REVIEW OF THERAPEUTICS

Pharmacologic Prophylaxis of Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery: Beyond β-Blockers

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Postoperative atrial fibrillation (POAF) is a frequent complication of cardiac surgery that increases patient morbidity, length of stay, and hospital costs. A substantial body of evidence exists evaluating various pharmacologic and nonpharmacologic methods to decrease the occurrence of POAF in an effort to decrease its burden on the health care system. Evidence-based guidelines support the use of β-blockers as standard prophylaxis of POAF in patients undergoing cardiac surgery. Traditional prophylactic therapy for POAF targets the sympathetic nervous system, refractory period, and atrial conduction. However, associations between the development of POAF and the inflammatory process, oxidative stress, and atrial remodeling have prompted the investigation of novel therapies targeting these processes. To evaluate the role of pharmacologic strategies beyond β-blockers in the prevention of POAF, we conducted a search of the PubMed database to identify studies published from 1950–February 2009. Emphasis was placed on how these therapies could be used in patients intolerant to β-blockers or as additive therapy in high-risk patients. We found that sufficient evidence exists to recommend the use of amiodarone, sotalol, and possibly magnesium as monotherapy in patients unable to take β-blockers or as add-on therapy for the prevention of POAF. Currently, available evidence does not support the use of propafenone, procainamide, digoxin, thiazolidinediones, triiodothyronine, or calcium channel blockers in the prevention of POAF. Preliminary evidence suggests that dofetilide, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins), nonsteroidal antiinflammatory drugs, corticosteroids, omega-3 fatty acids, ascorbic acid, *N*-acetylcysteine, and sodium nitroprusside may be effective in preventing POAF. Additional large-scale, adequately powered clinical studies are needed to determine the benefit of these agents before they can be considered for routine use.

Key Words: postoperative atrial fibrillation, prophylaxis, cardiothoracic surgery, cardiac surgery.

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Atrial fibrillation occurs in 15% to 50% of patients after cardiac surgery.[1, 2] Postoperative atrial fibrillation (POAF) most often develops between the second and fifth postoperative day, with a peak incidence in the first two to three days. While POAF can be self-limiting, it may also be associated with hemodynamic compromise, postoperative stroke, perioperative myocardial infarction (MI), ventricular arrhythmias, and heart failure.[3, 4] The development of POAF is associated with, on average, an additional hospital length of stay (LOS) of 1 to 1.5 days.[5, 6] Some studies, however, report that POAF increases hospital LOS by almost 5 days.[7, 8] POAF is also associated with higher hospital costs with an average increase of $10,000–12,600 per hospitalization.[7, 8]

Four sets of practice guidelines for the prevention of POAF in patients undergoing cardiac surgery exist which include the American College of Chest Physicians (ACCP) 2005 POAF Guidelines, the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) 2006 Atrial Fibrillation Guidelines, the ACC/AHA 2004 Coronary Artery Bypass Graft Surgery (CABG) Guidelines, and the European Association for Cardio-Thoracic Surgery (EACTS) 2006 POAF Guidelines.[1, 2, 9, 10] The guidelines are consistent in that they all strongly recommend using β-blockers to reduce POAF incidence (ACCP 2005 POAF Guidelines Strength A, ACC/AHA/ESC 2006 Atrial Fibrillation Guidelines and ACC/AHA 2004 CABG Guidelines Class I, and EACTS 2006 POAF Guidelines Grade A) (Table 1).

The Surgical Care Improvement Project (SCIP) National Quality Measures also state that all patients undergoing cardiac surgery should receive a β-blocker during the perioperative period if they were on a β-blocker prior to arrival.[11] Most institutions have incorporated this requirement into their preoperative order sets for all patients without contraindications. Though there are no studies examining POAF prophylaxis for patients intolerant to β-blockers, effective alternatives include sotalol and amiodarone, depending on the contraindication. Some relative contraindications to use of β-blockers may include acute decompensated heart failure, hypotension, bradycardia, second or third degree heart block, severe asthma or chronic obstructive pulmonary disease (COPD). The guidelines specify that amiodarone may be given as an alternative to or in addition to β-blockers in patients at high risk for POAF.[2, 9, 10] Only the European Association for Cardio-Thoracic Surgery (EACTS) guidelines support the use of magnesium and state that it may be given in addition to other strategies to reduce POAF.[2]

β-blockers clearly reduce the incidence of POAF. A large meta-analysis reports that in 27 randomized controlled trials with 3,840 patients, the incidence of atrial fibrillation in control patients was 33% compared to 19% in those taking β-blockers.[12] The importance of β-blockers is also affirmed by the two to five-fold increase in POAF when β-blockers are discontinued postoperatively.[13, 14] β-blocker withdrawal, mediated by an upregulation of β adrenergic receptors and sympathetic stimulation, are thought to play a role in this phenomenon.[13] Lertsburapa et al demonstrated that β-blocker withdrawal was a significant factor in patients who went on to develop POAF compared to those that did not develop POAF (13% versus 7%, p=0.04).[15] Logistic regression analysis in this same population found that β-blocker withdrawal was significantly associated with a greater than two-fold risk of developing POAF (Adjusted OR 2.17, 95% CI 1.11–4.25, p=0.04). Thus the guidelines emphasize the importance of reinitiating β-blockers postoperatively without delay.[1]

While β-blockers reduce the incidence of POAF, they do not eliminate it. Thus, there is a need for additional effective therapies.[1, 2] Certain drugs added to β-blockers have been shown to further reduce the incidence of POAF. Combinations shown tobe superior to β-blocker monotherapy include magnesium plus bisoprolol,[16] magnesium plus sotalol,[17] and amiodarone plus metoprolol.[18, 19] The use of these combinations may be useful in high-risk patients.

The guidelines suggest additive therapy can be considered for patients at high risk of developing POAF. Risk factors that have been identified to increase the risk of POAF include advanced age, history of atrial fibrillation, COPD, valvular surgery, hypertension, poor left ventricular function, chronic renal insufficiency, diabetes mellitus, rheumatic heart disease, withdrawal of preoperative β-blockers or angiotensin-converting enzyme inhibitors (ACEIs), and increased aortic cross-clamp and

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cardiopulmonary bypass (CPB) time.[20–22] No simple criteria exist that allow patients to be classified as high risk for the development of POAF. One study developed a risk index model (Multicenter Study of Perioperative Ischemia Atrial Fibrillation Risk Index) (Table 2)[20] to identify subjects at high risk for POAF. Patients receiving a risk score less than 14 were considered low risk, 14–31 were considered medium risk, and greater than 31 were considered high risk for developing POAF. Comparison of the predictive ability of the model revealed that the incidence of atrial fibrillation was similar in the derivation and validation cohorts across the three risk groups, and the area under the receiver operating characteristic curve applied to the final model was 0.77 (where >0.75 represents a model with good discriminate power). This risk scoring tool has been used to stratify patients into risk groups that may benefit from add-on prophylactic therapy.[23]

The purpose of this review is to summarize the evidence supporting the use of traditional pharmacologic therapies, other than β-blockers, for the prevention of POAF that target the sympathetic nervous system, refractory period, or alter cardiac conduction. Since recent research has focused on the inflammatory process, oxidative stress, and atrial remodeling, this review will also include the available evidence concerning novel therapies that may influence these pathways and impact the development of POAF. Emphasis will be placed on how these therapies could be used in patients intolerant to β-blockers or as additive therapy in high risk patients. A PubMed search was conducted to identify studies published from 1950 to February 2009 using the search terms postoperative, atrial fibrillation, and supraventricular tachycardia (SVT). Studies were limited to those conducted in adult humans published in English that evaluated use of drug therapy in the prevention of atrial fibrillation in patients undergoing CABG with or without concomitant valvular surgery. Studies limited to procedures not involving the heart were excluded. References of identified articles were reviewed for additional pertinent articles. To be included in the review, preoperative β-blocker use had to be reported in at least 50% of patients in all treatment groups receiving therapy. Regardless of preoperative β-blocker use, studies were also included that directly compared prophylactic therapy against β-blockers or continued β-blockers throughout the duration of hospitalization. Postoperative β-blockade was taken into consideration and use was reported if indicated by the authors. Therefore, usual care, control, or placebo groups in this review should indicate that a substantial number of patients were receiving concomitant β-blocker therapy. The authors identified these criteria for study inclusion in an effort to exclude studies where outcomes could be influenced by the phenomenon of β-blocker withdrawal.

Pathogenesis of POAF

The underlying mechanisms for the development of POAF after cardiac surgery are not precisely known, but are thought to be multifactorial. It has been proposed that certain causative mechanisms alter atrial refractoriness and slow atrial conduction which results in multiple reentry wavelets circulating within the atria.[21] Some of these mechanisms include pericardial inflammation, excessive production of catecholamines, and volume and pressure changes. 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, are all thought to impact the development of POAF. Once these conditions exist, a triggering event such as premature atrial contraction, electrolyte imbalance, and/or enhanced adrenergic or vagal stimulation initiates POAF. Neurohormonal activation is more widely recognized as a cause of POAF based on studies linking elevated norepinephrine and epinephrine concentrations to the development of POAF.[21, 24] Hence, the majority of interventions that reduce the incidence of POAF modulate sympathetic and parasympathetic systems or alter cardiac conduction and refractory periods (Table 1).

While the mechanisms involved in the development of POAF are multifactorial, there is increasing evidence that inflammation also plays a role. Such inflammation may be induced by extracorporeal circulation or CPB with subsequent elevations of C-reactive protein (CRP), interleukin-6 (IL-6), and the complement system.[3, 25–27] Angiotensin II has been shown to increase the production of proinflammatory cytokines, adhesion molecules, and selectins.[28, 29] White blood cell count may also be a predictor of POAF.[30] The degree of inflammation postoperatively can negatively affect atrial conduction and duration of atrial fibrillation.[31, 32]

Oxidative stress has also been implicated in the pathogenesis of atrial fibrillation as the atrial tissue undergoes oxidative challenge during CPB.[33] Patients with POAF have been shown to have increased acute myocardial oxidation when compared to patients that did not experience

POAF.[34] Specifically, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, an enzyme associated with the formation of the reactive oxygen species, superoxide, was found to be independently associated with increased risk of POAF.[35] This may be due to damage of cardiac myocytes through lipid peroxidation, breakdown of cell membrane, decreased mitochondrial function, calcium overload, and apoptosis.[36] Because NADPH is activated by numerous mediators including tumor necrosis factor-α (TNF-α), it has been proposed as a link between inflammation and oxidative stress in POAF.[37]

Based on these newly identified pathways, novel therapies for the prevention of POAF have been under investigation including renin-angiotensin-aldosterone-system modulators (including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers), HMG Co-A reductase inhibitors (statins), nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, thiazolidinediones (TZDs), omega-3 fatty acids, ascorbic acid, *N*-acetylcysteine, and sodium nitroprusside.

Antiarrhythmics

Propafenone, Procainamide, Digoxin and Calcium Channel Blockers

Given the availability of just a few trials with inconsistent results, propafenone is not currently recommended as first-line POAF prophylaxis.[1, 2, 9, 10] Its use may be limited by its proarrhythmic effects in patients with structural heart disease. Current available evidence also does not support the use of procainamide for POAF prophylaxis. Although based on limited evidence, preoperative "digitalization" was historically used to prevent POAF. Currently, digoxin does not have an indication for POAF prophylaxis but can be used for rate control once atrial fibrillation occurs.[1] Only the non-dihydropyridine calcium channel blockers (non-DHP-CCB) diltiazem and verapamil, have evidence supporting their effectiveness for POAF prophylaxis from a meta-analysis evaluating twelve small studies encompassing 719 patients.[38] However, two other meta-analyses found a non-significant reduction[39] and even an increase in the risk of POAF[40] with the CCBs. Therefore, the guidelines recommend against routine use of CCBs for POAF prophylaxis and that the non-DHP-CCBs, diltiazem or verapamil, be reserved for rate control only once POAF has occurred.[1, 10]

Sotalol

Sotalol, a class III antiarrhythmic with β-blocking activity, has been shown to be an effective therapy for the prevention of POAF. In most randomized, controlled trials meeting this reviews' predefined β-blocker criteria, sotalol was superior to placebo or usual care with absolute reductions in the incidence of POAF between 13% and 16% (Table 3).[18, 41–44] Two of these studies performed logistic regression to find that omission of preoperative β-blocker remained an independent predictor of POAF, regardless of sotalol use (p=0.002 and p=0.0145).[18, 43] One study, which failed to show a significant reduction in the incidence of POAF, was underpowered with only 42 patients enrolled.[45] Four published meta-analyses have also confirmed the efficacy of sotalol compared to placebo or usual care.[12, 40, 46, 47]

Sotalol appears to be more effective than conventional β-blockers in preventing POAF. Two studies found sotalol to be superior to metoprolol with absolute reductions in the incidence of POAF by 17% and 34%.[41, 48] Neither study, however, utilized current guideline-recommended preoperative β-blockade. Sotalol was also found to be significantly better than atenolol (10% versus 22%; p=0.013) with again limited utilization of preoperative β-blockade.[49] Another study that compared low- and high-dose sotalol against low- and high-dose propranolol failed to demonstrate a significant difference between the treatment groups.[50] However, fewer patients in both sotalol groups were on preoperative β-blockers when compared to the propranolol groups (p<0.05 for low dose sotalol). Nystrom et al compared pre-and postoperative sotalol to half-dose β-blocker therapy (78%) or no β-blocker therapy (22%) and found a significant reduction in the incidence of POAF (sotalol 10% vs. half dose β-blocker 29%, p=0.028).[51] Two meta-analyses demonstrated a greater benefit with sotalol compared to conventional β-blockers [(OR 0.42; 95% CI 0.26 to 0.65) and (OR 0.50; 95% CI 0.34 to 0.74)].[12, 47]

Sotalol has also been given in combination with magnesium in one study meeting predefined criteria for β-blockade. POAF occurred in 13.5% of the sotalol/magnesium group and 27% of the usual care group (p=0.025), suggesting that the combination of preoperative sotalol and magnesium may be superior to preoperative β-blockade alone.[52]

Sotalol has been compared to amiodarone in one randomized head-to-head trial and in one meta-analysis performed by the same research group using indirect comparisons.[46, 53] In the head-to-head trial, there was no significant difference in the incidence of POAF between patients randomized to amiodarone versus sotalol (sotalol 25% versus amiodarone 17%, p=0.21).[53] However, the duration

of atrial fibrillation was significantly shorter in the amiodarone group. The meta-analysis also failed to show a significant difference in the incidence of POAF between these two agents.[46]

No studies meeting this review's predefined β-blocker criteria demonstrated a significant reduction in LOS when sotalol was compared to usual care. Two meta-analyses assessed LOS and neither found a significant reduction when compared to placebo.[12, 46]

Despite its demonstrated effectiveness, which is probably superior to conventional β-blockade, sotalol is contraindicated in patients with severe renal insufficiency and should be avoided in patients with heart failure. Likewise, because of its propensenity to cause torsades de pointes, it should be avoided in patients with congenital long QT syndrome or a baseline corrected QT interval greater than 440 msec. Because of this, it has a class IIb recommendation for POAF prophylaxis behind β-blockers according to the ACC/AHA/ESC 2006 Atrial Fibrillation Guidelines[9] and the ACC/AHA 2004 CABG Guidelines.[10] Due to its β-blocking properties, sotalol would be contraindicated in patients intolerant of β-blockers. Amiodarone, which has a class IIa recommendation for POAF prophylaxis in the same guidelines would be an option for these patients.[9, 10] Sotalol could be considered, however, as add on therapy in high risk patients that can tolerate additional β-blockade.

