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# Pre and Post-Operative Treatments for Prevention of Atrial Fibrillation after Cardiac Surgery

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**Abstract:** Post-operative atrial fibrillation (AF) occurs in up to 40% of cardiac surgery patients and represents the most common post-operative arrhythmic complication. Post-operative AF is associated with impaired cardiac hemodynamics, increased incidence of serious complications (e.g. heart failure, stroke), prolonged hospitalization and increased healthcare costs. Therefore, treatment of post-operative AF would decrease health-care costs during hospitalization and improve the prognosis of patients following cardiovascular surgery. Current consensus guidelines recommend β-blockers, amiodarone and sotalol for post-operative AF prophylaxis. However, new pharmacological agents have been associated with a reduction in post-operative AF frequency, including inhibition of the renin angiotensin aldosterone system (RAAS) using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), statins, antioxidant agents, magnesium supplementation and antiarrhythmic drugs. The aim of this review is to analyse and determine the efficiency of existing therapies in the reduction of post-operative AF development.

**Keywords:** Post-operative atrial fibrillation, inflammation, remodeling, β-blockers, sotalol, amiodarone, renin-angiotensin-aldosterone system modulators, statins.

## INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is associated with decreased quality of life, and increased mortality and morbidity. Post-operative AF, the most common arrhythmia following cardiac surgery, is a growing problem and its incidence varies depending on the type of surgery [1]. AF after cardiac surgery occurs in approximately 30% of patients undergoing coronary artery bypass grafting (CABG) and in 40% of patients after valve surgery. At least half of patients undergoing combined valve and CABG surgery will develop post-operative AF [2]. This arrhythmia most often develops between the second and fifth postoperative day, with peak incidence in the first two to three days [3] and is associated with higher occurrence of heart failure and stroke, both resulting increased hospitalization and healthcare costs [4]. The occurrence of AF also correlates with a higher rate of other serious complications such as ventricular arrhythmias, postoperative myocardial infarction, and renal failure, among others [5]. Moreover, it has been suggested that post-CABG AF affects long-term survival [6].

Age appears to be one of the strongest predictors of post-operative AF [7]. It is well-known that aging causes degenerative changes in atrial anatomy [8]. Moreover, there are emerging data supporting a significant association between previous atrial changes (including fibrosis, inflammation inflammation and oxidative stress) and the development, recurrence and perpetuation of AF after surgery [9]. Several studies have suggested that AF may be induced by structural changes in the atria promoted by the activation of some of these processes after cardiac surgical dissection and/or manipulation [10]. Furthermore, it has been observed that AF induces electrophysiological changes in the atria causing a perpetuation of the arrhythmia (the so called electrical remodeling) and also structural and ultrastructural changes in atrial tissue (structural remodeling) [11].

Prevention and treatment of post-operative AF would decrease health-care costs during hospitalization and improve patient outcomes following cardiovascular surgery. However, despite the recent advances in pharmacological approaches to prevent the recurrence of AF, none of the currently available therapies are fully effective in the long-term [12]. It is easy to speculate that current therapies are failing in eliminating this arrhythmia because they usually target a single pathophysiological mechanism, whereas AF is a complex continuous process of electrical, structural, metabolomic, and autonomic remodeling of the atria that relates to AF itself ("AF begets AF"), and changes associated with aging [13].

The current guidelines from the American College of Chest Physicians, the American College of Cardiology, the American Heart Association and the European Society of Cardiology (ACCP/ACC/AHA/ESC) strongly recommend using β-blockers to reduce post-operative AF incidence [14-

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17] and most institutions have incorporated this requirement into their preoperative investigations for all patients without contraindications. However, while β-blockers reduce the incidence of AF after surgery, they do not eliminate it. Since cardiac structural remodeling, especially atrial fibrosis, is one of the key processes of occurrence, development and maintenance of AF, the use of therapies directed against remodeling could help in the prevention of post-operative AF. For that reason, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), both related to inhibition of the renin-angiotensin-aldosterone system (RAAS), have been utilized to reduce post-operative AF frequency. Other pharmacological agents such as statins, antioxidant agents, magnesium supplementation and antiarrhythmic drugs have been tested in the treatment of post-operative AF with varying success. The aim of this review is to analyze the potential beneficial effects of novel experimental pharmacological agents in reduction of post-operative AF.

## METHODS

Published data for this review were identified by search and selection in MEDLINE database and reference lists from relevant articles and reviews. A two-step approach was used. First, novel therapeutic agents were identified in a search with the keywords "atrial fibrillation" and "pharmacological agents". Second, the pharmacological agents identified with this search were used as keywords with the addition of the following keywords "post-operative atrial fibrillation", "electrical remodeling", "structural remodeling", "fibrosis", "inflammation" and "oxidative stress". Bibliographies of all selected articles and review articles about AF and/or novel therapeutic agents were reviewed for other relevant articles.

## PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

The underlying mechanisms for the development of AF after cardiac surgery are not completely understood, but are thought to be multifactorial [3]. Numerous predisposing factors such as advanced age, hypertension, diabetes, left atrial enlargement, left ventricular hypertrophy, intraoperative and postoperative factors such as atrial injury or ischemia, can favor the development of post-operative AF [10]. Undoubtedly the most common form of AF is associated with structural and electrical changes. The longer the AF persists, the more difficult it is to restore sinus rhythm and to prevent recurrence, being time a key factor for perpetuation. The persistence of AF may lead to changes in atrial function and structure, a process known as atrial remodeling. Atrial remodeling is an adaptive regulatory process of cardiac myocytes that occurs over time in order to maintain homeostasis against external stresses [18] and may occur at the ionic, genomic, cellular, and extracellular levels [19]. If the stressor is not removed early enough, this process can become irreversible and cellular and extracellular changes such as apoptosis, necrosis, and fibrosis can occur as early as after 1 month [19]. Two principal forms of remodeling have been described, at least in animal models of AF: (i) structural remodeling, which alters atrial tissue architecture and (ii) tachycardia-induced electrical remodeling, which alters cellular electrical properties [20, 21].

