo [136]. However, subjects of both studies were treated with beta-blockers as well. A recent prospective, randomized, placebo-controlled trial including 89 patients in the treatment group and 96 controls reported no benefit of routine ascorbic acid supplementation in the prevention of PoAF [30.3% versus 30.2%, p=0.98] [137]. Although preliminary evidence suggests that prophylactic antioxidants may reduce the incidence of PoAF, there is a lack of high-quality data; large-scale, adequately powered clinical studies are warranted to clarify the role of antioxidants in prevention of PoAF [20].

Expert Commentary and 5 year view

PoAF is a relatively common complication of surgery; however, the underlying mechanisms are poorly understood and likely multifactorial. Both acute factors related to surgery and preexisting substrate play an important role in the initiation and perpetuation of PoAF. Current prophylactic strategies to prevent PoAF are directed toward countering postoperative catecholamine surge with beta-blockers, stabilizing atrial electrical substrate with amiodarone or other antiarrhythmic agents or reducing inflammation with statins, corticosteroids or colchicine, and these strategies demonstrate some efficacy compared to placebo. Continuation of beta-blockers is recommended as a Class Ia indication in those already on it, with monitoring for hypotension or bradycardia in the post-operative period [32,39,40]. In those at high risk of cardiovascular events but not on beta-blockers, its initiation may be considered with slow up-titration of the dose, while it is not indicated in those at low risk of CV events. Prophylactic amiodarone use is recommended in high-risk individuals undergoing cardiac surgery or in those unable to tolerate beta-blockers [48] and in heart failure patients who develop AF with rapid ventricular rate response who are unable to tolerate the negative inotropic effect of the beta-blocker or diltiazem. Sotalol can be considered as an alternative in patients with high risk of PoAF with cardiac surgery with perioperative monitoring of the QT-interval. Statin therapy should be continued in those who are already on it, and, in those at high risk of PoAF, its initiation can be considered at least 2 weeks prior to cardiac surgery [32,40], In patients without cardiovascular disease, preoperative initiation of statin is not indicated for primary prevention of AF. RAAS

inhibitors such as ACEI or ARB can be continued in patients with heart failure with reduced ejection fraction or hypertension, with close monitoring for hypotension. Initiation of ACE or ARBs preoperatively in patients without cardiovascular disease is not recommended. The use of corticosteroids is associated with potential adverse effects and, therefore, it is also not routinely recommended for prevention of PoAF but may be considered in high-risk patients [75].

Overall, the selection of prophylactic intervention for PoAF needs to be individualized to a patient's condition and the risks and adverse events associated with each intervention. Drugs with potential risk of proarrhythmia or toxicity, such as sotalol and dofetilide, are not recommended for routine use and when used should be carefully monitored. Better identification of high-risk patients undergoing cardiac surgery and selective use of pharmacologic therapies helps to reduce PoAF, thereby reducing morbidity, length of hospital stay and related health care costs. However, these interventions are only partially effective in reducing PoAF mainly by counteracting acute triggering factors and have only limited impact on the underlying substrate that accompanies aging and aging-associated diseases that cause progressive atrial enlargement and fibrosis that increases predisposition to recurrent AF and its complications [8,21,22]. Additional research is therefore warranted to better understand molecular mechanisms underlying the development of AF and to identify novel therapeutic targets that can help prevent or reverse the substrate that increases predisposition to postoperative and later occurrence of AF.