Amiodarone

Amiodarone is class III antiarrhythmic agent that blocks alpha and β adrenergic receptors and sodium, calcium and potassium channels. It has been shown to be effective therapy for the prevention of POAF. In most randomized, controlled trials meeting this review's predefined β-blocker criteria, amiodarone was superior to placebo or usual care with absolute reductions in the incidence of POAF between 12% to 51%.[18, 23, 54–63] However five trials failed to show a significant benefit[64–67] and one found amiodarone increased[68] the incidence of POAF compared to placebo or usual care (Table 4). Despite those studies, six meta-analyses have confirmed the protective effect of amiodarone[16, 46, 47, 69–71] with the greatest reduction in risk of POAF of 52% when compared to placebo or usual care (OR 0.48; 95% CI 0.40–0.57).[47]

Some randomized controlled trials that evaluated amiodarone compared to placebo or usual care further analyzed their data to evaluate the subsets of patients that received β-blocker therapy meeting this review's predefined criteria for adequate use.[56, 65] Only the Atrial Fibrillation Suppression Trial (AFIST) I study which enrolled elderly patients greater than 60 years of age to receive amiodarone 7 g as a slow-load or 6 g as a fast-load and β-blockers found the incidence of POAF to be significantly lower in amiodarone patients receiving concomitant postoperative β-blockers compared to amiodarone alone (16% versus 35%, p=0.02).[56] Their results also reveal that the average metoprolol dose received postoperatively was approximately 100 mg in both groups. The authors sought to determine if the effect of amiodarone was synergistic with β-blockade. Using a risk-adjusted relative risk for developing POAF, they found a lower, but non-signifcant reduction using the combination (RR 0.79; 95% CI 0.33–1.89). The study by Redle et al found that the subset of amiodarone patients receiving β-blockers had a lower, but non-significant absolute reduction in the incidence of POAF by 15%, OR 0.43; 95% CI 0.13–1.32.[65]

Only one study has directly compared the effectiveness of amiodarone to the β-blocker propranolol for the prevention of POAF.[72] The authors found amiodarone was superior to propranolol with an absolute reduction in the incidence of POAF of 17% (amiodarone 16% versus propranolol 33%, p=0.05). (Table 4) While amiodarone was more effective, the duration of atrial fibrillation (58 hours versus 16 hours, p=0.05) and QT interval (425 msec versus. 391 msec, p=0.006) were significantly longer in patients receiving amiodarone compared to propranolol. A subanalysis of the patients randomized to the amiodarone group showed no difference in the incidence of POAF in patients receiving amiodarone plus postoperative β-blockers compared to those receiving amiodarone alone (19% versus 14%, p=NS).[72] Indirect comparisons of amiodarone versus control groups where β-blockers were used in all patients postoperatively revealed conflicting results with two studies showing benefit[67, 73] and two indicating neutral or inferior effects[68, 74] (Table 4).

Amiodarone has been given in direct combination with metoprolol,[18] magnesium,[74] and atrial septal pacing in Bachmanns's Bundle[60] for the prevention of POAF in three studies meeting this review's predefined β-blocker criteria. All three studies showed amiodarone in direct combination with the above pharmacologic and non-pharmacologic options were superior to placebo with absolute reductions in the incidence of POAF by 20% to 24%.[18, 60, 74] The combination of amiodarone plus oral metoprolol 50 mg twice daily decreased the risk developing POAF (Adjusted OR 0.37; 95% CI 0.18–0.77, p<0.01) compared to placebo.[18] The study included a high percentage of patients, 45%,

undergoing valvular surgery which is a known risk factor for the development of POAF. Therefore, the authors concluded that the combination of amiodarone and β-blocker metoprolol should be considered in patients undergoing cardiac surgery at high risk for POAF. Cagli et al also found that the combination of amiodarone plus IV magnesium was superior to amiodarone alone or placebo with absolute reductions in the incidence of POAF by 27% (p=0.01) compared to amiodarone and by 24% compared to placebo. All patients enrolled in that study also received a fixed preoperative dose of metoprolol 50 mg/day that continued postoperatively.[74] The AFIST II trial evaluating amiodarone with or without atrial septal pacing found that the combination of amiodarone plus pacing significantly reduced the incidence of POAF by an absolute difference of 22% (amiodarone + pacing 16% versus placebo + no pacing 38%, p=0.047) compared to placebo plus no pacing by an absolute difference of 24% (amiodarone + pacing 16% versus placebo + pacing 40%, p=0.04). Postoperative β-blocker use in all three groups was approximately 80% and the average metoprolol dose was 65–80 mg per day.[60]

Amiodarone has been directly compared to another antiarrhythmic, sotalol, for the prevention of POAF in a study by Mooss et al that was discussed in the sotalol section. This study found no significant difference in the incidence of POAF between patients randomized to amiodarone versus sotalol (sotalol 25% versus amiodarone 17%, p=0.21).[53] However, the duration of atrial fibrillation was significantly shorter in the amiodarone group.

Amiodarone has also been directly compared to non-pharmacologic methods of POAF prophylaxis including right atrial pacing[68], atrial septal pacing at Bachmann's Bundle[60] mentioned previously, and thoracic epidural blockade[75] in three studies meeting this review's predefined β-blocker criteria. Nydard et al compared amiodarone prophylaxis to a high thoracic epidural blockade (TEA) with the hypothesis that blocking sympathetic nervous system outflow would benefit patients at increased risk of POAF.[75] The results from two of these trials were conflicting as amiodarone reduced the incidence of POAF compared to the TEA method[75] and where amiodarone increased the incidence of POAF compared to right atrial pacing and control.[68] The only trial showing significant reduction in the incidence of POAF was found using the combination of amiodarone plus atrial septal pacing compared to placebo plus no pacing or placebo plus pacing, however postoperative β-blockers were used in more than 80% of all three groups.[60]

Two studies that evaluated the effect of amiodarone for the prevention of POAF sought to further analyze the effect of various high-risk subgroups on the treatment effects of amiodarone. One retrospective study investigated the impact of amiodarone outcomes using a risk index model developed by Mathew et al to assign patients who underwent cardiac surgery to a risk-stratified cohort of low (score less than 14 points) or elevated risk (score greater than or equal to 14 points) for the development of POAF.[23] When the risk stratification evaluation was made, 50% of patients were at an elevated risk for the development of POAF. Patients not receiving amiodarone prophylaxis in the elevated risk cohort had a higher incidence of POAF occur compared to those that did receive amiodarone prophylaxis (43% versus 28%, OR 0.52; 95% CI 0.31–0.88, p=0.015). The greatest cost savings with amiodarone prophylaxis were seen in patients at elevated risk for POAF. The second study was a prospective trial that randomized patients in a double-blind, 1:1 ratio, blocked in groups of 10, and stratified for age (< 65 and ≥ 65 years), surgical procedure (CABG alone versus valve replacement/repair surgery with or without CABG), and preoperative treatment (with or without β-blockers).[61] Compared to placebo, they found that the incidence of POAF was higher in patients aged > 65 years (Absolute RR 19.5; 95% CI 7.3–31.7), patients who had valve repair/replacement with or without CABG surgery (Absolute RR 20.3; 95% CI 3.6–31), and patients who did not receive preoperative β-blockers (Absolute RR 19.6; 95% CI 8–31.1).[61]

Three studies using amiodarone for the prevention of POAF showed a significant reduction in LOS with amiodarone by a range of one to three days.[54, 62, 76] Pooled data from two meta-analyses found a decreased, but statistically nonsignificant, risk of death with amiodarone of 11% and 16%, respectively.[69, 77] Pooling data to further evaluate LOS found a significant reduction when amiodarone was compared to placebo or usual care in three of five meta-analyses.[12, 46, 69, 70, 77] The greatest reduction LOS was reported by Crystal et al with a decrease of 0.91 days (95% CI –1.59 to –0.23).[12] Two meta-analyses also showed a benefit for amiodarone in reducing the risk of stroke by 53% (OR 0.47; 95% CI 0.23–0.96) and 61% (OR 0.39; 95% CI 0.21–0.76).[69, 70]

Various dosing regimens using IV and/or oral amiodarone with varying administration times have been used in the POAF prevention trials. One meta-analysis evaluated 14 randomized, controlled trials

in 2,864 patients (of which 9 studies meeting this review's predefined β-blocker criteria were included in their analysis).[71] Cumulative amiodarone doses used in the studies were stratified into low (< 3000 mg), medium (3000–5000 mg), or high (> 5000 mg) and timing was divided into preoperative or postoperative administration. The investigators found the odds of developing POAF appeared to be higher in the low-dose group. Yet, no significant differences were noted in the odds ratios of developing POAF among the groups: low dose (OR 0.58; 95% CI 0.44–0.77); medium dose (OR 0.45; 95% CI 0.30–0.69); high dose (OR 0.44; 95% CI 0.33–0.58), respectively, p=0.238. The odds of developing POAF were not significantly different in patients whom amiodarone prophylaxis was started preoperatively and continued postoperatively compared to those where amiodarone prophylaxis was only started postoperatively, (OR 0.50; 95% CI 0.39–0.63) versus (OR 0.48; 95% CI 0.37–0.63), respectively, p=0.862. Therefore these authors conclude that doses >3000mg may be more effective than lower doses and preoperative initiation of amiodarone may be unnecessary.[71]

Amiodarone has a complex side effect profile that includes pulmonary and liver toxicity, QTc interval prolongation, thyroid abnormalities, and visual disturbances. Patients with any of these pre-existing conditions may be at more risk using amiodarone for the prevention of POAF and the risk versus benefit must be evaluated individually. Side effects of amiodarone are typically associated with large cumulative doses and prolonged use. However, dosing regimens for prophylaxis of POAF tend to be of short duration, use lower cumulative dosing, and may use more convenient oral doses with or without a short course of IV amiodarone to avoid side effects associated with IV administration. A meta-analysis of 18 trials (of which 11 trials meeting this review's predefined β-blocker criteria were included in their analysis) specifically evaluated specific safety endpoints of bradycardia, hypotension, heart block, nausea, cerebral vascular accident, myocardial infarction and death using amiodarone for the prevention of POAF in cardiac surgery patients. They found that amiodarone was associated with increased risk of developing bradycardia and hypotension with the greatest risk using regimens containing IV amiodarone. They also found that initiating prophylaxis during the postoperative period and using regimens with average daily doses exceeding 1 g were associated with bradycardia and hypotension.[77] These last two findings seem contrary to the results from Buckley et al, but these meta-analyses evaluated the prophylactic amiodarone regimens on two different major outcomes of the incidence of POAF to evalate efficacy[71] compared to incidence of bradycardia and hypotension to evaluate safety.[77]

Amiodarone also inhibits p-glycoprotein and certain cytrochrome P450 enzymes and can potentiate the effects of certain medication such as warfarin, simvastatin, digoxin, class Ia antiarrhythmics, and cyclosporine. Caution must be exercised during coadministration of amiodarone to patients taking these and other medications known to cause QTc prolongation, such as fluoroquinolones, macrolide antibiotics, and azole antifungals.

Amiodarone has proven its effectiveness compared to placebo or usual care for the prevention of POAF and decreased LOS in patients undergoing cardiac surgery and appears to show benefit in addition to β-blocker therapy. Due to the established efficacy and safety of β-blockers, amiodarone has a class IIa recommendation for POAF prophylaxis behind β-blockers according to the ACC/AHA/ESC 2006 Atrial Fibrillation Guidelines[9] and the ACC/AHA 2004 CABG Guidelines.[10] The guidelines also support amiodarone as prophylactic therapy in patients unable to tolerate β-blockers or in high-risk patients with or without β-blocker therapy. Patients that may benefit the most from receiving the combination of amiodarone and a β-blocker for the prevention of POAF could be patients that are elderly, undergoing concomitant valve surgery, use β-blockers preoperatively, or are stratified as high risk using scoring tools. Blood pressure and heart rate should be monitored closely as the combination of amiodarone and β-blocker could increase the risk of developing bradycardia and hypotension. If amiodarone is added, the patient's medication profile, physical and laboratory exams should be reviewed to evaluate the presence of drug-drug interactions or medication side effects.

Dofetilide

Dofetilide has been compared to placebo for postoperative atrial tachycardia (POAT) prophylaxis in one study meeting this review's predefined β-blocker criteria (Table 5).[78] The investigators found that patients receiving dofetilide prophylaxis experienced a significant reduction in the incidence of POAT, including atrial fibrillation and atrial flutter, when compared to placebo (18% versus 36%, p<0.017). There was no significant decrease in mean LOS. Although the use of postoperative β-blockers was not reported, the authors conclude that the dofetilide group experienced a significant

decrease in POAT independent of concomitant β-blocker use based on multivariate logistic regression accounting for preoperative β-blocker use. Due to cost, stringent prescribing and monitoring guidelines, and lack of robust head-to-head trials, dofetilide is not currently recommended as first line for POAF prophylaxis. Like sotalol, it also carries a greater risk of torsades de pointes and should be avoided in patients with prolonged QT intervals. It could be considered for add on therapy in high-risk patients or in patients intolerant of β-blockers but should first be compared to other traditional class III antiarrhythmics such as amiodarone or sotalol in head-to-head trials.