### Structural Remodeling

There are some evident morphologic changes that occur along AF development. It has been observed changes in the dimensions of the left atrium, myocyte hypertrophy or necrosis and a mononuclear cell infiltrate [22]. These structural changes (with or without electrical changes) could explain the delay in return of atrial systole after successful cardioversion [23]. However, in recent years, atrial fibrosis has been recognized as the hallmark of arrhythmogenic structural remodeling [24]. Advanced interstitial fibrosis in human AF would predict an impairment of atrial conduction at the microscopic level and may render the atrial myocardium discontinuous, resulting in a branching structure [25]. Tissue fibrosis results from an accumulation of fibrillar collagen deposits, occurring most commonly as a dynamic reparative process to replace degenerating myocardial parenchyma with concomitant reactive fibrosis [26]. Different enzymes, such as the matrix metalloproteinase (MMP) family, help with the degradation of extracellular components [27]. As expected, a differential up-regulation of several MMPs and a down-regulation in the tissue inhibitors of metalloproteinases (TIMPs) were observed in AF, as an evidence of changes of matrix regulation [28]. Although the precise mechanism of atrial fibrosis is not entirely clear, data from animal models implicate angiotensin-converting enzyme (ACE) and angiotensin II as upstream regulators of profibrotic molecules such as transforming growth factor β-1 [29].

On the other hand, there are accumulating data suggesting inflammation and abnormal oxidative stress as pivotal pathophysiological features involved in the development, recurrence and persistence of AF [10]. In several pathophysiological conditions, including post-cardiac surgery, inflammation augments oxidative stress and vice versa. It is therefore tempting to speculate that oxidative stress and inflammation interrelate at some level facilitating atrial remodeling [30]. An inflammatory contribution to AF after cardiac surgery was observed for the first time in a small study showing an elevation in levels of C-reactive protein (CRP)-complement complexes that were greater in patients who developed AF [31,32]. Moreover, levels of other inflammatory cytokines (e.g. Interleukin-6, IL-6) are increased in patients with AF [33].

Oxidative stress has also been implicated in the pathogenesis of AF in animal models and humans [34,35]. Patients undergoing CABG surgery increased plasma lipid peroxidation and decreased cardiac glutathione levels following release of the cross clamp, and these changes persist for at least one day following cardiac surgery [36]. Similarly, there is direct evidence of increased free radical production in canine hearts subjected to rapid ventricular pacing [35]. Peroxynitrite formation may be an important contributor to cardiac myocyte dysfunction in a wide array of diseases [34,37].

### Electrical Remodeling

"AF begets AF", i.e. AF alters atrial electrophysiology in a way that favors AF initiation and maintenance; a phenomenon called "electrical remodeling" [38]. The major mechanisms of "electrical remodeling" are initiated by increased

atrial rate. Excitation-contraction coupling is initiated by depolarization of the cell membrane by an action potential that triggers opening of voltage-dependent L-type $Ca^{2+}$ channels and that this entrance of $Ca^{2+}$ promotes the release of more $Ca^{2+}$ from the sarcoplasmic reticulum in a process called $Ca^{2+}$-induced $Ca^{2+}$ release. $Ca^{2+}$ binds to troponin C activating the actin-myosin filaments, and the myocyte starts to contract [39]. At rapid atrial rates, inward calcium current significantly increases myocyte calcium load. Because high intracellular calcium concentrations can be toxic, adaptive mechanisms rapidly reduce the load to protect the cell [19]. Thus, one of the defence mechanisms includes that the membrane channel responsible for calcium entry becomes less active. This way, the reduction in the $Ca^{2+}$ entry helps to prevent $Ca^{2+}$ overload. However, because calcium channel is a key contributor to the action potential plateau, inactivation of the calcium channel decreases the action potential duration, reduces the refractory period, and promotes the induction and maintenance of AF by multiple-circuit re-entry and perpetuation of AF [40].

## CURRENT PHARMACOLOGICAL THERAPIES IN POST-OPERATIVE AF

### Beta-Blockers

Beta-blocking agents have shown to have central actions that tend to reduce sympathetic efferent activity and promote cardiac vagal outflow [41]. Current guidelines strongly recommend using β-blockers to reduce post-operative AF incidence [14-17] and for that reason, preoperative beta-blocker administration is standard in all patients without contraindications. Moreover, the Surgical Care Improvement Project (SCIP) National Quality Measures recommends that all patients undergoing cardiac surgery should continue β-blocker, if they were on a β-blocker prior to arrival [3]. Indeed, the β-blockers are the most widely studied drugs for prophylaxis. However, there is heterogeneity in the results across studies. Many studies include patients treated with non-selective β-blockers such as propanolol [42]. However, non-selective β-blockers are associated with lower patient tolerability than cardioselective β-blockers and for that reason the latter have increased in popularity in the treatment of several coronary diseases [43]. It is widely accepted that highly selective β-blockers provide a cardioprotective effect in elderly and diabetic patients and those with reduced respiratory function [43]. Despite the differences found in the literature, β-blockers clearly reduce the incidence of AF after cardiac surgery. A large meta-analysis reported that in 27 randomized controlled trials with 3840 patients, the incidence of post-operative AF in control patients was 33% compared to 19% in those taking β-blockers, although an inexplicable and marked heterogeneity was found between trials [44]. The importance of β-blockers is also affirmed by the two to five-fold increase in AF after cardiac surgery when β-blockers are discontinued postoperatively [45]. The efficacy of metoprolol against placebo therapy in preventing post-operative AF was evaluated in 1000 patients undergoing cardiac surgery and compared with placebo, the incidence of post-operative AF was significantly lower in metoprolol group (39% vs. 31%), representing a relative risk reduction of 20% [1]. In other case cohort study, 80 patients were on carvedilol after surgery and another 80 were not (control group) and it was observed that the incidence of paroxysmal AF was significantly lower in the carvedilol than in the control group (15% vs 34%) with particularly efficacy in elderly patients. Moreover, the hospital stay after CABG was five days shorter in the carvedilol group than in the control group [46]. However, this shorter hospital length of stay was not observed in other larger trials [42,44,47].