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Reference annotations

* Of interest

** Of considerable interest

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Key issues

- Atrial fibrillation complicating cardiac surgery continues to be a major problem that increases the postoperative risk of stroke, myocardial infarction, heart failure, costs and long-term survival.
- Several antiarrhythmic and non-antiarrhythmic medications have been used for the prevention of postoperative atrial fibrillation, but the effectiveness of these strategies has been limited due to a poor understanding of the basis for the increased susceptibility of the atria to fibrillation in the postoperative setting.
- The interaction of acute surgery-related factors such as sympathetic activation, inflammation, renin-angiotensin aldosterone system activation, trauma and oxidative stress with an underlying abnormal atrial structural substrate precipitates electrical instability and onset of atrial fibrillation in the immediate postoperative period, and these factors are the target for pharmacological prevention of postoperative atrial fibrillation.
- The selection of prophylactic intervention needs to be individualized to a patient's condition and the risks and adverse events associated with each intervention.
- In patients at high risk for cardiovascular events or myocardial ischemia undergoing cardiac surgery, beta-blockers should be continued or initiated to reduce postoperative atrial fibrillation with avoidance of hypotension or bradycardia. In patients at low risk for surgery, beta-blocker initiation or use of high dose without titration is not recommended.
- In high-risk individuals undergoing cardiac surgery or in patients unable to tolerate beta-blockers, amiodarone is recommended for reduction of postoperative atrial fibrillation or control of rapid ventricular rate response in patients with heart failure with reduced ejection fraction.
- In patients with stable ventricular systolic dysfunction, it is reasonable to continue angiotensin-converting enzyme inhibitors with close hemodynamic monitoring. Initiation of angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists for the prevention of postoperative atrial fibrillation is, however, not recommended.
- Statins should be continued in patients undergoing vascular surgery, favoring statins with a long half-life, and its preoperative initiation considered 2 weeks before surgery in those at high risk for cardiovascular events. In patients without cardiovascular disease, preoperative initiation of statin is not indicated for primary prevention of atrial fibrillation.
- The overall data at this time do not support the routine use of magnesium supplementation, anti-inflammatory agents or antioxidants such as corticosteroids, colchicine, N-acetyl cysteine, omega-3 polyunsaturated fatty

acids or ascorbic acid for the prevention of postoperative atrial fibrillation in patients going for cardiac surgery.

- Since current interventions for reduction of postoperative atrial fibrillation are only partially effective, additional research to improve understanding of molecular mechanisms underlying the development of AF is warranted to identify novel therapeutic targets that can help prevent or reverse the substrate that increases predisposition to PoAF.