Magnesium

Decreased postoperative magnesium levels have been associated with increased incidence of POAF.[24] In fact, using multivariate logistic regression, plasma magnesium concentrations less than 0.9mmol/L are an independent predictor of POAF (OR 6.7).[66] Magnesium supplementation has been extensively studied for POAF prophylaxis in a variety of delivery forms (Table 6). Many large, randomized, controlled trials with magnesium meeting this review's predefined β-blocker criteria failed to demonstrate superiority to usual care with no magnesium in the prevention of POAF. These trials included various delivery forms of magnesium including IV infusion,[66, 79–81] IV infusion based on serum levels,[82] magnesium supplementation in maintenance fluids[83] and in supplementation through cardioplegia solution.[84] A few of these trials also included higher risk patients experiencing unstable angina[79] or undergoing concomitant valvular surgery.[80]

A few studies meeting this review's predefined β-blocker criteria have demonstrated a significant benefit of magnesium when compared to usual care with absolute reductions in the incidence of POAF by 16% to 34%.[85–87] Magnesium was administered as a one time dose, median 5 g, intraoperatively in one study[86] and as an IV infusion for 3–5 postoperative days in the other two studies (2.5 g daily and 3 g daily).[85, 87] Two of these studies included retrospective data.[86, 87] Maslow et al also assessed the combined use of intraoperative β-blockers and magnesium. They found a 5% incidence of POAT in the combination group compared to 19% for patients receiving either agent alone and a 33% incidence for patients receiving neither agent ($p<0.05$).[86] However, because all three studies report little, if any, postoperative use of β-blockers, it is difficult to determine if magnesium supplementation would be of benefit in addition to conventional β-blockade from this data.

Various dosing regimens of magnesium have been utilized for the prevention of POAF. Wistbacka et al assessed the effect of high dose versus low dose magnesium started during surgery and continued through postoperative day two. High dose was defined as magnesium sulfate 4.2 ± 0.7 g followed by magnesium chloride 11.9 ± 2.8 g until postoperative day one and then 5.5 ± 1.0 g until postoperative day two (n=41). Low dose was defined as magnesium sulfate 2.9 ± 0.5 g on postoperative day one and 1.4 ± 0.1 g on postoperative day two. They found a significant reduction in the incidence of POAF in the high dose group (24.3%) versus the low dose group (45%), $p<0.01$.[88] While most patients were on preoperative β-blockers, there is no report of postoperative β-blocker use.

Magnesium has not been shown to be superior to β-blockers, but may be effective in combination with β-blockers. In two studies, adding magnesium to propranolol did not lead to a significant reduction in POAF over β-blockers alone, though their combination was superior to placebo in one trial (19% versus 38%, respectively, $p=0.02$).[80, 89] The combination of magnesium plus bisoprolol was found to be superior to a control group in which 82% of patients stayed on their preoperative β-blockers (20% versus 42%, respectively, $p=0.030$).[16] In addition to reducing the incidence of POAF, this study also demonstrated a significant reduction in median LOS in the combination group compared to control (7 days versus 9 days, $p=0.022$). One study demonstrated that the postoperative combination of magnesium and sotalol was superior to either agent alone.[90] Thus, combination therapy with β-blockade and/or sotalol may be a consideration for patients at high risk of POAF.

Magnesium has also been compared to amiodarone in a study meeting this review's predefined β-blocker criteria, but there was no significant difference in the incidence of POAF between the two treatments.[66] One study did demonstrate that using a combination of magnesium and amiodarone led to a greater reduction in POAF when compared to amiodarone alone (9% versus 36%, $p=0.01$).[74] However, the incidence of POAF with amiodarone monotherapy was not significantly better than placebo (36% versus 33%, p=NS) which may be due to the fact that all patients received β-blockers pre- and postoperatively.

Magnesium has not consistently had an effect on LOS when compared to usual care. One study actually observed a significantly longer LOS when compared to usual care with no differences in the incidence of POAF.[81]

Between 1998 and 2008, seven meta-analyses

have been published evaluating the effect of magnesium for the prevention of POAF.[40, 47, 91–95] These analyses included trials both with and without concomitant β-blockade. The earliest, published by Woodend et al, did not show a significant benefit of using magnesium for POAF prophylaxis.[40] The other six analyses did show a statistically significant benefit from magnesium.[47, 91–95] However, one analysis[47] identified significant heterogeneity not explained by dose. In this analysis, the largest effect of magnesium was evident in two trials with no use of β-blockers (OR 0.05, 95% CI 0.02–0.16) and the smallest effect in the trials in which β-blockers were used postoperatively (OR 0.83, 95% CI 0.60–1.16).

One meta-analysis evaluated both dose and timing of magnesium administration.[94] Interestingly, lower cumulative doses (mean cumulative dose 8.2 g) significantly reduced the incidence of POAF (OR 0.36, 95% CI 0.23–0.56), while higher doses (mean cumulative dose 15 g) did not (OR 0.99, 95% CI 0.70–1.42). They also found that preoperative administration was most beneficial (OR 0.46, 95% CI 0.31–0.67) compared to intraoperative or postoperative administration. Three meta-analyses evaluated LOS, but only one demonstrated a significant reduction of 0.29 days (95% CI –0.54 to –0.05, p=0.02).[91, 92, 94]

Due to conflicting results, prophylactic magnesium therapy is not universally utilized at this time, though some providers prescribe it in addition to β-blockers and/or amiodarone. There is also little consensus among the guidelines about its utilization (Table 1). Compared to prophylaxis of POAF with amiodarone or sotalol therapy, magnesium is certainly less toxic with fewer contraindications. It could be considered as add on therapy in higher risk patients or in patients intolerant of β-blockers and antiarrhythmics. Doses of magnesium sulfate between 2.5–5 g have been most commonly used.[85–87] Blood pressure should be monitored carefully as the combination of postoperative β-blockers and magnesium was shown to significantly increase the incidence of hypotension compared to β-blockade alone (24.4% versus 43.5%, p=0.01).[89] Regardless of utilization, magnesium levels should be monitored carefully and maintained throughout the postoperative period.

Renin-Angiotensin-Aldosterone-System (RAAS) Modulators

An increasing number of investigations are being conducted to evaluate the association between the renin-angiotensin-aldosterone-system (RAAS), the inflammatory process, and atrial fibrillation. Interruption of the RAAS by angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) prevents the production of the regulatory hormone angiotensin II, which plays a key role in controlling blood pressure, vascular smooth muscle tone, aldosterone release, and sodium resorption from the renal tubules.[29] Beyond these actions, angiotensin II has been implicated in increasing the production of pro-inflammatory cytokines (i.e., IL-6, IL-8, TNF-α), adhesion molecules, selectins, and the recruitment of neutrophils.[29] Histologic evidence exists that persistent and paroxysmal atrial fibrillation leads to altered angiotensin II receptor expression.[28, 29] Genetic polymorphisms in the angiotensinogen gene are also two to three times more likely to have non-familial atrial fibrillation,[96] further supporting the role RAAS plays in the development of atrial fibrillation. ACEIs and ARBs have been shown to reduce the incidence of atrial fibrillation in patients with congestive heart failure (CHF), hypertension, or post MI.[97]

Three potential mechanisms have been suggested to explain the antiarrhythmic benefits of ACEIs and ARBs against atrial fibrillation. It is proposed that they improve left ventricular hemodynamics, reduce atrial stretch, suppress angiotensin-induced fibrosis, and direct modulation of potassium and calcium ion channel function. These ACEI/ARB-induced changes decrease atrial vulnerability and may diminish the initiation of atrial fibrillation.[28]

Two studies meeting this review's predefined β-blocker criteria have been conducted to assess the efficacy of ACEIs or ARBs in reducing the incidence of POAF in cardiac surgery patients (Table 7). One study randomized patients to an active intervention of ACEI or combination of ACEI/ARB and then compared these two treatment groups to a historical control. Greater than 85% of patients randomized to ACEI or combination were also on β-blockers preoperatively and 97% of patients in the historical control were on β-blockers.[98] Despite the high percentage of preoperative β-blocker use in the control group, the combination of an ACEI/ARB or an ACEI alone proved superior to usual care with absolute reductions in the incidence of POAF compared to controls by 23% and 21%, respectively. There was no difference in the magnitude of the reduction of the incidence of POAF using the combination of an ACEI/ARB compared to an ACEI alone. The authors also found that both the combination ACEI/ARB or ACEI alone significantly reduced the risk of POAF by 72% and 66%, respectively (RR 0.28; 95% CI 0.09–0.83 and RR

0.34; 95% CI 0.12–0.93, respectively). The other study examined the effect of ACEI or ARBs on development of POAF from a nested cohort of patients from the AFIST II and III trials.[99] This study also found that preoperative use of ACEIs or ARBs were protective in reducing the risk of POAF by 29%, however the magnitude of the reduction was not statistically significant (adjusted OR 0.71; 95% CI 0.42–1.20). The clinical reduction in risk of POAF in patients on ACEIs or ARBs could have been influenced by 84% of the total population of patients receiving postoperative β-blockade and 38% receiving amiodarone for POAF prophylaxis, therefore it remains unclear from that study the independent effect ACEIs or ARBs on POAF. Multivariate logistic regression analysis found that postoperative β-blocker (adjusted OR 0.47, 95% CI 0.24–0.89) and prophylactic amiodarone (adjusted OR 0.32, 95% CI 0.18–0.57) were both negative predictors of POAF, thus decreasing the risk for POAF by 53% and 68%, respectively.[99]

Cohort studies conducted to evaluate the risk factors associated with the development of POAF found that preoperative and postoperative use of ACEIs or ARBs decreased the risk of POAF by 38% (OR 0.62; 95% CI 0.48-0.79; p<0.001) and that withdrawal of ACEI or ARB increased the risk of POAF by 1.7 times (OR 1.69; 95% CI 1.38–2.08; p<0.001).[20] Another study found no significant reduction in the risk of POAF associated with ACEI or ARB use when compared to controls (OR 0.95; 95% CI 0.57–1.56; p=0.83). A significant reduction may not have been observed in the latter study as patients were propensity score matched for common predictors of atrial fibrillation and patients only received an ACEI or ARB within 24 hours of cardiac surgery. The authors hypothesized that no benefit was derived if the predominant effect of ACEI or ARBs in preventing POAF in cardiac surgery patients is through preventing or regressing pathogenic atrial remodeling resulting from chronic use of these medications.[100]

Patients in whom an ACEI or an ARB for should not be considered or used with caution for the prevention of POAF are those with a history of angioedema, acute renal insufficiency, bilateral renal artery stenosis, hyperkalemia, or history of ACEI induced cough. Increased blood pressure monitoring may be necessary with the addition of ACEI or ARB to standard prophylaxis with a β-blocker since the combination could lead to hypotension or decompensation.

While only one study found a significant benefit from using the combination of ACEI/ARBs or an ACEI alone, further trials are underway to prospectively evaluate the impact of ACEIs or ARBs on the development of POAF. These studies will provide more definitive evidence concerning the effectiveness of ACEI and ARBs in the prevention of POAF following cardiac surgical procedures.[97]

HMG Co-A Reductase Inhibitors

HMG Co-A reductase inhibitors (statins) may possess pleiotropic activity beyond lipid lowering effects and may be protective against POAF. They have been shown to reduce oxidative stress by inhibiting oxidant enzymes, upregulating antioxidant enzymes, and enhancing nitric oxide bioavailability.[101] It is also proposed that they possess direct antiarrhythmic effects mediated through cell membrane stabilization, down-regulation of the RAAS, and protection of ischemic myocardium.[102] They also have been shown to reduce the expression of inflammatory mediators (i.e., IL-6, IL-8, TNF-α, CRP, cyclooxygenase 2)[103, 104] and decrease the expression of CD11b with consequential decreased adherence to endothelial cells of vein grafts.[103] Therefore, statins may favorably impact the acute inflammatory response and alter atrial refractoriness or sympathetic activation that could lead to POAF after cardiac surgical procedures.