### Sotalol

Sotalol is a unique beta-blocker, with potassium channel blocking properties (Class II and III antiarrhythmic effects), and has been used for the prevention of post-operative AF [5]. The effectiveness of sotalol vs placebo and sotalol vs conventional β-blockers in preventing AF after surgery has been analyzed in several clinical trials [1,3,44,47]. A recent meta-analysis [44] analyzed 8 trials (1294 patients in total) evaluating the effect of sotalol to reduce post-operative AF. Sotalol was associated with a reduction in AF incidence (37% in placebo group to 17% in sotalol group) with no significant heterogeneity between trials. Sotalol and other β-blockers were compared directly in 4 trials including 900 patients [44]. Once again, sotalol reduced incidence of post-operative AF from 22% in the other β-blocker group to 12% in the sotalol group with no significant heterogeneity. Other prospective, randomized, double-blind, placebo-controlled study with 85 patients was carried out to assess the efficacy of preoperatively and postoperatively oral sotalol in preventing the occurrence of post-operative AF [48]. In this analysis, moderate doses of sotalol (mean dose of 190 mg per day) were administrated 24 to 48 hours before scheduled surgery and continued for up to 4 days post-surgery. In addition, all other drugs were continued unchanged except β-blockers, halved if the dose was superior of 200 mg per day (only two patients). Thus, this study design avoided the occurrence of β-blocker withdrawal and assessed the feasibility and effectiveness of a strategy where sotalol is utilized together with others β-blockers to minimize untoward effects of this drug combination. There was a significant reduction in post-operative AF when comparing patients receiving placebo (38%) when patients on sotalol (12.5%) and a trend towards a reduction in length of hospital stay [48]. In this study only 5% of patients developed bradycardia, which required discontinuation of the drug, and none of the patients developed ventricular arrhythmias including torsade de pointes, probably as a result of the moderate doses of sotalol administered. As observed in this study, it remains unclear which is the beneficial effect of sotalol; but it was observed a significant increase in the QTc interval suggesting that the beneficial effects of sotalol were partly related to its type III membrane activity. However, in other studies, there were no beneficial effects when comparing the administration of sotalol with other β-blockers [49] and the incidence of side effects were higher in those patients on sotalol [47].

### Amiodarone

Amiodarone is the most potent of all antiarrhythmic drugs currently in use. It is a potassium channel blocker with

significant effects on sodium and calcium channels as well as on β-receptor blocking properties [1]. Several studies have analyzed the impact of amiodarone on post-operative AF, with four randomized placebo-controlled trials (PAPABEAR: Prophylactic oral Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization [50]; SPPAF: Study of Prevention of Postoperative Atrial Fibrillation [51], AFIST: Atrial Fibrillation Suppression Trial [52], and the ARCH: Amiodarone Reduction in Coronary Heart trial [53]). In PAPABEAR, oral amiodarone (10 mg/kg daily) or placebo was administered 6 days prior to surgery through 6 days after surgery in 601 patients underwent non-emergent CABG surgery and/or valve replacement, and it was observed that AF occurred in fewer amiodarone patients (16.1%) than in placebo patients (29.5%). Two different studies using oral [54] and intravenous amiodarone [55] in patients underwent open heart surgery, reported similar reduction in post-operative AF incidence. No important side effects were observed during the PAPABEAR trial, and only 11% of patients on amiodarone had to reduce the dosage or discontinue the treatment. No significant reduction in post-operative stay was observed in any of the three studies. In the SPPAF trial [51], the efficacy on preventing the development of AF after cardiac surgery using amiodarone plus metoprolol was compared with metoprolol alone, sotalol and placebo in 253 patients segregated into 4 groups. Patients receiving combination therapy and those receiving sotalol had a significantly reduction in the frequency of AF of 23.6% and 22.1%, respectively when compared with placebo. Once again there were no significant differences in the length of stay [51]. In the AFIST trial [52], 220 patients were enrolled with different preoperative amiodarone treatment depending on the available days before the cardiac surgery. It was observed that patients on amiodarone had a lower frequency of AF when comparing with placebo group (22.5% *vs* 38.0%). Moreover, a reduction in cerebrovascular accidents and ventricular tachycardia, as well as in independent predictors of symptomatic fibrillation was obtained in the amiodarone group [52]. In the ARCH trial [53], low-dose intravenous amiodarone was safe and effective in reducing the incidence of atrial fibrillation after heart surgery, but did not significantly alter the length of hospital stay. Indeed, the greatest reduction in the length of stay in a meta-analysis when amiodarone was compared to placebo was reported by Crystal *et al.* [44], with a decrease of 0.91 days, thus reducing significantly the cost of care. However, the major drawback of amiodarone is that it has to be administrated several days before surgery and it is known to have a complex side effect profile that includes pulmonary and liver toxicity, QTc interval prolongation, thyroid abnormalities, visual disturbances, bradycardia and hypotension, typically associated with large cumulative doses and prolonged use [3,56].