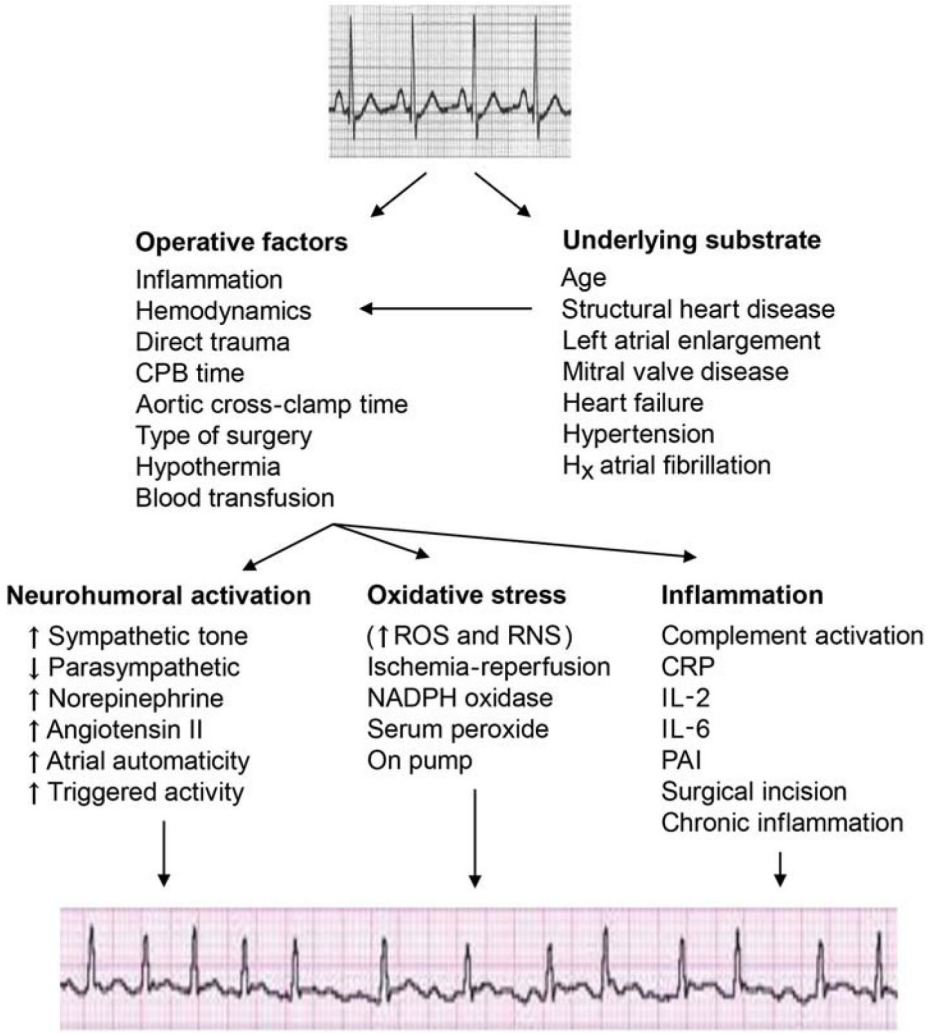

Figure 1. Acute and Chronic Factors Increasing Susceptibility to Postoperative Atrial Fibrillation

CPB: cardiopulmonary bypass, CRP: c-reactive protein, IL: interleukin, PAI: plasminogen activator inhibitor, ROS: reactive oxygen species, RNS: reactive nitrogen species.

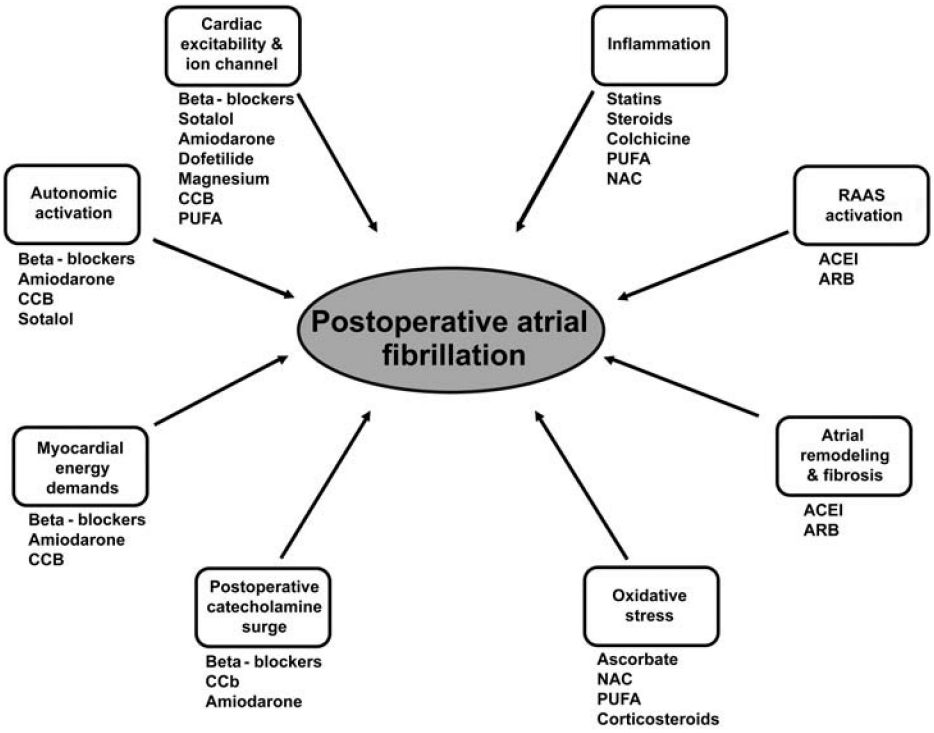

Figure 2. Pathophysiological Factors Increasing Predisposition to Postoperative Atrial Fibrillation (PoAF) and Therapeutic Interventions That Has Been Tested in Clinical Trials to Prevent PoAF

PUFA: polyunsaturated fatty acids, RAAS: renin angiotensin aldosterone system, ACEI: angiotensin converting enzymes inhibitor, ARB: angiotensin receptor blocker, NAC: N-acetyl cysteine, CCB: calcium channel blockers.