Two studies meeting this review's predefined β-blocker criteria have prospectively evaluated the use of statins in randomized trials compared to placebo or control. These studies found statins to be superior with absolute reductions in the incidence of POAF by 14% to 22% with statins compared to placebo or control (Table 7).[105, 106] The largest and most robust of these three trials was the Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery study (ARMYDA-3) in which a significant reduction in POAF of 22% and a reduction in LOS of 0.6 days was observed with a statin compared to placebo.[105] Song et al also found a significant reduction in POAF of 14%, but no difference in LOS when compared to the control group.[106] Of note, both of these studies enrolled only patients who had no previous history of statin use. Therefore, these patients could have less risk of pre-existing atherosclerotic disease and subsequently been at lower risk for developing POAF.[105, 106]

The remaining statin trials meeting this review's predefined β-blocker criteria in CABG patients were observational studies in which cohorts or matched patients were studied. Statins significantly reduced the incidence of POAF, with an absolute reduction of 4% to 11% compared to patients not receiving statins.[15, 107–109] There was, however, one study in

which no benefit was observed with statins compared to patients not taking statins.[110]

One study evaluated the combination of a statin and β-blocker on the incidence of POAF. Atorvastatin and β-blocker monotherapy reduced the risk of POAF by 61% (OR 0.39; 95% CI 0.18–0.85) and 81% (OR 0.19; 95% CI 0.08–0.44), respectively. However, the combination of atorvastatin and β-blocker reduced the risk by 90% (OR 0.10; 95% CI 0.02–0.25).[105] The combination of preoperative and postoperative β-blocker use and amiodarone prophylaxis in 40% of patients may have also influenced the results in the statin group in which POAF was reduced by 32% (OR 0.68; 95% CI 0.46–0.96).[15]

A long-term study, not included in Table 7, indicates statins' benefit may extend beyond the immediate postoperative period and in outcomes other than POAF. The study showed that statins reduced the composite endpoint of death, MI, and unstable angina at both 60 days (OR 0.09; 95% CI 0.01–0.70, p=0.02) and one year post-CABG (OR 0.26; 95% CI 0.015–0.4, p<0.0001).[111] Kaplan-Meier 30 day atrial fibrillation-free survival curves also indicated benefit with statins.[105, 106, 108, 109] One meta-analysis confirmed the protective benefit of preoperative statins for POAF and early all cause mortality. This study also found a significant reduction in the risk of stroke by 26% with statins when compared to controls (OR 0.74; 95% CI 0.60–0.91).[112]

One study by Lertsburapa et al attempted to determine the optimal dose of statins for the prevention of POAF. They analyzed patients by converting their statin dose to atorvastatin equivalents. Relative statin doses ≥ 40mg of atorvastatin resulted in the greatest reduction in POAF by 55% (OR 0.45; 95% CI 0.21–0.99).[15] The 20 mg atorvastatin dose still showed a significant benefit (OR 0.6; 95% CI 0.23–0.99), while the <20 mg dose showed no significant benefit (OR 0.75; 95% CI 0.47–1.20). A retrospective study in CABG/valve patients, not included in the Table 7 because the control group not assigned to statins used β-blockers in only 36% of the population, found that simvastatin 40 mg and atorvastatin 40 mg had the greatest effect on POAF with it occurring in 24% (p=0.004) and 16% (p<0.0001) of the patients compared to those not receiving statins (38%).[113] Simvastatin 20 mg and atorvastatin 20 mg maintained efficacy with POAF occurring 26% (p=0.047) and 21% (p=0.012) respectively compared to control, but no benefit was found using 10 mg or 80 mg of either drug.[113]

Statins have shown benefit in reducing the risk of POAF, LOS, and 30 day atrial fibrillation-free survival. It is less clear which statin, what dose, and for what duration will achieve the greatest benefit. While the combination of statins with standard β-blocker therapy is safe, certain statins, such as simvastatin, should only be used in reduced doses with the combination of amiodarone due to the risk of myalgias or rhabdomyolysis.[114] Larger, prospective, randomized control clinical trials are necessary to confirm that statins are effective in reducing the occurrence of POAF in addition to β-blockers.

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Inflammation appears to lead to the development of atrial arrhythmias.[26, 115, 116] Abnormalities in inflammatory biomarkers have been found in patients undergoing cardiac surgeries.[3, 25–27] Only two studies meeting this review's predefined β-blocker criteria have evaluated NSAIDs for the prevention of POAF (Table 7).[117, 118] One study found intravenous ketorolac superior to usual care with an absolute reduction in the incidence of POAF by 19% (p=0.017) and a shorter LOS by 1.2 days (p=0.009).[117] Greater than 91% of patients in the NSAID and usual care groups were receiving perioperative β-blocker therapy which could have influenced these favorable results. The other study was a nested cohort of patients from the AFIST I, II, and III trials which used postoperative NSAIDS found an absolute reduction in the incidence of POAF by 14% (p=0.003).[118] The aforementioned study by Ruffin et al and two other studies evaluated the association between NSAIDs and the development of POAF. The studies found that using NSAIDs reduced the risk of POAF by 46% (OR 0.54; 95% CI 0.32–0.90),[118] 51% (OR 0.49; 95% CI 0.22-0.46),[20] and 41% (Adjusted OR 0.59; 95% CI 0.35–0.99),[15] Significantly more patients in the NSAID group by Ruffin, et al received postoperative β-blockers and about 45% of patients in those groups received prophylactic amiodarone therapy, which could have influenced their favorable results.

NSAIDs pharmacologic activity include their ability to inhibit cyclo-oxygenase 2 (COX-2) enzymes. The COX-2 inhibitor valdecoxib has been shown to significantly increase the risk of cardiovascular events of myocardial infarction, cardiac arrest, stroke and pulmonary embolism, by 3.7 fold versus placebo. This was thought to be mediated by COX-2 inhibition-mediated platelet aggregation resulting from the suppression of prostacyclin.[119] As a result of this study, NSAIDs have a black box warning stating a contraindication to their use for postoperative pain following CABG.

If an NSAID is used for the prevention of POAF, a more COX-2 selective NSAID should be avoided, and therapy should be discontinued or reconsidered in patients with a history of cardiovascular or cerebrovascular events, increased risk for bleeding or renal insufficiency.

While NSAIDs are commonly administered analgesics used for postoperative pain as adjuvants to opioid therapy in non-cardiac surgery patients, their widespread use would be limited by the FDA black box warning. They seem to offer a protective effect against the development of POAF in cardiac surgery patients receiving standard β-blocker therapy. More trials would be necessary to evaluate their safety, optimal agent, dose, and duration of NSAIDs for the prevention of POAF targeting the inflammatory process.

Corticosteroids

Corticosteroids have been traditionally utilized in cardiac surgeries to reduce inflammation to achieve early extubation, enhance pulmonary function recovery, or decrease postoperative nausea and vomiting. Inflammatory biomarkers increase in patients undergoing cardiothoracic surgery and inflammation appears to play a role in the development of POAF.

Studies evaluating corticosteroids meeting this review's predefined β-blocker criteria have used various types of intravenous steroids, doses, and regimens, with a maximum postoperative duration of three days (Table 7). Two studies used β-blockers and found that corticosteroids were superior to placebo with absolute reductions in the incidence of POAF by 18% to 30%.[120, 121] However two trials failed to show a significant benefit[122, 123] in reducing incidence of POAF compared to placebo or usual care. Halonen et al further reported that after adjusting for potential unbalanced confounders, that hydrocortisone continued to be effective in reducing the risk of POAF by 46% (HR 0.54; 95% CI 0.35–0.83) with treatment of only 5.6 patients needed to prevent one occurrence of POAF.[121] The authors further performed a meta-analysis combining results from their trial with two other similar trials for a total of 621 patients.[120,123] They found that corticosteroid therapy significantly reduced the risk of POAF by 33% (OR 0.67; 95% CI 0.54–0.84).[121] Two other meta-analyses confirmed this finding where corticosteroids significantly reduced the risk of POAF by 29% (OR 0.71; 95% CI 0.59-0.87) and 45% (OR 0.55; 95% CI 0.39–0.78) and show a significant decrease in LOS with steroids of 0.6 days and 1.6 days.[124, 125]

It is currently unknown which corticosteroid and particular dose provide optimal protection against POAF. Baker et al converted the steroid dosing to dexamethasone equivalence based on total cumulative dose and relative potencies and found that reduction in POAF appeared greatest in patients receiving intermediate doses of corticosteroids (50–120 mg dexamethasone equivalent), while lower (≤ 8 mg dexamethasone equivalent) and higher (236–2850 mg dexamethasone equivalent) dosing resulted in blunted effects.[125]

While corticosteroids can attenuate biomarkers shown to regulate the inflammatory response leading to the development of POAF, they are also associated with side effects that may inhibit their widespread use. Cardiac surgery patients who received corticosteroids had higher peak white blood cell counts up to 14 days postoperatively, higher blood glucose levels and larger insulin requirements,[126] and greater risk of wound and infectious complications.[124] Therefore, it may be necessary to avoid corticosteroids in patients with uncontrolled hyperglycemia, infection, or edema.

While some studies found a reduction in the incidence of POAF using corticosteroids as prophylaxis in cardiac surgery patients receiving standard β-blocker therapy, there is no consensus on which steroid, dose, and duration has the greatest benefit. None of the guidelines currently recommend the use of steroids due to the low quality of evidence.[1] Corticosteroids may play a future role in targeting the inflammatory process in patients undergoing cardiothoracic surgery, however larger clinical trials are necessary to confirm if corticosteroids are effective in reducing the occurrence of POAF in addition to β-blockers.

Thiazolidinediones

Thiazolidinediones (TZDs) may affect POAF through pleiotropic anti-inflammatory activity against macrophage activation and pro-inflammatory cytokines.[127, 128] One study meeting this review's predefined β-blocker criteria evaluated a nested cohort study of diabetic patients from the AFIST I, II, and III trials[19, 60, 129] assessed whether the use of TZDs affected the incidence of POAF in diabetic patients who were also receiving β-blockers and amiodarone (Table 7).[130] In addition to substantial pre- and postoperative β-blocker use, 43.8% of control patients and 35% of TZD patients received amiodarone. Despite this, the study was unable to show a significant reduction in POAF. This may have been due to a lack of power due to small sample size, dilution of effect from concomitant β-blocker and/or amiodarone use, or

increased fluid retention associated with TZD use. In this same analysis, statins did demonstrate a significant reduction in POAF (28% versus 37%, p<0.05).[15] This suggests that the most likely reason TZDs were of no benefit is due to their risk of fluid accumulation, thereby attenuating any anti-inflammatory effect. At this time, TZDs can not be recommended as an option for POAF prophylaxis, either alone or in combination with β-blockers.

Omega-3 Fatty Acids

The ability of omega-3 fatty acids to reduce the occurrence of POAF is thought to result from a stabilizing effect on the myocardium, anti-inflammatory properties, and possibly antioxidant activity.[131, 132] Only one study met this review's predefined β-blocker criteria, and they assessed the impact of N-3 polyunsaturated fatty acids (PUFA) on the incidence of POAF (Table 7).[133] They demonstrated an absolute reduction in incidence of POAF by 18% (p=0.013) and a shorter LOS by 0.9 day (p=0.017) compared to control patients. Perioperative β-blocker use in this study did not influence the prevalence of POAF. Of all patients taking PUFAs, 46 (57%) were on concomitant β-blocker therapy. In this group seven (15%) developed POAF and five (15.1%) of those not taking β-blockers developed POAF. In patients not randomized to PUFA, 35% (16/46) of patients on β-blockers experienced POAF while 31% (11/35) of patients not taking β-blockers had POAF. Further studies are warranted to determine if omega-3 fatty acids are viable add-on therapy or an alternative for patients unable to take β-blockers for the prevention of POAF.

Ascorbic Acid

The ability of ascorbic acid (vitamin C) to prevent POAF is thought to occur due its antioxidant properties and potential to attenuate inflammation and electrical remodeling.[134] Vitamin C has been studied in two prospective trials meeting this review's predefined β-blocker criteria: one non-randomized, non-blinded study with matched controls[135] and another a randomized, non-blinded, non-placebo controlled study (Table 7).[136] Both studies found ascorbic acid superior to control with absolute reductions in the incidence of POAF by 19% to 22%.[135, 136] There were no significant reductions in mean LOS. Both studies had substantial rates of both pre- and post-operative β-blocker utilization, suggesting that this may be a viable option for add-on therapy in high-risk patients. Due to the low cost and relative safety of this drug, larger placebo-controlled trials appear to be warranted.

N-Acetylcysteine

N-acetylcysteine (NAC) has been theorized to prevent POAF based on its antioxidant activity as a free radical scavenger and ability to reduce cellular damage in the atrium.[137] Two recent studies meeting this review's predefined β-blocker criteria, which were randomized and placebo-controlled, found conflicting results with NAC for the prevention of POAF (Table 7).[138, 139] The first study failed to demonstrate a significant reduction in the incidence of POAF (7% with NAC versus 12% with placebo, p=0.7). A more recent study, which included valve surgeries, found NAC superior to placebo with an absolute reduction in the incidence of POAF by 16%.[139] After controlling for perioperative β-blocker use, NAC was still associated with a significant reduction in POAF (OR 0.17, 95% CI 0.04–0.69, p=0.01). Neither study found a significant reduction in LOS. Both studies reported substantial preoperative β-blocker use while Ozaydin et al also reported substantial postoperative β-blocker utilization. A larger clinical trial is necessary to determine if NAC is effective in reducing the occurrence of POAF in addition to β-blockers.

Sodium Nitroprusside

It has been suggested that sodium nitroprusside (SNP) can reduce the incidence of POAF by replenishing nitric oxide function that may be disrupted due to ischemia-reperfusion injury with CABG surgery and administration of nitric oxide (NO) donors, such as SNP, could recover this function.[140] SNP may also reduce POAF by reducing left atrial stretching due to preload and afterload reduction. Only one pilot study meeting this review's predefined β-blocker criteria has evaluated sodium nitroprusside (SNP) as an agent for POAF prophylaxis compared to placebo.[140] This study found SNP superior to placebo with an absolute reduction in the incidence of POAF by 24% and shorter LOS by 1.8 days (Table 7). This study also showed a significant reduction in serum CRP levels in patients given SNP when compared to placebo (p<0.05), suggesting some possible effects on inflammation. Though not significant, more patients randomized to SNP received preoperative β-blockers when compared to the placebo group (68% versus 58% p=0.303). Postoperative β-blocker use was not addressed. Currently, SNP is routinely used in institutions for the management of

postoperative hypertension. Patients receiving this medication may also experience an additional benefit of arrhythmia prevention.

Triiodothyronine

The rationale behind the use of triiodothyronine (T3) for POAF prophylaxis lies in the observation that CPB results in a euthyroid, sick, or low T3 state.[141] The mechanism by which T3 may prevent POAF is unknown.[142] One study meeting this review's predefined β-blocker criteria demonstrated that intravenous administration of T3 starting at the time of cross clamp removal was superior to placebo with an absolute reduction in the incidence of POAF by 22%.[141] (Table 7) All patients had a left ventricular ejection fraction of less than 40%. While T3 administration was associated with significantly higher postoperative cardiac indices and lower systemic vascular resistance, there was no significant difference in LOS.[143] The authors previously reported data from this same study but included those patients with a history of preoperative atrial fibrillation.[143] In this earlier study, there were no significant differences in the incidence of SVT between the two treatment groups. The authors do not report postoperative β-blocker use but suggest that because the study population was more ill (ejection fraction <40%), β-blockade may not be as effective and add-on therapy would be warranted. None of the guidelines currently recommend the use of T3 due to low quality of evidence.[1] T3 should not be routinely utilized until more data becomes available supporting its use for the prevention of POAF prophylaxis.