## NOVEL PHARMACOLOGICAL THERAPIES IN POST-OPERATIVE AF

### Inhibitors of the Renin-Angiotensin-Aldosterone System

Angiotensin (Ang) II, which is an octapeptide, is generated by angiotensin converting enzyme (ACE) from Ang I (a decapeptide), which is formed by renin from angiotensinogen. Ang production in the heart depends on kidney-derived renin and/or prorenin. Both are taken up from the circulation, either through diffusion into the cardiac interstitium or by binding to cardiac cells, and prorenin is activated to renin in cardiac cells [57]. Ang II binds primarily to Ang II type 1 receptor (AGTR1) to promote cell growth. Ang II also stimulates to aldosterone synthase (CYP11B2) for the synthesis and release of aldosterone, which promotes fluid retention and cardiac fibrosis [58]. Ang II, apart from having arrhythmogenic effects, has other physiologic effects which include stimulation of atrial fibrosis and hypertrophy secondary to activation of mitogen-activated protein kinases, uncoupling gap junctions, impaired calcium handling, alteration of ion channel dynamics, activation of mediators of oxidative stress, and promotion of inflammation [59]. The presence of common genetic variants, or polymorphisms, in all these genes can modify RAAS activation and/or receptor function and can play a role as a mediator of atrial remodeling in AF. In animal models, inhibitors of RAAS appear to prevent AF by attenuating changes in cardiac structure and function [60]. In these studies, these drugs prevented left atrial dilation, atrial fibrosis, conduction velocity slowing, and these changes were associated with a lower rate of AF induction with atrial pacing [61]. Moreover, patients with AF have an increase in atrial tissue ACE concentration. ACE is a membrane-bound enzyme which is located in vascular endothelial cells and is widely distributed in the body. It converts Ang I to active Ang II and inactivates a vasodilator and natriuretic peptide bradykinin. Ang II, the end product of the renin–angiotensin system is a potent vasopressor peptide and exerts most of its known cellular actions through the angiotensin II type 1 receptor (AGT1R). Stimulation of the AGT1R results in vasoconstriction, increased atherogenesis, inflammation, growth, proliferation, or coagulation depending on local conditions [57].

In two meta-analysis involving non-surgical patients with AF, use of ACE inhibitors and angiotensin receptor blockers (ARBs) reduced the risk of developing new-onset AF and the recurrence of AF by nearly 50% [60,62]. Similar results were obtained in a cohort of 186 patients with long-lasting persistent AF [63], although in this case an ARB (irbesartan) was used in combination with amiodarone. This study showed that patients treated with amiodarone and irbesartan had a lower 2-month recurrence rate of AF and a longer time to first arrhythmia recurrence when comparing with amiodarone alone. On the other hand, the effect of inhibitors of the RAAS in post-operative AF is more controversial. There are several studies carried out to assess the efficacy of ACEIs or ARBs in reducing the incidence of post-operative AF in cardiac surgery patients. In one of them, 128 consecutive patients undergoing CABG and/or valve surgery were segregated into three groups [64]. Patients were randomized to a first group on ACEI, a second group was administered ACEI plus candesartan (an ARB) and patients without inhibitors of the RAAS constituted the control group. ACEI plus candesartan or an ACEI alone proved significant superior results to usual care with absolute reductions in the

incidence of post-operative AF compared to controls by 23% and 21% respectively, although candesartan proved no additional effect on the rates of post-operative AF when added to ACEI [64]. In other study, 85 consecutive patients undergoing rheumatic valve surgery were enrolled and randomly assigned to an irbesartan plus amiodarone or an amiodarone group [65]. The combination of amiodarone and irbesartan (ARB) reflected a 57.4% reduction in the risk of recurrence of AF when comparing with amiodarone alone, which might be due to preventing the atrial remodeling. Moreover, the maintenance of sinus rhythm by treatment with irbesartan plus amiodarone for 1 year was 69.8%, which was significantly higher than by treatment with only amiodarone (40.5%) [65]. A prospective international multicenter observational study of 4657 patients undergoing CABG surgery was developed to validate different drugs that offer protection against post-operative AF [66]. The authors found that treatment with preoperatively and postoperatively ACE inhibitors, postoperative potassium supplementation and NSAID administration were associated with a reduced incidence of AF [66].

However, the most recent AF suppression trials (AFIST II and III) have evaluated 338 patients undergoing CABG and/or valvular surgery of which 175 (51.8%) received an ACEI or ARB preoperatively and 163 (48.2%) did not [67]. In total, post-operative AF occurred in 29% of patients receiving a preoperative ACEI or ARB and in a 36% whom did not, although this association was not found statistically significant, probably as a result of the low number of patients enrolled in this trial. A recent study with 757 patients underwent CABG showed no reduction in the occurrence of AF after cardiac surgery when ACEI or ARBs were administered [4]. It is reasonable to establish that further studies are needed to better delineate the role of the RAAS related medications on reduction of post-surgical AF.

### 3-Hydroxy-3-Methyglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors

HMG-CoA reductase inhibitors or statins exert pleiotropic effects targeting multiple inflammatory and oxidative stress pathways, and also protect atrial myocytes during ischemia associated with rapid atrial rates by increasing the production of endothelial nitric oxide [12]. Moreover, statins down-regulate Rac1 activity by suppressing its isoprenylation and have a favorable impact on risk for AF, blunting the decrease in atrial effective refractory period induced by rapid atrial pacing [68]. The pleiotropic actions of statins include improvement of endothelial function, antioxidant effects, anti-inflammatory properties and stabilization of the atherosclerotic plaque [69]. Apart from the benefit derived by reducing inflammation, statins improve myocardial remodeling, modifying the expression of enzymes involved in extracellular matrix turnover, such as the MMP family [70]. Recently, inflammatory mechanisms have attracted interest, given that activation of the complement system and release of pro-inflammatory cytokines occur after cardiac surgery [10]. However, the effects of statins are not only related with a reduction of post-operative AF. The incidence of cardiovascular events in the first 6 months after surgery, including death from cardiac causes, non-fatal acute myocardial infarction, ischaemic stroke and unstable angina, can also be reduced with perioperative use of atorvastatin in patients who must undergo vascular surgery [71].