Table

Summary of some of the clinical trials assessing efficacy of pharmacological agents on prevention of postoperative atrial fibrillation

Study	Design	Number of subjects	Type of surgery	Medication	Outcomes
Beta-blockers					
Andrews et al. [35]	MA	1,549	CABG	Betablockers vs. placebo	OR 0.28, 95% CI 0.21–0.36
Burgess et al. [66]	MA	4,452	CABG, valve or both	Beta-blockers vs. placebo	OR 0.36, 95% CI 0.28–0.47
Crystal et al. [36]	MA	3,840	CABG, valve or both	Betablockers vs. placebo	OR 0.39, 95% CI 0.28–0.52;
Haghjoo et al. [46]	RCT	120	CABG	Carvedilol vs. metoprolol	Carvedilol reduced the risk of PoAF by 18% (p=0.022)
Halonen et al.[34]	RCT	240	CABG, valve or both	Intravenous metoprolol vs. oral metoprolol	Metoprolol IV vs. oral: 16.8 vs. 28.1%, p<0.036
Amiodarone					
Mitchell et al.[56]	RCT	601	CABG, valve or both	Oral amiodarone vs. placebo	OR 0.52, 95% CI 0.34–0.69
White et al. [55]	RCT	160	CABG, valve or both	Intravenous plus oral amiodarone vs. placebo	Amiodarone reduced the risk of AF by 43% and the risk of symptomatic AF by 68% (p=0.037 and p=0.019)
Crystal et al. [36]	MA	1,384	CABG, valve or both	Amiodarone vs. placebo	OR 0.48, 95% CI 0.37–0.61
Burgess et al. [66]	MA	3,295	CABG, valve or both	Amiodarone vs. placebo	OR 0.48, 95% CI 0.40–0.57
Buckley et al. [57]	MA	2,864	CABG, valve or both	Amiodarone vs. placebo comparing low (<3,000 mg), medium (3,000-5,000 mg), or high (>5,000 mg) amiodarone dosing	OR 0.58, 95% CI 0.44-0.77 OR 0.45, 95% CI 0.30-0.69 OR 0.44, 95% CI 0.33-0.58
Sotalol					
Crystal et al. [36]	MA	1,294	CABG, valve or both	Sotalol vs. placebo	OR 0.35, 95% CI 0.26–0.49
Burgess et al. [66]	MA	1,240	CABG, valve or both	Sotalol vs. betablocker	OR 0.42, 95% CI 0.26–0.65
Gomes et al. [68]	RCT	85	CABG, valve or both	Sotalol vs. placebo	Sotalol reduced risk of PoAF by 26%, p=0.008
Dofetilide					
Serafimovski et al. [69]	RCT	133	CABG, valve or both	Dofetilide vs. control	Dofetilide reduced PoAF by 18%, p<0.017
Non-dihydropyridine calcium channel blockers					
Wijeysundera DN [71]	MA	3,327	CABG, valve or both	CCB vs. control	OR 0.62, 95% CI 0.41- 0.93; p=0.02
Statin					