Conclusion

Sufficient evidence exists to recommend the use of amiodarone, sotalol, and possibly magnesium in the prevention of POAF as monotherapy in patients unable to take β-blockers or as add-on therapy in patients at high risk of developing POAF. This review did not identify sufficient evidence to support the use of propafenone, procainamide, digoxin, thiazolidinediones, triiodothyronine, or calcium channel blockers. Other drugs that may be beneficial for prophylaxis, especially as add-on therapy to β-blockers include dofetilide, renin-angiotensin-aldosterone-system modulators, statins, NSAIDs, corticosteroids, omega-3 fatty acids, ascorbic acid, *N*-acetylcysteine, and sodium nitroprusside. For most of these agents, there is a need for additional large-scale, adequately powered clinical studies to determine their benefit before they can be considered for routine use.

Newer studies evaluating the usefulness of pharmacologic therapies targeting inflammatory pathways and atrial remodeling will be needed to provide additional evidence for agents that reduce the incidence of POAF, especially in those patients that may be unable to tolerate β-blockade. More studies evaluating therapy in combination with β-blockers using established pharmacologic and non-pharmacologic strategies may also be helpful to enhance the body of knowledge for treatment modalities to prevent POAF. Using evidence based pharmacologic and non-pharmacologic therapies in addition to novel agents and identifying high risk patients may further reduce the incidence of POAF and lead to improvements in the overall morbidity outcomes and burden to the health care system.

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Table 1. Guideline Recommendations for Pharmacotherapy for the Prevention of POAF in Cardiac Surgery

Medication or Class	ACCP 2005 POAF Guidelines[1]			ACC/AHA/ESC 2006 AF Guidelines[9]; ACC/AHA 2004 CABG Guidelines[10]		EACTS 2006 POAF Guidelines[2]	
	Strength	Quality of Evidence	Net Benefit	Class	Level of Evidence	Grade	Level of Studies
β-blockers	A	Fair	Substantial	I[9] I[10]	A[9] B[10]	A	1a
Sotalol	B	Good	Intermediate	IIb	B[9,10]	A	1b
				-consider if β-blockers contraindicated[10]		- may be more effective than β-blockers	
Amiodarone	B	Good	Intermediate	IIa	B[10]	A	1a/1b
				-consider in patients at high risk for POAF if β-blockers contraindicated		-if β-blockers contraindicated	
				IIa	A[9]	A	1b
				-consider in patients at high risk for POAF		-give in addition to β-blockers in high risk patients	
Verapamil	D	Low	None	-	-	-	-
Diltiazem	D	Low	None	-	-	-	-
Magnesium	D	Low	None	-	-	A	1a/1b
Digoxin	I	Low	None	-	-	-	-
Dexamethasone	I	Low	Conflicting	-	-	-	-
Triiodothyronine	D	Low	None	-	-	-	-
Procainamide	D	Low	None	-	-	-	-

Table 2. Multicenter Study of Perioperative Ischemia Atrial Fibrillation Risk Index[20]

Predictor of POAF after CABG	Risk Score Point Assignment
Age (Y)	
< 30	6
30–39	12
40–49	18
50–59	24
60–69	30
70–79	36
≥ 80	42
History of Atrial fibrillation	7
History of COPD	4
Concurrent valve surgery	6
Withdrawal of postoperative treatment	
β-blocker	6
ACEI	5
β-blocker treatment	
Preoperative and postoperative	–7
Postoperative	–11
Preoperative and postoperative ACEI treatment	–5
Postoperative treatment	
Potassium supplementation	–5
NSAIDs	–7
	= Total Points[a]

[a]Risk Groups based on summative total point assignment using predictors from table: Low risk = Score < 14, Medium risk = Score 14–31, High risk = Score >31

Table 3. Sotalol Clinical Trials

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, OL, C N=130[41]	Metoprolol 0.1 mg/kg IV postop then 150 mg PO QD (n=39) vs. Sotalol 0.3 mg/kg IV postop then 240 mg PO QD (n=41) vs. Control (n=50)	Metoprolol CABG 100% (39/39) vs. Sotalol CABG 100% (41/41) vs. Control CABG 100% (50/50)	[a]Metoprolol 15.3% (6/39) vs. Sotalol 2.4% (1/41) vs. Control 36% (18/50) P values: p<0.05 Metoprolol vs. Control, p<0.001 Sotalol vs. Control, p<0.05 Sotalol vs. Metoprolol	NR	NR
P, R, SB N=429[50]	Low dose Sotalol 40 mg PO q8h (n=74) vs. low dose Propranolol 10mg PO q6h (n=66) vs. high dose Sotalol 80 mg PO q8h (n=133) vs. high dose Propranolol 20 mg PO q6h (n=156), all started 4–6 h postop until POD 6	Low dose Sotalol CABG 100% (74/74) vs. low dose Propranolol CABG 100% (66/66) vs. high dose Sotalol CABG 100% (133/133) vs. high dose Propranolol CABG 100% (156/156)	[a]Low dose Sotalol 13.9% (10/72) vs. low dose Propranolol 18.8% (12/64) (18.8%) vs. high dose Sotalol 10.9% (13/119) vs. high dose Propranolol 13.7% (19/139) (13.7%), p=NS	NR	Preop β-blocker: Low dose Sotalol 60% (44/74) vs. low dose Propranolol 82% (54/66) vs. high dose Sotalol 77% (103/133) vs. high dose Propranolol 80% (125/156), p<0.05 in low dose Sotalol compared to other three groups, all other comparisons NS
P, R, DB, PC N=300[42]	Sotalol 40 mg PO q6h started 4–6h post surgery until POD 6 (n=150) vs. Placebo (n=150)	[b]CABG, valve, CABG + valve, or miscellaneous procedures	[a]Sotalol 16% (24/150) vs. Placebo 33% (49/150), p<0.005	LOS: NR Mortality: Sotalol 0 vs. Placebo 0	Preop β-blocker: Sotalol 79% (118/150) vs. Placebo 72% (108/150), p=NS
P, R, C N=101[51]	Sotalol 160 mg PO AM of surgery then 160 mg PO BID starting POD 1 (n=50) vs. Control (any β-blocker half dose postop or no β-blockers) (n=51)	Sotalol CABG 100% (50/50) vs. Control CABG 100% (51/51)	Sotalol 10% (5/50) vs. Control 29% (15/51), p=0.028	LOS: NR Mortality: Sotalol 0 vs. Control 0	Preop β-blocker: Sotalol 84% (42/50) vs. Control 78% (40/51), p=NS
P, R, C N=42[45]	Sotalol 1 mg/kg IV over 2 h postop then maintenance infusion 0.15 mg/kg IV for 24 h, 3h later, 80 mg PO q8–12 h x 3 months (n=25) vs. Control (n=17)	Sotalol CABG 100% (25/25) vs. Control CABG 100% (17/17)	[a]Sotalol 16% (3/19) vs. Control 29% (5/17), p=NS	LOS: Sotalol 10 ± 1.5 vs. Control 10.2 ± 1.7, p=NS Mortality: NR	Preop β-blocker: Sotalol 64% (16/25) vs. Control 53% (9/17), p=NS
P, DB, PC N=214[43]	Sotalol 80 mg PO BID x 3 months starting day of surgery (n=107) vs. Placebo (n=107)	Sotalol CABG 100% (107/107) vs. Placebo CABG 100% (107/107)	Sotalol 26% (28/107) vs. Control 44% (47/107), p=0.0065	NR	Preop β-blocker: Sotalol 83% (89/107) vs. Placebo 72% (77/107), p=NR
P, R, SB N=191[48]	Sotalol 40 mg PO TID (n=93) vs. Metoprolol 25 mg PO TID postop x 6 d (n=98)	Sotalol CABG 100% (93/93) vs. Metoprolol CABG 100% (98/98)	Sotalol 17% (16/93) vs. Metoprolol 31% (30/98), p<0.01	NR	Preop β-blocker: Sotalol 9% (8/93) vs. Metoprolol 9% (9/98), p=NS

Table 3. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, C N=206[44]	Sotalol 80 mg PO BID started POD 1 (n=103) vs. Control (n=103)	Sotalol CABG 100% (103/103) vs. Control CABG 100% (103/103)	[a]Sotalol 16% (16/103) vs. Control 48% (50/103), p<0.00001	LOS: Sotalol 10 vs. Placebo 10, p=NS Mortality: Sotalol 1% (1/103) vs. Control 1% (1/103), p=NS	Preop β-blocker: Sotalol 67% (69/103) vs. Control 68% (70/103), p=NR
P, R, DB, PC N=160[53]	Sotalol 80 mg PO BID (n=76) vs. Amiod 15 mg/kg IV over 24 h then 200 mg PO TID (n=83) started at surgery and continued 7d or DC	Sotalol CABG 86% (65/76) and valve 4% (3/76) and CABG + valve 10% (8/76) vs. Amiodarone CABG 82% (68/83) and valve 7% (6/83) and CABG + valve 11% (9/83)	Sotalol 25% (19/76) vs. Amiod 17% (14/83), p=0.21	LOS: Sotalol 6.0 ± 2.4 vs. Amiod 5.5 ± 1.8, p=0.112 Mortality: Sotalol 3% (2/76) vs. Amiod 0%, p=NR	Preop β-blocker: Sotalol 75% (57/76) (75%) vs. Amiod 76% (63/83), p=NR Postop β-blocker: Sotalol 81% (61/76) vs. Amiod 86% (71/83), p=NR
P, R, DB, PC N=253[18]	Metoprolol 50 mg PO BID + Amiod 400 mg PO TID x 2d, 800 mg x 2d then 400 mg x 5 d (n=63) vs. Metoprolol (n=62) vs. Sotalol 80 mg PO TID (n=63) vs. Placebo (n=65) started 24–48 h preop and continued up to 8d postop	[b]Metoprolol + Amiod CABG 73% (46/63) and valve 43% (27/63) vs. Metoprolol CABG 68% (42/62) and valve 36% (22/62) vs. Sotalol CABG 62% (39/63) and valve 51% (32/63) vs. Placebo CABG 54% (35/65) and valve 49% (32/65)	Metoprolol + Amiod 30.2% (19/63) vs. Metoprolol 40.3% (25/62) vs. Sotalol 31.7% (20/63) vs. Placebo 53.8% (35/65) P values: p=0.008 Amiod + Metoprolol vs. Placebo, p=0.013 Sotalol vs. Placebo, p=0.16 Metoprolol vs. Placebo	LOS: Metoprolol + Amiod 12 ± 9 vs. Metoprolol 12 ± 8 vs. Sotalol 11 ± 3 vs. Placebo 13 ± 9, p=NS Mortality: Metoprolol + Amiod 1.6% (1/63) vs. Metoprolol 1.6% (1/62) vs. Sotalol 0% vs. Placebo 0%, p=NS	Preadmission β-blocker: Metoprolol + Amiod 41.3% (26/63) vs. Metoprolol 38.7% (24/62) vs. Sotalol 39.7% (25/63) vs. Placebo 33.8% (22/65), p=NS [c]Preop β-blocker: Metoprolol + Amiod 100% (63/63) vs. Metoprolol 100% (62/62) [d]Postop β-blocker: Metoprolol + Amiod 100% (63/63) vs. Metoprolol 100% (62/62)
P, R, OL, C N=253[49]	Atenolol 50 mg PO QD (n=153) vs. Sotalol 80 mg PO BID started 24 h preop (n=100)	Atenolol CABG 87% (133/153) and valve 7% (11/153) and CABG + valve 5% (8/153) vs. Sotalol CABG 75% (75/100) and valve 9% (9/100) and CABG + valve 6% (6/100)	Atenolol 22% (34/153) vs. Sotalol 10% (10/100), p=0.013	LOS: NR Mortality: Atenolol 5.8% (9/153) vs. Sotalol 8% (8/100), p=NS	[e]Preop β-blocker: Atenolol 12.4% (19/153) vs. Sotalol 10% (10/100), p=NS

Table 3. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
R, C, Propensity Matched Analysis N=178[52]	Sotalol 40 mg PO BID starting POD 1 x 6 wks + Magnesium 2 g IV post surgery and on POD 1 (n=89) vs. Control (n=89)	Sotalol + Mag CABG 100% (89/89) vs. Control CABG 100% (89/89)	Sotalol + Mag 13.5% (12/89) vs. Control 27.0% (24/89), p=0.025	Median LOS: Sotalol + Mag 7 vs. Control 7, p=NR Mortality: Sotalol + Mag 1.1% (1/89) vs. Control 4.5% (4/89), p=0.17	Preop β-blocker: Sotalol + Mag 66.3% (6/89) vs. Control 64.0% (57/89), p=0.75

P=Prospective, R=Randomized, DB=Double-Blind, SB=Single-Blind, PC=Placebo-Controlled, C=Controlled, OL=Open Label
[a]Supraventricular tachycardia
[b]Number of patients that underwent CABG ± valve not specified
[c]Preop prophylactic treatment initiated 24–48 h before surgery
[d]Prophylactic treatment continued in all groups up to 8 d postop
[e]Preop atenolol

Table 4. Amiodarone Clinical Trials

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, DB, PC N=120[64]	Amiod 15 mg/kg IV x 24 h after removal of cross clamp, then 200 mg PO TID x 5d (n=60) vs. Placebo (n=60)	Amiod CABG 100% (60/60) vs. Placebo CABG 100% (60/60)	[a]Amiod 8.3% (5/60) vs. Placebo 20% (12/60), p=0.07	Median LOS: Amiod 7 (6-15) vs. Placebo 7 (6-38), p=NR Mortality: NR	Preop β-blocker: Amiod 78% (47/60) vs. Placebo 80% (48/60), p=NR
P, R, DB, PC N=124[54]	Amiod 200 mg PO TID x 7 d preop, then 200 mg/d until DC (n=64) vs. Placebo (n=60)	Amiod CABG 44% (28/64) and valve 34% (22/64) and CABG + valve 14% (9/64) and Other 8% (5/64) vs. Placebo CABG 40% (24/60) and valve 32% (19/60) and CABG + valve 22% (13/60) and Other 7% (4/60)	Amiod 23% (15/64) vs. Placebo 42% (25/60), p=0.03	LOS: Amiod 6.5 ± 2.6 vs. Placebo 7.9 ± 4.3, p=0.04 Mortality: Amiod 5% (3/64) vs. Placebo 3% (2/60), p=1.00	Preop β-blocker: Amiod 40.6% (26/64) vs. Placebo 30% (18/60), p=NR Postop β-blocker: Amiod 92% (24/26) vs. Placebo 94% (17/18), p=0.98
P, R, DB, PC N=143[65]	Amiod 2 g PO in divided doses 1–4 d preop then 400 mg PO x 7 d postop (n=73) vs. Placebo (n=70)	Amiod CABG 100% (73/73) vs. Placebo CABG 100% (70/70)	POAF: Amiod 24.7% (18/73) vs. 32.8% (23/70), p=0.30	LOS: Amiod 6.4 vs. Placebo 7, p=0.72 Mortality: Amiod 5.5% (4/73) vs. Placebo 1.4% (1/70), p=NS	Preop β-blocker: Amiod 58.9% (43/73) vs. Placebo 58.6% (41/70), p=NS Postop β-blocker: Amiod 41.1% (30/73) vs. Placebo 32.9% (23/70), p=NS