As far as we know, Dotani and colleagues [72], were the first to report a restrospective cohort study with 104 patient receiving statins compared with 219 patients off statins after CABG. In this study, statin treatment (atorvastatin, simvastatin, lovastatin, pravastatin and fluvastatin) was associated with a reduced incidence of arrhythmias after CABG in both univariate and multivariate analysis, however, there was an increase in the cardiovascular adverse outcomes when comparing patients taking other lipid-lowering drugs with those taking statins, suggesting that the beneficial effects of statins were related with their pleiotropic effects, such as its antithrombotic effect, endothelial function improvement, or by reducing reperfusion injury [72]. Interestingly, in another study, statin use was associated with a threefold decrease in the odds of developing AF with no difference on C-reactive protein (CRP) and IL-6 levels suggesting that the preoperative use of statins was associated with a protective effect against post-operative AF, independently of CRP and IL-6 levels [7]. On the other hand, in a more recent study, authors described that 20 mg/day of atorvastatin significantly reduced the incidence of post-operative AF (18% *vs* 41%), and postoperative peak of CRP level (15%), both of them compared with placebo [73]. Survival analysis also confirmed a significantly better post-operative AF-free survival in the statin group. In addition, preoperative atorvastatin therapy was an independent factor associated with a significant reduction in AF after CABG, whereas higher post-operative CRP levels were related with increased risk [73].

In other study, it has been observed that statins have the capacity of reducing the AF recurrence in patients with paroxysmal AF after a dual-chamber pacemaker insertion [74]. After one year of follow-up, patients without recurrence were more likely to be on statin therapy (54%) when compared with patients off statins (25%) and statin treatment was the only significant predictor of AF recurrence in a multivariate logistic regression model [74]. More recently, the effect of statin pre-treatment on patients undergoing on-pump cardiac procedures with surgical ablation for paroxysmal or persistent AF was investigated [75]. Statin therapy was associated with higher rates of freedom from AF for paroxysmal AF at three and six months and for persistent AF after six months. Importantly, statin pre-treatment was independently predictive for freedom from AF at discharge and at three months [75].

As it had been demonstrated that statins could play an important role in remodeling, Marín *et al.* [76] hypothesized a protective role of statins in post-operative AF. They studied 234 consecutive patients who underwent coronary artery bypass grafting and measured plasma levels of matrix metalloproteinase-1 (MMP-1) and its inhibitor, TIMP-1, at baseline and at 24 hours after surgery. In multivariate analysis, statin administration was related to a decrease in arrhythmia and was associated with increased TIMP-1 levels and TIMP-1/MMP-1 ratio, thus suggesting that statin use may be protective against AF after coronary artery bypass

grafting, possibly due to alterations in the extracellular matrix and remodeling after cardiac surgery [76].

The largest and most robust trial of atorvastatin carried out until now is the Atorvastatin for Reduction of Myocardial Dysrhythmia After cardiac surgery study (ARMYDA-3) [77]. In this trial, 200 patients without previous statin treatment were enrolled and 40 mg/day were administered 7 days before surgery. Atorvastatin significantly reduced the incidence of AF versus placebo in more than 20% and a reduction in length of stay of 0.6 days was observed when atorvastatin was compared to placebo. Again, peak CRP levels were lower in patients without AF and multivariable analysis showed that atorvastatin treatment conferred a 61% reduction in risk of post-operative AF, whereas high post-operative CRP levels were associated with increased risk [75]. A meta-analysis of more than 30000 patients underwent cardiac surgery with pre-operative statin therapy demonstrated substantial clinical benefits in patients [78]. This meta-analysis showed, with no heterogeneity between studies, that mortality was significant lower in post-operative patients who received pre-operative statin therapy compared with controls, with an absolute risk reduction of 1.5%. Regarding AF, although significant heterogeneity was observed, pre-operative statin treatment resulted in a 4.3% of significant absolute risk reduction. Finally, overall stroke incidence was lower in patients on statin therapy when compared to controls with no heterogeneity between studies [78]. To summarize the available data regarding statins in post-operative AF, the low cost and low risk of statin therapy may support their routine early initiation in moderate or high-risk patients with no history of AF who are "statin-naive" [10]. Despite one study attempting to determine the optimal dose of atorvastatin for the prevention of post-operative AF [79], it is unclear which statin, what dosage, and for what duration will achieve the greatest benefit. For that reason, future large randomized placebo-controlled clinical trials should be conducted to evaluate the impact of the use of statins on preventing AF after cardiac surgery.

## ANTIOXIDANT AGENTS

Three are the most important antioxidant compounds that could reduce the occurrence of post-operative AF as deduced by the bibliography. They are polyunsaturated fatty acids (PUFAs), ascorbic acid and N-acetylcysteine (NAC). The ability of PUFAs —mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)— to reduce post-operative AF is thought to result from a stabilizing effect on the myocardium, anti-inflammatory properties, antioxidant activity and regulation of mitogen-activated protein kinase activity [3, 59]. In addition, PUFAs are universal constituents of biological membranes and modulate membrane fluidity and activity of multiple membrane proteins, this way, the modulation of a great number of cardiac ion channels may be the primary mechanism of the antiarrhythmic effects of PUFAs in AF [12]. In experimental AF, pre-treatment with PUFAs was associated with smaller increases in activity of atrial MMPs, a reduction in the content of collagen type I and III ribonucleic acid (RNA), as well as prevention of changes in expression and re-distribution of connexins Cx40 and Cx43 [59]. Two studies demonstrated the potential of PUFA in post-operative AF patients. In the first of them, 160 patients were pre-treated with fish oil capsules for 5 days before CABG surgery and a significant absolute reduction in incidence of post-operative AF by 18% and a significant shorter length of stay by 0.9 day compared to control patients was observed without influence of β-blockers use [80]. In the second one, perioperative intravenous infusion of soya oil was associated again with a significantly lower incidence of AF and a shorter hospital stay [81]. However, these observations have not been reproduced in a study administering fish oil to 108 patients undergoing cardiac surgery [82].

The ability of ascorbic acid (vitamin C) to prevent post-operative AF is thought to occur due its antioxidant properties and potential to attenuate inflammation and electrical remodeling [3]. As far as we know, pre-treatment with vitamin C has been studied in two prospective trials. In the first of them, the overall incidence of postoperative AF or flutter in the ascorbate-treated group was 16.3%, significantly lower than the incidence of atrial arrhythmias in the control group, 34.9%. Moreover, univariate and multivariate analysis demonstrated that ascorbate usage alone would have a clear beneficial effect [35]. In the other study, the reduction in the incidence of post-operative AF was even higher (22%) comparing with controls but there were no significant reduction in the hospital stay. In both studies a great number of patient were on pre- and post-operative β-blocker utilization, suggesting that this may be a viable option for add-on therapy in high-risk patients, and the low cost and relative safety of this drug, warrant the execution of new larger placebo-controlled trials [83].