Study	Design	Number of subjects	Type of surgery	Medication	Outcomes
Patti et al. [83]	RCT	200	CABG, valve or both	Atorvastatin vs. placebo	OR 0.39, 95% CI 0.18–085
Liakopoulos et al. [84]	MA	31,725	CABG, valve or both	Statin vs. control	Reduced AF significantly (24.9 vs. 29.3%; OR 0.67, 95%CI: 0.51-0.88)
Chen et al. [85]	MA	774	CABG, valve or both	Statins vs. placebo	OR 0.57, 95% CI 0.45-0.72
Magnesium					
Burgess et al. [66]	MA	2,896	CABG, valve or both	Magnesium vs. control	OR 0.57, 95% CI 0.42–0.77
Miller et al. [97]	MA	2,490	CABG, valve or both	Magnesium vs. control	0.54, 95% CI 0.38 - 0.75
Steroids					
Baker et al. [120]	MA	990	CABG, valve or both	Corticosteroid vs. control	OR 0.55, 95% CI 0.39–0.78
Halonen et al. [101]	RCT	241	CABG, valve or both	Hydrocortisone vs. placebo	OR 0.63, 95% CI 0.45–0.87
Ho et al. [99]	MA	3,323	CABG, valve or both	Corticosteroid vs. control	0.74; 95% CI 0.63 - 0.86
Whitlock et al. [100]	MA	3,205	CABG, valve or both	Corticosteroid vs. control	0.71, 95% CI 0.59 - 0.87
Prasongsukarn et al. [102]	RCT	88	CABG	Methyprednisolone vs. placebo	Methylprednsisolone reduced PoAF by 30%, p=0.003
Colchicine					
COPPS [107]	RCT	336	CABG, valve, aorta surgery and combined surgery	Postoperative colchicine vs. placebo	(12.0% vs. 22.0%, p=0.021)
COPPS2 [108]	RCT	360	CABG, valve, aorta surgery and combined surgery	Preop colchicine vs. placebo	34% vs. 42%
Renin-angiotensin-aldosterone inhibitors					
Coleman et al. [112]	Retrospective	1,469	CABG, valve or both	ACEI or ARB vs. control	OR 0.95, 95% CI 0.57–1.56
Miceli et al. [113]	Retrospective	10,023	CABG	ACEI vs. control	OR: 1.34, 95% CI: 1.18 to 1.51
N-acetyl cysteine					
Ozaydin et al. [117]	RCT	115	CABG, valve or both	NAC vs. placebo	OR 0.20; 95% CI 0.05 - 0.77
Ozaydin et al. [119]	RCT	311	CABG or CABG and valve	NAC+Carvedilol vs. Carvedilol NAC+Carvedilol vs. Metoprolol	OR 0.3 (0.13-0.68, p=0.004 OR 0.17 (0.08-0.37), p<0.0001
Baker et al. [120]	MA	1,300	CABG, valve or both	NAC vs. placebo	OR 0.63; 95% CI 2-58
Wang et al. [122]	MA	1,407	CABG, valve or both	NAC vs. placebo	OR = 0.67; 95% CI, 0.37-1.22; p=0.19
n-3 polyunsaturated fatty acids					

Study	Design	Number of subjects	Type of surgery	Medication	Outcomes
Calo et al. [125]	RCT	160	CABG	PUFA vs. placebo	PUFA reduced PoAF by 17%, p=0.013
Mariani et al. [132]	MA	1,990	CABG, valve or both	PUFA vs. control	OR 0.86; 95% CI, 0.71 to 1.04
Costanzo et al. [131]	MA	2,687	CABG, valve or both	PUFA vs. control	OR, 0.66; 95% CI, 0.50-0.87; p=0.003 in CABG patients
Mozaffarian et al. [128]	RCT	1,516	CABG, valve or both	PUFA vs. placebo	OR 0.96 95% CI, 0.77-1.20; p=0.74
Sarvanan et al. [129]	RCT	108	CABG	PUFA vs. placebo	No significant difference in AF (95% CI, 6% to 30%, p=0.28)
Ascorbic acid					
Eslami et al. [135]	RCT	100	CABG	Ascorbic acid vs. placebo	OR 0.119; 95% CI 0.025-0.558
Papoulidis et al. [136]	RCT	170	CABG	Ascorbic acid vs. placebo	Ascorbic acid reduced PoAF by 17%, p=0.041
Bjordahl et al. [137]	RCT	176	CABG	Ascorbic acid vs. placebo	No significant difference in PoAF between both groups (30.3% vs. 30.2 %, p=0.98)

ACEI: Angiotensin-converting inhibitors; AF: Atrial fibrillation; ARB: Angiotensin receptor blockers; CABG: coronary artery bypass graft; CCB: Calcium channel blocker, MA: Metaanalysis; NAC: N-acetyl cysteine; OR: odds ratio; PoAF: Postoperative atrial fibrillation P UFA: Polyunsaturated fatty acids; RCT: randomized clinical trials