Table 4. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, DB, PC N=300[55]	Amiod 1 g/24 h IV infusion x 2 d started within 3 h of entering ICU (n=158) vs. Placebo (n=142)	Amiod CABG 86% (136/158) and valve 5% (8/158) and CABG + valve 9% (14/158) vs. Placebo CABG 83% (118/142) and valve 4% (6/142) and CABG + valve 12% (17/142) and Other 1% (1/142)	Amiod 35% (56/158) vs. Placebo 47% (67/142), p=0.01	LOS: Amiod 7.6 ± 5.9 vs. Placebo 8.2 ± 6.2, p=0.34 Mortality: Amiod 0% vs. Placebo 1.4% (2/142), p=0.13	Preop β-blocker: Amiod 52.5% (83/158) vs. Placebo 50.7% (72/142), p=NS Postop β-blocker DC'd at DC: Amiod 11.4% (17/158) vs. Placebo 18.1% (25/142), p=0.18
P, R, DB, PC N=147[66]	Amiod 900 mg/d IV infusion postop x 3 d (n=49) vs. Magnesium 4 g/24 h IV x 3 d (n=47) vs. Placebo (n=51)	Amiod CABG 100% (49/49) vs. Mag CABG 100% (47/47) vs. Placebo CABG 100% (51/510)	Amiod 14% (7/49) vs. Mag 23% (11/47) vs. Placebo 27% (14/51) P values: p=0.14 Amiod vs. Placebo, p=0.82 Mag vs. Placebo, p=NR Amiod vs. Mag	LOS: NR Mortality: Amiod 2% (1/49) vs. vs. Mag 0% vs. Placebo 2% (1/51), p=NR	Preop β-blocker: Amiod 55.1% (27/49) vs. Mag 51.1% (24/47) vs. Placebo 64.7% (33/51), p=NR
P, R, DB N=102[72]	Amiod 1 g/d IV x 48 h, then 400 mg PO QD until DC (n=50) vs. Propranolol 1 mg IV q6 h x 48 h, then 20 mg PO QID until DC (n=52)	Amiod CABG 90% (45/50) and valve 8% (4/50) and CABG + valve 2% (1/50) vs. Propranolol CABG 94% (49/52) and valve 2% (1/52) and CABG + valve 4% (2/52)	Amiod 16% (8/50) vs. Propranolol 32.7% (17/52), p=0.05	LOS: Amiod 8.8 ± 3.5 vs. Propranolol 8.4 ± 2.7, p=NS Mortality: NR	Preop β-blocker: Amiod 42% (21/50) vs. Propranolol 58% (30/52), p=NS Postop β-blocker: Amiod 42% (21/50) vs. Propranolol 100% (52/52), p=NR

Table 4. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, DB, PC N=220[19]	Amiod (n=120) vs. Placebo (n=100) administered as a "slow load" or "fast load": "**Slow-Load" group (n=120) ≥ 5d before surgery**: Amiod 7 g PO over 10 d beginning preop Day 5 (n=64) vs. Placebo (n=56) "**Fast-Load" group (n=100) < 5d but > 1d before surgery**: Amiod 6 g PO over 6 d beginning preop Day 1 (n=56) vs. Placebo (n=44)	Amiod CABG 79% (95/120) and valve 7% (8/120) and CABG + valve 14% (17/120) vs. Placebo CABG 77% (77/100) and valve 11% (11/100) and CABG + valve 12% (12/100)	Amiod 23% (28/120) vs. Placebo 38% (38/100), p=0.01	LOS: Amiod 9.16 ± 8.2 vs. Placebo 9.35 ± 7.8, p=0.86 Mortality: Amiod 3% (4/120) vs. Placebo 4% (4/100), p=0.79	Preadmission β-blocker: Amiod 71% (85/12) vs. Placebo 74% (74/100) Preop β-blocker: Amiod 88% (106/120) vs. Placebo 91% (91/100), p=0.41 Postop β-blocker: Amiod 64% (77/120) vs. Placebo 63% (63/100), p=NR

Table 4. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, DB, PC N=220[57]	Amiod (n=120) vs. Placebo (n=100): "**Slow-Load" group (n=100) ≥ 5d before surgery**: Amiod 200 mg PO TID x 5 d preop, 400 mg PO BID day of surgery, 400 mg PO BID on POD 1–4 (n=56) (total Amiod 7 g) vs. Placebo (n=44) "**Fast-Load" group (n=120) <5d but >1d before surgery**: Amiod 400 mg PO QID x1 d preop, 600 mg PO BID day of surgery, 400 mg PO BID on POD 1–4 (n=64) (total Amiod 6 g) vs. Placebo (n=56)	[b]Slow-Load Amiod valve 23% (13/56) vs. Fast-Load Amiod valve 13% (8/64) vs. Placebo valve 19% (19/100)	Slow-Load Amiod 19.5% (11/56) vs. Fast- Load Amiod 25% (16/64) vs. Placebo 38% (38/100) P values: p=0.013 Slow-Load Amiod vs. Placebo, p=0.059 Fast-Load Amiod vs. Placebo	LOS: Slow-Load Amiod 9.3 ± 10.8 vs. Fast-Load Amiod 9 ± 5.1 vs. Placebo 9.4 ± 7.8 LOS P values: p=0.93 Slow-Load Amiod vs. Placebo, p=0.78 Fast-Load Amiod vs. Placebo Mortality: Slow-Load Amiod 5.4% (3/56) vs. Fast-Load Amiod 1.6% (1/64) vs. Placebo 4% (4/100) Mortality P values: p=0.149 Slow-Load Amiod vs. Placebo, p=0.351 Fast-Load vs. Placebo	Preop and Postop β-blocker: Slow-Load 85.7% (48/56) vs. Fast-Load 89.1% (57/64) vs. Placebo 91% (91/100) P values: p=0.225 Slow-Load vs. Placebo p=0.439 Fast-Load vs. Placebo
P, R, DB, PC N=200[58]	Amiod 15 mg/kg PO 4 h after arrival in ICU, then 7 mg/kg/d PO until discharge (n=100) vs. Placebo (n=100)	Amiod CABG 100% (100/100) vs. Placebo CABG 100% (100/100)	Amiod 12% (12/100) vs. Placebo 25% (25/100), p=0.016	LOS: Amiod 6.8 ± 1.3 vs. Placebo 7.1 ± 2, p=0.38 Mortality: NR	Preop β-blocker: Amiod 67% (67/100) vs. Placebo 66% (66/100), p=NR Postop β-blocker: Amiod 0 vs. Placebo 0

Table 4. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, C N=241[59]	Amiod 300 mg IV over 1 h, then 900 mg over 24 h postop, then 450 mg IV POD 1, then 200 mg PO TID until DC (n=72) vs. Metoprolol + Digoxin: Metoprolol 100 mg/d PO preop, Digoxin 0.5 mg x 2 on day of surgery, then digoxin 0.25 mg PO + Metoprolol 100 mg PO POD1 until DC (n=77) vs. Control (n=92)	Amiod CABG 100% (72/72) vs. Metop + Digoxin CABG 100% (77/77) vs. Control CABG 100% (92/92)	Amiod 8.3% (6/72) vs. Metop + Digoxin 16.8% (13/77) vs. Control 33.6% (31/92) P values: p<0.001 Amiod vs. Control, p<0.01 Metop + Digoxin vs. Control	NR	Postop β-blocker: Metop + Dig 100% (77/77), other groups NR

Table 4. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, PC, 2x2 factorial design N=160[60]	Amiod 1,050 mg/d IV infusion within 6h postop, then 400 mg PO TID on POD 1–4 (n=77) vs. Placebo (n=83) Then randomized to [c]Pacing (n=73) or No Pacing (n=87) using 2x2 factorial design	[b]Amiod valve 20% (15/77) vs. Placebo valve 23% (19/83), Pacing valve 21% (15/73) vs. No pacing valve 22% (19/87)	Amiod 22.1% (17/77) vs. Placebo 38.6% (32/83), Pacing 27.4% (20/73) vs. No pacing 33% (29/87) P values: p=0.037 Amiod vs. Placebo, p=0.523 Pacing vs. No Pacing Amiod + Pacing 15.8% (6/38) vs. Placebo + Pacing 40% (14/35) vs. Placebo + No Pacing 37.5% (18/48) P values: p=0.04 Amiod + Pacing vs. Placebo + Pacing, p=0.047 Amiod + Pacing vs. Placebo + No Pacing	LOS: Amiod 7.88 ± 6.16 vs. Placebo 11.36 ± 16.83, Pacing 10.01 ± 16.86 vs. No pacing 9.41 ± 8.43 LOS P values: p=0.08 Amiod vs. Placebo, p=0.77 Pacing vs. No Pacing Mortality: Amiod 1.3% (1/77) vs. Placebo 2.4% (2/83), Pacing 0% vs. No pacing 3.4% (3/87) P values: p=0.948 Amiod vs. Placebo, p=0.309 Pacing vs. No Pacing	Preop β-blocker: Amiod 70.1% (54/77) vs. Placebo 74.7% (62/83), Pacing 72.6% (53/73) vs. No pacing 72.4% (63/87) Preop β-blocker P values: p=0.639 Amiod vs. Placebo, p=0.880 Pacing vs. No Pacing Postop β-blocker: Amiod 80.5% (62/77) vs. Placebo 83.1% (69/83), Pacing 86.3% (63/73) vs. No pacing 78.2% (68/87) Postop β-blocker P values: p=0.823 Amiod vs. Placebo, p=0.260 Pacing vs. No Pacing

Table 4. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, pilot study of 36 patients to one of 2 arms (Pacing or Amiodarone) compared to a Historical control group N=69[68]	Amiod 900 mg/d IV cont infusion x 48 h (n=18) vs. Right Atrial Pacing (RAP) x 48 h (n=18) vs. Historical Control group that received β-blockers (n=33)	Amiod CABG 100% (18/18) vs. RAP CABG 100% (18/18) vs. Control CABG 100% (33/33)	Amiod 27.8% (5/18) vs. RAP 5.6% (1/18) vs. Control 18.2% (6/33), p>0.05	Median LOS: Amiod 6 vs. RAP 6 vs. RAP 5, p=NS for all groups Mortality: NR	Preop β-blocker: Amiod 72.2% (13/18) vs. RAP 72.2% (13/18) vs. Control (63.6% (21/33), p>0.05 Postop β-blocker: Amiod 100% (18/18) vs. RAP 100% (18/18) vs. Control 100% (33/33)
P, R, DB, PC N=160[53]	Amiod 15 mg/kg IV over 24 h at surgery, then Amiod 200 mg PO (n=83) vs. Sotalol 80 mg PO 2 h before surgery, then 80 mg PO BID both continued for 7 d or until DC (n=76)	Amiodarone CABG 82% (68/83) and valve 7% (6/83) and CABG + valve 11% (9/83) vs. Sotalol CABG 86% (65/76) and valve 4% (3/76) and CABG + valve 10% (8/76) vs.	Amiod 17% (14/83) vs. Sotalol 25% (19/76), p=0.21	LOS: Amiod 5.5 ± 1.8 vs. placebo 6 ± 2.4, p=0.112 Mortality: Amiod 0% vs. Sotalol 3% (2/76), p=0.23	Preop β-blocker: Amiod 76% (63/83) vs. Sotalol 75% (57/76), p=NR Postop β-blocker: Amiod 86% (71/83) vs. Sotalol 81% (61/76), p=0.476

Table 4. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, DB, PC N=253[18]	Amiod 1,200 mg PO x 2 d (divided into 3 single doses), then 800 mg for another 2 d, then 400 mg/d for another 5 d + Metoprolol 50 mg PO BID (n=63) vs. Metoprolol (n=62) vs. Sotalol 80 mg PO TID (n=63) vs. Placebo (n=65) starting 24–48 h before surgery & continued for up to 8 d postop	[d]Metoprolol + Amiod CABG 73% (46/63) and valve 43% (27/63) vs. Metoprolol CABG 68% (42/62) and valve 36% (22/62) vs. Sotalol CABG 62% (39/63) and valve 51% (32/63) vs. Placebo CABG 54% (35/65) and valve 49% (32/65)	Amiod + Metoprolol 30.2% (19/63) vs. Metoprolol 40.3% (25/62) vs. Sotalol 31.7% (20/63) vs. Placebo 53.8% (35/65) P values: P=0.008 Amiod + Metoprolol vs. Placebo, p=0.16 Metoprolol vs. Placebo, p=0.013 Sotalol vs. Placebo	LOS: Amiod + Metoprolol 12 ± 9 vs. Metoprolol 12 ± 8 vs. Sotalol 11 ± 3 vs. Placebo 13 ± 9, p=NS Mortality: Amio + Metoprolol 1.6% (1/63) vs. Metoprolol 1.6% (1/62) vs. Sotalol 0% vs. Placebo 0%, p=NS	Preadmission β-blocker: Metoprolol + Amiod 41.3% (26/63) vs. Metoprolol 38.7% (24/62) vs. Sotalol 39.7% (25/63) vs. Placebo 33.8% (22/65), p=NS [e]Preop β-blocker: Metoprolol + Amiod 100% (63/63) vs. Metoprolol 100% (62/62) [f]Postop β-blocker: Metoprolol + Amiod 100% (63/63) vs. Metoprolol 100% (62/62)
P, R, C, 2x2 factorial design N=163[75]	Amiod 1,800 mg PO 1d preop, then Amiod 900 mg/d IV postop x 3 d (n=36) vs. Thoracic epidural (TEA) (n=44) vs. TEA + Amiod (n=35) vs. Control (n=48)	Amiod CABG 100% (36/36) vs. TEA 100% (44/44) vs. TEA + Amiod 100% (35/35) vs. Control 100% (48/48)	Amiod 28% (10/36) vs. TEA 50% (22/44) vs. TEA + Amiod 29% (10/35) vs. Control 42% (20/48), p=NR	Median LOS (range): Amiod 7 (5-18), TEA 8 (6-36), TEA + Amiod 8 (5-88), Control 8 (5-21), p=NR Mortality: Amiod groups (Amiod & TEA + Amiod) 2.8% (2/71) vs. Non-Amiod gps 0%, p=NR	Preop β-blocker: Amiod 72% (26/36) vs. TEA 61% (26/44) vs. TEA + Amiod 57% (20/35) vs. Control 56% (27/48), p=NS Postop β-blocker: Amiod 72% (26/36) vs. TEA 61% (26/44) vs. TEA + Amiod 57% (20/35) vs. Control 56% (27/48), p=NS
Randomly selected Amiod group with Case- control N=143[73]	Amiod 0.73 mg/min IV on call to OR x 48h, then Amiod 400 mg PO q12h x 3d (n=53) vs. Control group (case control matched) (n=92)	Amiod CABG 100% (51/51) vs. Control CABG 100% (92/92)	Amiod 5.88% (3/51) vs. Control 26.08% (24/92), p=NR	LOS: Amiod 5.3 ± 2.76 vs. Control 6.7 ± 8.40, p=NS Mortality: NR	Preop β-blocker: Amiod 80% (41/51) vs. Control 97% (90/92), p=NR Postop β-blocker: Amiod 100% (51/51) vs. Control 100% (92/92)