N-acetylcysteine (NAC) has been theorized to prevent post-operative AF based on its antioxidant activity as a free radical scavenger and ability to reduce cellular damage in the atrium [3]. Moreover, NAC is a precursor to glutathione, which is the most abundant intracellular non-protein thiol pool against oxidative stress and a major redox molecule with various functions. Glutathione scavenges free radicals and other reactive oxygen species, reacts with other metabolites as well as with nitric oxide, and participates in the generation of prostaglandins [84]. Oxidative stress and other noxious stimuli could deplete cellular glutathione, and hence exert adverse biological effects, which could be prevented by the administration of NAC. Moreover, treatment with NAC influences multiple pathways including thiol-sensitive active protein kinase G, calcineurin-nuclear factor of activated T cells, phospho-p38 pathways and glutathiolation of cardiac α-actin [69]. Two recent studies have found contradictory results about NAC and the reduction of AF after cardiac surgery. One of them did not find any significant differences between patients on NAC and patients off [85], while the other found NAC superior to placebo with an absolute reduction in the incidence of AF by 16% in 115 patients undergoing coronary artery bypass and/or valve surgery. Moreover, even in the multivariate logistic regression analysis, the use of NAC was an independent predictor of postoperative AF [86]. However, larger clinical trials are needed to determine the efficacy of NAC in reducing AF after cardiac surgery.

Mega-dose folate, the spirulina-derived phytonutrient phycocyanobilin (PhyCB) and coenzyme Q10 are less

studied antioxidant supplementation that could be used as therapies for prevention of remodeling and decrease post-operative AF. PhyCB, a biliverdin derivative, has been shown to mimic the inhibitory impact of biliverdin on NADPH oxidase activity and has been shown that has broad-ranging anti-inflammatory and cytoprotective properties in rodents [87]. High-dose folate, once inside the cell, is rapidly reduced to tetrahydrofolate compounds which have outstanding antioxidant activity [68]. Folate pre-treatment was observed to help in preserving bioenergy status and efficient cardiac function during the ischemic phase in rats with an occlusion of the left coronary artery, thus supporting its role as a myocardial antioxidant in the context of cardiac remodeling [68]. Coenzyme Q10, while serving as a crucial cofactor in the mitochondrial respiratory chain, also provides important antioxidant protection for mitochondrial membranes and has been found to improve cardiac function [68]. However, further studies are necessary to asses the effectiveness of these last three antioxidant compounds reducing post-operative AF.

## MAGNESIUM SUPPLEMENTATION

Magnesium (Mg) is a cofactor for the sodium-potassium adenosine triphosphatase enzyme ($Na^+/K^+$-ATPase) which regulates membrane potential and post-operative AF usually coincides with a reduction in Mg levels [42]. Due to conflicting results, prophylactic Mg supplementation alone therapy is not universally utilized at this time, although some clinicians prescribe it in addition to β-blockers and/or amiodarone. Mg supplementation alone has been extensively studied for post-operative AF prophylaxis, but most of trials failed to demonstrate reduction in AF after cardiac surgery when compared with usual care [88, 89]. However, some studies did find a significant reduction in the incidence of post-operative AF [90, 91]. Moreover, in two systematic meta-analysis, magnesium supplementation reduced the frequency of AF after surgery when comparing with the control group, although significant heterogeneity was observed between trials [5]. As commented before, although there are controversial data regarding the effect of Mg supplementation alone, it seems to be more effective in combination with β-blockers [3]. Thus, in a study with 100 consecutive patients segregated into two groups (a prophylaxis group receiving after surgery bisoprolol plus intravenous Mg and a control group receiving no combined treatment but remaining their preoperative drugs, including β-blockers) the incidence of post-operative AF was significantly lower with an absolute difference of 22% between the prophylaxis and the control group [42]. More importantly, in elderly patients, only a 17% of patients developed AF while in the control group this value rose to 65% of patients. Moreover, this study also demonstrated a significant reduction in median length of hospital stay of 2 days in the prophylaxis group compared to control [42]. However, the combination of sotalol plus $MgCl_2$ did not show more effectiveness than sotalol alone in the prevention of tachyarrhythmias after CABG and this combination could also induce serious bradyarrhythmias [92]. Due to these contradictory results, there is little consensus among the guidelines about its utilization although magnesium is certainly less toxic and has fewer contraindications than amiodarone and sotalol [3].

## ANTIARRHYTHMIC AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

There are several studies analyzing the effect of non-steroidal anti-inflammatory and antiarrhythmic agents different from sotalol and amiodarone in the reduction of post-operative AF but until now the data is contradictory and its use is not recommended by the guidelines. Dofetilide is a class III antiarrhythmic producing selective blockade of the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current IKr, but with no relevant blockade of other repolarizing potassium currents [93]. In a double-blind, randomized, placebo-controlled study of 133 patients undergoing CABG with or without valve surgery, the incidence of post-operative AF in the placebo arm was 36%, and in the dofetilide arm 18%, with an absolute risk reduction of 18% [94]. Moreover, patients who developed AF after surgery in the dofetilide arm had a 1.0-day decrease in mean hospital length of stay versus placebo. It is worth noting that there was no incidence of torsades de pointes or any other side effect in either group. In a larger study, the effect of two different antiarrhythmic drugs, cibenzoline and disopyramide, were compared [95]. Both of them are class I anti-arrhythmic drugs having negative inotropic effects, and for that reason, these drugs should not be used intra venous in patients with an impaired left ventricular systolic function. The efficacy of intra venous cibenzoline for the termination of post-operative paroxysmal AF was significantly better than that of disopyramide with an absolute difference of 24%, especially in patients with pre-administration of oral β-adrenergic blockers and those with smaller left atrium, probably due to differences in the channels blocked by cibenzoline and disopyramide: Cibenzoline inhibits the IKur channel, which is specifically distributed in atrial muscle cells, as well as sodium channels, the IKs channel, and calcium channels, while disopyramide does not inhibit these channels [95]. Ibutilide is another class III antiarrhythmic agent that is effective for the conversion of AF after cardiac surgery [96]. In a study with 201 patients suffering from AF after cardiac surgery, treatment with ibutilide resulted in significantly higher conversion rates than placebo, and the efficacy was dose related [96].

Abnormalities in inflammatory biomarkers have been found in patients undergoing cardiac surgeries [3]. There are few studies evaluating the effects of different anti-inflammatory drugs to prevent AF after surgery. In one of them [97], one hundred patients were randomized to two groups: one received 30 mg ketorolac intravenously every 6 hours and 600 mg of oral ibuprofen three times a day when the patient was able to take oral medications and the other group received conventional treatment. An absolute reduction in the incidence of post operative AF by 19% and a shorter hospital length of stay by 1.2 days was observed when compared both groups [97]. The other study, a larger cohort from the AF Suppression Trials (AFIST) I, II and III, administered post-operative NSAIDs and found an absolute reduction in the incidence of AF after cardiac surgery by 14% [98]. In a multicenter prospective observational study of 4657 patients undergoing CABG surgery, NSAID administration was significantly associated with a reduced incidence of AF [66]. On the other hand, NSAIDs

**Table 1. Experimental Pharmacological Agents Preventing Post-Operative AF**

| Agent | Mechanism of Action | Favorable Effects | Unfavorable Effects | References |
|---|---|---|---|---|
| Lisinopril; Cilazapril; Ramipril; Quinapril; Perindopril; Fosinopril | ACE inhibitors | **[63]; [65]** Reduction in the incidence of post-operative AF in cardiac surgery patients. | **[4]; [66]** No significant reduction in post-operative AF occurrence.<br>No reduction in hospital LOS | [4]; [63]; [65]; [66] |
| Irbesartan, Candesartan | AT1-R blocker | **[64]** Irbesartan plus Amiodarone reduced the risk of recurrence of AF and maintenance of sinus rhythm for 1 year higher than Amiodarone alone. | **[63]** Candesartan proved no additional effect on post-operative AF when added to an ACEI.<br>**[4]; [66]** No significant reduction in post-operative AF occurrence. | [4]; [63]; [64]; [66] |
| Statins (Atorvastatin; Simvastatin; Lovastatin; Pravastatin; Fluvastatin) | Inhibition of Rho-Aand RacI small GTPases, among others pleiotropic effects | **[71]** Reduced incidence of FA after CABG in both univariate and multivariate analysis.<br>**[75]** In multivariate analysis, decrease in AF and increased TIMP-1 levels.<br>**[76]** Reduction in the incidence of AF versus and reduction in hospital LOS.<br>**[77]** Lower mortality and stroke incidence | It is not clear among studies which are the appropriate duration, doses and type of statin that should be administered. | [7]; [71]; [72]; [73]; [74]; [75]; [76] |
| PUFAs | Modulate membrane fluidity and activity of membrane proteins | **[79] [80]** Reduction in incidence of post-operative AF and a significant shorter LOS. | **[81]** Neither observed reduction in AF after cardiac surgery nor in LOS. | [79]; [80]; [81] |
| Ascorbic acid, NAC, Folate, CoQ10 | Antioxidant properties | Reduction in the incidence of post-operative AF in some studies. | No reduction in hospital LOS. | [35]; [67]; [82]; [84]; [85]; [86] |
| Magnesium | Cofactor for the Na+/K+-ATPase | **[89]; [90]** Reduction in the incidence of post-operative AF.<br>**[42]** Reduction in AF overall in elderly patients. Shorter LOS. | **[87]; [88]** No reduction compared with usual care.<br>**[91]** Sotalol plus MgCl2 no reduction in AF and induce serious bradyarrhythmias. | [5]; [42]; [87]; [88]; [89]; [90]; [91] |
| Dofetilide, Cibenzoline | Selective blockade of cardiac ion channels | **[93]** Reduction in incidence of post-operative AF and a shorter LOS. | Contradictory data and its use is not recommended by the guidelines | [93]; [94] |
| NSAIDs | Anti-inflammatory effects | **[65]; [95]; [96]** Reduction in incidence of post-operative AF and **[95]** a shorter LOS. | Risk of cardiovascular events, MI, cardiac arrest, stroke and pulmonary embolism | [65]; [95]; [96] |
| Corticosteroids | Anti-inflammatory effects | No hemodynamic side effects, reduction of post-operative FA **[97; 98; 99; 100; 101; 102; 103]**, mechanical ventilation and LOS **[100]** | Hyperglycemia requiring insulin; potential risk of infection **[100]** | [97]; [98]; [99]; [100]; [101]; [102]; [103] |

Abbreviations: ACE: Angiotensin II converting enzyme; AT1-R: Angiotensin II receptor type 1;AF: Atrial fibrillation; LOS: Length of stay; PUFAs: Polyunsaturated fatty acids; NAC: N-acetylcysteine; CoQ10: Coenzime Q10; Na+/K+-ATPase: sodium-potassium adenosine triphosphatase; NSAIDs: Non-Steroidal Anti-inflammatory Drugs; MI: myocardial infarctation.

pharmacologic activity include their ability to inhibit cyclo-oxygenase 2 (COX-2) enzymes and this inhibition can promote platelet aggregation resulting from the suppression of prostacyclin, increasing the risk of cardiovascular events, of myocardial infarction, cardiac arrest, stroke and pulmonary embolism [3]. For that reason, if an NSAID is used for the prevention of post-operative AF, a less COX-2 selective NSAID should be elected and therapy should be discontinued or reconsidered in patients with a history of cardiovascular or cerebrovascular events, increased risk for bleeding or renal insufficiency [3]. Thus, more trials are necessary to evaluate the safety, optimal dose, and duration of NSAIDs treatment for the prevention of post-operative AF.