Table 4. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, DB, PC N=601[61]	Amiod 10 mg/kg (divided 2 doses/d) PO starting 6 d preop through POD 6 (n=299) vs. Placebo (n=302)	Amiod CABG 65% (194/299) and valve 27% (81/299) and CABG + valve 8% (24/299) vs. Placebo CABG 65% (195/302) and valve 24% (72/302) and CABG + valve 12% (35/302)	[a]Amiod 16.1% (48/299) vs. Placebo 29.5% (89/302), p<0.001	LOS: Amiod 8.2 ± 7.4 vs. Placebo 8.9 ± 8.1, p=0.11 Mortality: Amiod 2.3% (7/299) vs. Placebo 3.3% (10/302), p=0.62	Preop β-blocker: Amiod 58.9% (176/299) vs. Placebo 55.6% (168/302), p=0.46 Postop β-blocker: Amiod 49.5% (148/299) vs. Placebo 49.7% (150/302), p=0.94
P, R- arms for amiod or diltiazem compared to a retrospective control group N=180[67]	Diltiazem IV 0.1 mg/kg/h until 24 h after aortic cross clamp time, then oral β-blocker until DC (n=60) vs. Amiod 300 mg IV postop then 1 g IV QD x 48 h, then 400 mg IV QD x 48 h, then oral β-blocker until DC (n=60) vs. Retrospective group of Control patients who received standard β-blocker prophylaxis POD 1–3 until DC (n=60)	Amiod CABG 100% (60/60) vs. Diltiazem 100% (60/60) vs. Control 100% (60/60)	Amiod 11.7% (7/60) vs. Diltiazem 10% (6/60) vs. Control 23.3% (14/60) P values: p=0.093 Amiod vs. Control, p=0.05 Diltiazem vs. Control, p=0.769 Amiod vs. Diltiazem	LOS: NR Mortality: Diltiazem 0% vs. Amiod 0% vs. Control 1.7% (1/60), p=NR for all groups	Preop β-blocker: NR Postop β-blocker: Amiod 100% (60/60) vs. Diltiazem 100% (60/60) Control 100% (60/60)

Table 4. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
Retro, Cohort study N=2,046[76] Patients receiving any prophylactic regimen used in AFIST I & II were matched 1:10	Amiod (n=186) vs. Control (n=1,860)	[b]Amiod valve 20% (37/186) vs. Control valve 22% (1389/1860)	Amiod 23.1% (43/186) vs. Control 29.9% (556/1,860), p=0.05	LOS: Amiod 8.6 ± 6 vs. Control 11.6 ± 14, p=0.003 Mortality: NR	Postop β-blocker: Amiod 68.3% (127/186) vs. Control 71.5% (1330/1860), p=0.36
P, R, DB, PC N=136[74]	Amiod + Mag: Amiod 5 mg/kg IV in 30 min x1 + Magnesium sulfate 1.5 g IV in 10 min (n=44) vs. Amiod 5 mg/kg IV in 30 min x1 (n=44) vs. Placebo (n=48), all early postop	Amiod + Mag CABG 100% (44/44) vs. Amiod CABG 100% (44/44) vs. Placebo CABG 100% (48/48)	Amiod + Mag 9% (4/44) vs. Amiod 36% (16/44) vs. Placebo 33% (16/48) P values: p=0.023 Amiod + Mag vs Placebo, p=0.01 Amiod + Mag vs. Amiod p=NS Amiod vs. Placebo	NR	Preop and Postop β-blocker: Amiod + Mag 100% (44/44), Amiod 100% (44/44), Placebo 100% (48/48), p=1.000
Retro, Observational study using institutional specific data from the Society of Thoracic Surgeons (STS) database N=509[23]	Amiod ≥1 d of IV and/or PO POD 0–4, prior to the onset of POAF (n=302) vs. Control (n=207)	Amiod CABG 81% (245/302) and valve 28% (85/302) vs. Control CABG 78% (161/207) and valve 31% (64/207)	Amiod 22% (67/302) vs. Control 31% (64/207), p=0.027	LOS: Amiod 9 ± 6.5 vs. Control 9.1 ± 8, p=0.707 Mortality: NR	Preop β-blocker: Amiod 68% (205/302) vs. No Control 66% (136/207), p=0.607 Postop β-blocker: Amiod 66% (200/302) vs. Control 67% (138/207), p=0.917

Table 4. continued

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, DB, PC N=110[62]	Amiod 600 mg PO 1 d before and POD 2–7 + Amiod IV periop with a 300 mg IV bolus for 1h + 20 mg/kg/d IV on POD1 (n=55) vs. Placebo (n=55)	Amoid CABG 100% (55/55) vs. Placebo CABG 100% (55/55)	Amiod 34% (19/55) vs. Placebo 85% (47/55), p<0.0001	LOS: Amiod 11.3 ± 3.4 vs. Placebo 13 ± 4.2d, p=0.03 Mortality: NR	Preop β-blocker: Amiod 75% (41/55) vs. Placebo 73% (40/55), p=0.83
P, R, DB, PC N=250 pts[63]	Amiod 300 mg IV over 20 min POD1, then Amiod 600 mg PO BID POD 2–5 (n=125) vs. Placebo (n=125)	Amiod CABG 100% (113/113) vs. Placebo CABG 100% (110/110)	Amiod 12% (14/113) vs. Placebo 29% (32/110), p<0.05	LOS: NR Mortality: Amiod 0.9% (1/113) vs. Placebo 0.9% (1/110), p=NR	Preop β-blocker: Amiod 87% (109/125) vs. Placebo 86% (108/125), p=NR

P=Prospective, R=Randomized, DB=Double-Blind, SB=Single-Blind, PC=Placebo-Controlled, C=Controlled, OL=Open Label
[a]Atrial Fibrillation and Atrial Flutter
[b]Authors only state percent of patients receiving valvular surgery, no percentages given for CABG alone, valve alone or CABG + valve
[c]Atrial septal pacing at Bachmann's Bundle
[d]Number of patients that underwent CABG + valve not specified
[e]Preop prophylactic treatment initiated 24-48h before surgery
[f]Prophylactic treatment continued in all groups up to 8d postop

Table 5. Dofetilide Clinical Trials

Trial Design; Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, DB, PC N=133[78]	Dofetilide per package insert started on day of surgery x 7 d PO/NG until DC (n=67) vs. Placebo (n=66)	Dofetilide CABG 95.5% (64/67) and CABG + valve 4.5% (3/67) vs. Placebo CABG 90.0% (60/66) and CABG + valve 9.1% (6/66)	[a]Dofetilide 18% (12/67) vs. Placebo 36% (24/66), p<0.017	LOS: Dofetilide 5.7± 3.5 vs. Placebo 6.7 ± 3.8, p=NS Mortality: NR	Preop β-blocker: Dofetilide 76.1% (51/67) vs. Placebo 74.2% (49/66), p=0.84

P=Prospective, R=Randomized, DB=Double-Blind, SB=Single-Blind, PC=Placebo-Controlled, C=Controlled, OL=Open Label

[a]Postoperative atrial tachycardia

Table 6. Magnesium Clinical Trials

Trial Design, Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, DB, PC N=130[83]	Magnesium chloride 50 mmol IV x 48 h postop in maintenance fluids (n=66) vs. Placebo (n=64)	Mag CABG 100% (66/66) vs. Placebo CABG 100% (64/64)	Mag 16.7% (11/66) vs. Placebo 23.4% (15/64), p=NS	LOS: NR Mortality: Mag 1.5% (1/66) vs. Placebo 0%, p=NS	Preop β-blocker: Mag 69.7% (46/66) vs. Placebo 64.1% (41/64), p=0.62
P, R in pts with unstable angina N=98[79]	Magnesium sulfate 16 mmol IV from induction to cross clamp and second dose after release of cross clamp (n=50) vs. Control (n=48)	Mag CABG 100% (50/50) vs. Control CABG 100% (48/48)	Mag 44% (22/50) vs. Control 37.5% (18/48), p=NS	NR	Preop β-blocker: Mag 68% (34/50) vs. Control 77% (37/48), p=NR
P, R, DB N=81[88]	High dose Magnesium sulfate 4.2 ± 0.7 g (mean) before CPB followed by Magnesium chloride IV 11.9 ± 2.8 g until POD 1 and then 5.5 ± 1.0 g until POD 2 (n=41) vs. low dose Mag sulfate 2.9 ± 0.5 g after CPB at POD 1 and 1.4 ± 0.1 g POD 2 (n=40)	High Mag CABG 100% (41/41) vs. low Mag CABG 100% (40/40)	High Mag 24.3% (10/41) (24.3%) vs. low Mag 45% (18/40), p<0.01	NR	Preop β-blocker: High Mag 97.6% (40/41) vs. low Mag 97.5% (39/40), p=NS
P, R, DB, PC N=50[85]	Magnesium sulfate 100 mEq POD 1 then 25 mEq/d IV POD 2–5 IV cont infusion (n=25) vs. Placebo (n=25)	Mag CABG 100% (25/25) vs. Placebo CABG 100% (25/25)	Mag 4% (1/25) vs. Placebo 20% (5/25), p=0.02	NR	Preop β-blocker: Mag 100% (25/25) vs. Placebo 100% (25/25) Postop β-blocker: Mag 0 vs. Placebo 0
P, R, C N=50[84]	Magnesium sulfate 13–15 mmol/L in cardioplegia solution (n=25) vs. Control (n=25)	Mag CABG 100% (25/25) vs. Control CABG 100% (25/25)	Mag 20% (5/25) vs. Control 32% (8/25), p=NS	LOS: NR Mortality: Mag 0 vs. Control 0	Preop β-blocker: Mag 76% (19/25) vs. Control 68% (17/25), p=NR
R, C N=108[86]	Intraoperative Magnesium IV, median dose 5 g (n=42) vs. Control (n=66)	Mag CABG 100% (42/42) vs. Control CABG 100% (66/66)	[a]Mag 12% (5/42) vs. Control 29% (19/66), p=0.03	LOS: Mag 5.0 ± 4.9 vs. Control 4.9 ± 3.5, p=NS Mortality: NR	Preop β-blocker: Mag 85.7% (36/42) vs. Control 92.4% (61/66), p=NR

Table 6. continued.

Trial Design, Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R N=167[89]	Propranolol 20 mg PO/NG QID started at ICU admission (n=82) vs. Propranolol + Mag 18 g IV over 24 h started intraop (n=85)	Propranolol CABG 100% (82/82) vs. Propranolol + Mag CABG 100% (85/85)	Propranolol 19.5% (16/82) vs. Propranolol + Mag 22.4% (19/85), p=0.65	LOS: Propranolol 5.9 ± 2.8 vs. Propranolol + Mag 6.3 ± 3.3, p=0.38 Mortality: Propranolol 1.2% (1/82) vs. Propranolol + Mag 1.2% (1/85), p=0.74	Preop β-blocker: Propranolol 95% (78/82) vs. Propranolol + Mag 84.7% (72/85), p=NS
P, R, DB, PC N=147[66]	Amiod 900 mg/d IV infusion postop x 72h (n=49) vs. Magnesium sulfate 4 g/d IV x 3 d (n=47) vs. Placebo (n=51)	Amiod CABG 100% (49/49) vs. Mag CABG 100% (47/47) vs. Placebo CABG 100% (51/51)	Amiod 14% (7/49) vs. Mag 23% (11/47) vs. Placebo 27% (14/51) P values: p=0.14 Amiod vs. Placebo, p=0.82 Mag vs. Placebo	LOS: NR Mortality: Amiod 2% (1/49) vs. Mag 0% vs. Placebo 2% (1/51), p=NR	Preop β-blocker: Amiod 55% (27/49) vs. Mag 51% (24/47) vs. Placebo 65% (33/51), p=NR
P, R, C N=387[80]	Magnesium sulfate 12 g IV over 96 h post op x 4 d (n=63) vs. Digoxin 1 mg IV after CPB then 0.25 mg IV QD x 4 d (n=62) vs. Mag + Digoxin (n=62) vs. Propranolol 1 mg IV q6h then 10 mg PO QID x 4 d (n=71) vs. Mag + Propranolol (n=69) vs. Control (n=60)	[b]CABG ± valve	[c]Mag 38% (24/63) vs. Digoxin 31% (19/62) vs. Mag + Digoxin 37% (23/62) vs. Propranolol 18% (13/71) vs. Propranolol + Mag 19% (13/69) vs. Control 38% (23/60) P values: p=0.01 Control vs. Propranolol, p=0.02 Control vs. Mag + Propranolol, p=0.01 Propranolol vs. Mag, p=0.01 Mag vs. Mag + Propranolol, p=0.02 Mag + Digoxin vs. Propranolol, p=0.02 Mag + Digoxin vs. Mag + Propranolol, all other comparisons NS	LOS: Mag 8.2 ± 3.1 vs. Digoxin 7.4 ± 1.3 vs. Mag + Digoxin 8.4 ± 5.0 vs. Propranolol 8.0 ± 2.3 vs. Mag + Propranolol 8.4 ± 5.3 vs. Control 8.0 ± 2.9, p=0.69 Mortality: Mag 0% vs. Digoxin 0% vs. Mag + Digoxin 0% vs. Propranolol 0% vs. Mag + Propranolol 1.4% (1/69) vs. Control 0%, p=0.46	Preop β-blocker: Mag 69.9% (44/63) vs. Digoxin 75.8% (47/62) vs. Mag + Digoxin 72.6% (45/62) vs. Propranolol 76.1% (54/71) vs. Mag + Propranolol 75.4% (52/69) vs. Control 71.7% (43/60), p=0.95

Table 6. continued.