## CORTICOSTEROIDS

Corticosteroids are potent inhibitors of the pro-inflammatory cascade and have been demonstrated to limit the increase in IL-6, IL-8, tumor necrosis factor-α (TNF-α), CRP, and oxygen free radicals after cardiopulmonary bypass [99]. Although the exact mechanisms by which corticosteroids prevent post-operative AF are not entirely clear, CRP may play a key role in this process [100]. In patients with AF,

CRP localizes in atrial tissue, activates complement, and induces inflammation. Furthermore, CRP specifically binds to phosphatidylcholine generating lysophosphatidylcholine, which may cause cell membrane dysfunction by inhibiting the exchange of sodium and calcium in the sarcolemmal vesicles [101]. Thus, corticosteroid prophylaxis may offer some beneficial effects through a number of different mechanisms, including improvement in myocardial or pulmonary cell integrity, reduction in the expression of endothelial adhesion molecules, complement activation, and cytokine release [102].

Several studies have analyzed the effect of different corticosteroids in reducing post-operative AF. Dexamethasone was incidentally found to reduce in a significant manner post-operative AF in 235 patients undergoing CAGB and valve surgery combination [103]. However, other studies showing a decreasing in AF after cardiac surgery deserve mention. Prasongsukarn and colleagues [104], randomized in a prospective trial 86 patients scheduled for CABG surgery to 1 gr of methylprednisolone or placebo before surgery and 4 mg of dexamethasone every 6 hours for 1 day after surgery or placebo. Postoperative AF was significantly lower in steroid group (21%) compared to placebo group (51%). In other study, 68 patients undergoing CABG surgery were enrolled and randomized to 1 g intravenous methylprednisolone or placebo before surgery. Methylprednisolone was found to reduce significantly the incidence of postoperative AF vs placebo (12% vs 34%, respectively) [105]. A double-blind, randomized multicenter trial enrolled 241 consecutive patients undergoing first on-pump CABG surgery, aortic valve replacement, or combined CABG surgery and aortic valve replacement [100]. Patients were randomized to receive either 100 mg hydrocortisone or matching placebo and it was observed that the incidence of post-operative AF was significantly lower in the hydrocortisone group (30%) than in the placebo group (48%). In addition, patients receiving hydrocortisone did not have higher rates of superficial or deep wound infections, or other major complications.

Two meta-analyses were developed to assess the benefits and risks of corticosteroid use in adult cardiac surgery. The first of them included 3323 patients from 50 randomized controlled trials [102]. Corticosteroid prophylaxis reduced the risk of AF (25.1% versus 35.1%), length of stay in the intensive care unit (0.37 days) and hospital (0.66 days) compared with placebo. Moreover, the use of corticosteroid was not associated with an increased risk of all-cause infection, although very high doses of corticosteroid were associated with prolonged mechanical ventilation, thus suggesting that low-dose corticosteroid is as effective as high-dose in reducing the risk of post-operative AF and causes fewer potential side effects. The other meta-analysis identified 7 relevant studies that included 1046 patients [99]. The use of corticosteroids was associated with a significant reduction in the risk of post-operative AF, although significant heterogeneity was noted as the corticosteroid regimen was very different between studies. However, when the low-dose and very high-dose studies were excluded, the treatment effect was highly significant with no heterogeneity.

All these studies show that moderate-dosage corticosteroid could be considered for the prevention of AF in patients undergoing cardiac surgery. However, the optimal dose, dosing interval, and duration of therapy are unclear and need to be clarified. Moreover, the interaction between corticosteroids, β-blockers, amiodarone and other pharmacologic agents requires further study.

## CONCLUSION

The importance of post-operative AF as a cardiac arrhythmia should not be underestimated, particularly during the perioperative period. Postoperative AF is known to be associated with adverse patient outcomes including increased length of postoperative hospital stay, greater hospitalization costs, transient ischemic attack, stroke, heart failure, myocardial infarction, ventricular tachyarrhythmias, and death [1]. Current guidelines from the ACC/AHA/ESC recommend β-blockers, amiodarone, and sotalol as prophylactic therapies for postoperative AF. However, new pharmacologic agents targeting inflammatory pathways and atrial remodeling will be needed to reduce the incidence of AF after surgery. This way, the advent of new prophylactic therapies such as RAAS modulators, statins, magnesium supplementation, antioxidant compounds, NSAIDs and corticosteroids alone or in combination with β-blockers can help in the prevention of post-operative AF.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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## ABBREVIATIONS

| | | |
|---|---|---|
| AF | = | Atrial fibrillation |
| CABG | = | Coronary artery bypass grafting |
| ACCP | = | American College of Chest Physicians |
| ACC | = | American College of Cardiology |
| AHA | = | American Heart Association |
| ESC | = | European Society of Cardiology |
| RAAS | = | Renin-angiotensin-aldosterone system |
| ACEI | = | Angiotensin-converting enzyme inhibitor |
| ARB | = | Angiotensin receptor blockers |
| CRP | = | C-reactive protein |
| IL-6 | = | Interleukin-6 |
| Ang | = | Angiotensin |
| AGTR1 | = | Angiotensin II type 1 receptor |
| CYP11B2 | = | Aldosterone synthase |

| | | |
|---|---|---|
| MMP | = | Matrix metalloproteinase |
| TIMP | = | Tissue inhibitor matrix metalloproteinase |
| HMG-CoA | = | 3-Hydroxy-3-methyglutaryl-coenzyme A. |
| PUFA | = | Polyunsaturated fatty acids |
| $Na^+/K^+$-ATPase | = | Sodium-potassium adenosine triphosphatase |
| NSAID | = | Non-Steroidal Anti-inflammatory Drugs |
| TNF-α | = | Tumor necrosis factor-α |

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