Trial Design, Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, DB, C N=85[82]	Magnesium sulfate IV based on intraoperative levels (n=43) vs. Control (uncorrected) (N=42)	Mag CABG 100% (41/41) vs. Control CABG 100% (40/40)	[d]Mag 10% (4/41) vs. Control 13% (5/40), p=NS	NR	Preop β-blocker: Mag 70% (30/43) vs. Control 64% (27/42) , p=NR
P, R, DB, PC N=147[90]	SotaIol PO 16–24 h post CABG + Magnesium chloride IV 50 mmol/d after induction of anesthesia x 36 h (n=74) vs. Sotalol (n=73)	Mag + Sotalol CABG 100% (74/74) vs. Sotalol CABG 100% (73/73)	[e]Mag + Sotalol 34% (25/74) vs. Sotalol 26% (19/73), p=0.36	LOS: NR Mortality: Mag + Sotalol 0 vs. Sotalol 0	Preop β-blocker: Mag + Sotalol 91% (67/74) vs. Sotalol 86% (63/73), p=NS
P/R N=200[87]	Magnesium sulfate 10 mmol IV over 4 h QD x 3 d postop (n=100) vs. Control (n=100)	Mag CABG 100% (100/100) vs. Control CABG 100% (100/100)	Mag 16% (16/100) vs. Control 35% (35/100), p=0.002	LOS: Mag 16.6 ± 7.8 vs. Control 16.7 ± 6.8, p=0.95 Mortality: NR	Preop β-blocker: Mag 65% (65/100) vs. Control 69% (69/100) Postop β-blocker: Mag 2% (2/100) vs. Control 7% (7/100), p=0.10
P, R, DB, PC N=160[81]	Magnesium sulfate 2.5 g IV over 30 min intraop infusion (n=80) vs. Placebo (n=80)	Mag CABG 100% (80/80) vs. Placebo CABG 100% (80/80)	Mag 20% (16/80) vs. Placebo 22.5% (18/80), p=0.9	LOS: Mag 7 ± 3.8 vs. Control 6 ± 2.8, p=0.004 Mortality : Mag 0 vs. Placebo 0	Preop β-blocker: Mag 67.5% (54/80) vs. Control 52.5% (42/80), p=NR
P, R, DB, PC N=136[74]	Amiod 5 mg/kg IV in 30 min + Magnesium sulfate 1.5 g IV in 10 min (n=44) vs. Amiod (n=44) vs. Placebo (n=48), all early postop	Amiod + Mag CABG 100% (44/44) vs. Amiod CABG 100% (44/44) vs. Placebo CABG 100% (48/48)	Amiod + Mag 9% (4/44) vs. Amiod 36% (16/44) vs. Placebo 33% (16/48) P values: p=0.023 Amiod + Mag vs. Placebo, p=0.01 Amiod + Mag vs. Amiod, p=NS Amiod vs. Placebo	NR	Preop and Postop β-blocker: Amiod + Mag 100% vs. Amiod 100% vs. Placebo 100%, p=1.000
R, C, Propensity Matched Analysis N=178[52]	Sotalol 40 mg PO BID starting POD 1 x 6 weeks + Magnesium 2 g IV post surgery and on POD 1 (n=89) vs. Control (n=89)	Sotalol + Mag CABG 100% (89/89) vs. Control CABG 100% (89/89)	Sotalol + Mag 13.5% (12/89) vs. Control 27.0% (24/89), p=0.025	Median LOS: Sotalol + Mag 7 vs. Control 7, p=NR Mortality: Sotalol + Mag 1.1% (1/89) vs. 4.5% (4/89) Control, p=0.17	Preop β-blocker: Sotalol + Mag 66.3% (6/89) vs. Control 64.0% (57/89), p=0.75

Table 6. continued.

Trial Design, Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality	Preop and/or Postop β-blocker use
P, R, C N=100[16]	Postop bisoprolol 2.5 mg PO BID + Magnesium sulfate 2 g IV on arrival to ICU then 600 mg PO TID x 1 wk (n=50) vs. Control (stayed on preop β-blocker) (n=50)	Bisoprolol + Mag CABG 100% (50/50) vs. Control CABG 100% (50/50)	Bisoprolol + Mag 20% (10/50) vs. Control 42% (21/50), p=0.030	Median LOS: Bisoprolol + Mag 7 (2-14) vs. Control 9 (2-19), p=0.022 Mortality: Bisoprolol + Mag 0 vs. Control 0	Preop β-blocker: Bisoprolol + Mag 88% (44/50) vs. Control 82% (41/50), p=NS

P=Prospective, R=Randomized, DB=Double-Blind, SB=Single-Blind, PC=Placebo-Controlled, C=Controlled, OL=Open Label

[a]Postoperative atrial tachycardia

[b]15 patients underwent CABG + valve

[c]Supraventricular tachycardia

[d]Day 3 atrial fibrillation

[e]Atrial ectopy

Table 7. Clinical Trials Evaluating Novel Therapies Targeting Inflammation, Oxidative Stress, and Atrial Remodeling

Trial Design Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality %	Preop and/or Postop β-blocker use
Renin-Angiotensin-Aldosterone-System (RAAS) Modulators (ACEIs or ARBs)					
P, Cohort (nested cohort study from AFIST II,III[a] N=338[99]	Preop ACEI/ARB (n=175) vs. No ACE/ARB (n=163)	[b]ACEI/ARB valve 11% (20/175) vs. No ACEI/ARB valve 11% (18/163)	Preop ACEI/ARB 29.1% (51/175) vs. No ACEI/ARB 36.2% (59/163), p=NS	NR	Preop β-blocker: ACEI/ARB 76.6% (134/175) vs. No ACEI/ARB 76.6% (125/163), p=0.98 Postop β-blocker: ACEI/ARB 82.3% (144/175) vs. No ACEI/ARB 76.6% (140/163), p=0.37 Prophylactic amiodarone: ACEI/ARB 38.3% (67/175) vs. No ACEI/ARB 37.4% (61/163), p=0.87
P, R treatment groups[c] compared to a historical control N=128[98]	ACEI (n=49) vs. ACEI + Candesartan (n=49) vs. Control (n=30)[a] Mean time to initiation of candesartan & index operation was 23.4 ± 8.4 d (range 10–42)	ACEI CABG 85% (42/49) and valve 12% (6/49) and CABG + valve 2% (1/49) vs. ACEI + candesartan CABG 92% (45/49) and valve 8% (4/49) vs. Control CABG 100% (30/30)	ACEI 12.2% (6/49) vs. ACEI + Candesartan 10.2% (5/49) vs. Control 33.3% (10/30) P values: p=0.02 ACEI vs. Control, p=0.01 ACEI + Candesartan vs. Control, p=NS ACEI vs. ACEI + Candesartan	NR	Preop β-blocker: ACEI 85.7% (42/49) vs. ACEI + Candesartan 91.8% (45/49) vs. Control 96.7% (29/30), p=NS
HMG-CoA Reductase Inhibitors (Statin)					
P, Propensity matched pairs in a department registry N=1,308[107]	Preop statin (n=654) vs. No statin (n=654)	Statin CABG 100% (654/654) vs. No statin CABG 100% (654/654)	[d]Statin 9.2% (60/654) vs. No statin 12.8% (84/654), p=0.03	LOS: NR Mortality: Statin 0.92% (654) vs. No statin 1.4% (9/654), p=0.44	Preop β-blocker: Statin 68% (446/654) vs. No statin 66% (434/654), p=0.48
P, R, DB, PC N=323[105] No prior statin use	Atorvastatin 40 mg PO QD starting 7 d preop through DC (n=101) vs. Placebo (n=99) Open label atorvastatin to all pts at DC indefinitely	Atorvastatin CABG 83% (84/101) and valve ± CABG 16% (16/101) vs. Placebo CABG 75% (74/99) and valve ± CABG 25% (25/99)	Atorvastatin 35% (35/101) vs. Placebo 57% (56/99), p=0.003	LOS: Atorvastatin 6.3 ± 1.2 vs. Placebo 6.9 ± 1.4, p=0.001 Mortality: Atorvastatin 2% (2/101) vs. Placebo 2% (2/99), p=NR	Preop β-blocker: Atorvastatin 72% (73/101) vs. Placebo 60% (59/99), p=0.08

Table 7. continued

Trial Design Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality %	Preop and/or Postop β-blocker use
Retro, Cohort study N=3,346[110]	Gp 1= Statin untreated hyperlipidemia (n=167) vs. Gp 2= Statin treated hyperlipidemia (n=2,592) vs. Gp 3= Statin untreated normolipidemia (n=587) preop	Gp 1 CABG 100% (167/167) vs. Gp 2 CABG 100% (2,592/2,592) vs. Gp 3 CABG 100% (587/587)	[e]Gp1: 9% (15/167) vs. Gp2: 8% (201/2,592), Gp3: 8% (46/587), P values: p=0.55 Gp1 vs. Gp2, all other comparisons p=NR	Median LOS: Gp1: 9 (7-13)[f] vs. Gp2: 8 (6-12), p=0.14, Gp3: 8 (7-12) Median LOS P values: p=0.14 Gp1 vs. Gp2, all other comparisons p=NR Mortality: Gp1 2.4% (4/167) vs. Gp2 2.6% (67/2592), vs. Gp3 2.6% (15,587) Mortality P values: p=1.0 Gp1 vs. Gp2, a p=NS all other comparisons	Preop β-blocker: Gp1: 73% (121/167) vs. Gp2 79% (2,049/2,592) vs. Gp3: 70% (408/587) P values: p=0.05 Gp1 vs. Gp2, p <0.05 Gp 3 vs. Gp2, all other comparisons p=NR
Retro, Observational N=405[108]	Preop statin (n=218) vs. No statin (n=187)	Statin CABG 100% (218/218) vs. No statin CABG 100% (187/187)	Statin 29.5% (64/218) vs. No statin 40.9% (76/187), p=0.021	LOS: Statin 7.8 ± 4 vs. No statin 8.4 ± 4.7, p=0.134 Mortality: Statin 0% vs. No statin 0.5% (1/187), p=0.999	Preop β-blocker: Statin 66.2% (144/218) vs. No statin 73.1% (137/187), p=0.151
P, Observational N=362[109]	Preop statin (n=267) vs. No statin (n=95)	Statin CABG 99% (263/267) and CABG + valve 1% (4/267) vs. No statin CABG 98% (93/95) and CABG + valve 2% (2/95)	Statin 8.2% (22/267) vs. No statin 16.8% (16/95), p=0.03	NR	Preop β-blocker: Statin 92.9% (248/267) vs. No statin 88.4% (84/95), p=0.2

Table 7. continued

Trial Design Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality %	Preop and/or Postop β-blocker use
P, R, C, OL N=124[106] No previous statin use	Atorvastatin 20 mg PO 3 d preop, then 30 d postop (n=62) vs. Control (atorvastatin started at DC and continued 30 d postop) (n=62)	Atorvastatin CABG 100% (62/62) vs. Control CABG 100% (62/62)	Atorvastatin 13% (8/62) vs. Control 27% (17/62), p=0.04	LOS: Statin 6.9 ± 3.2 vs. No statin 7.2 ± 3.3, p=0.58 Mortality: Atorvastatin 0 vs. Control 0	Preop β-blocker: Atorvastatin 73% (45/62) vs. Control 69% (43/62), p=0.69
Observational study of previously conducted prospective, nested cohort of pts from AFIST I,II,III trials N=555[15]	Preop statin (n=331) vs. No statin (n=224)	[b]Statin valve 9% (30/331) vs. No statin valve 23% (51/254), p <0.001	Statin 27.8% (92/331) vs. No statin 36.6% (82/224), p<0.05	NR	Preop β-blocker: Statin 79.8% (264/331) vs. No statin 64.7% (145/224), p<0.001 Postop β-blocker: Statin 86.4% (286/331) vs. No statin 80.4% (180/224), p=0.06
Nonsteroidal Antiinflammatory Drug (NSAID)					
P, R, C N=100[117]	Ketorolac 30 mg IV q6 h x 1 in ICU until PO then ibuprofen 600 mg PO TID x 7 d or DC (n=51) vs. Control (n=49)	NSAID CABG 100% (51/51) vs. Control CABG 100% (49/49)	NSAID 9.8% (5/51) vs. Control 28.6% (14/49), p=0.017	LOS: NSAID 4.9 ± 1.4 vs. Control 6.1 ± 2.9, p=0.009 Mortality: NSAID 0% (0/51) vs. Control 2% (1/49), p=0.49	*Periop* β-blocker: NSAID 94.1% (48/51) vs. Control 91.8% (45/49), p=0.71
P, Cohort (nested cohort study from AFIST I,II,III) N=555[118]	NSAID postop (n=127) vs Control (n=428)	[b]NSAID valve 10% (13/127) vs. Control valve 16% (68/428)	[g]NSAID 20.5% (26/127) vs. Control 34.6% (148/428), p=0.003	NR	Preop β-blocker: NSAID 73.2% (93/127) vs. Control 73.8% (316/428), p=0.892 Postop β-blocker: NSAID 89.8% (114/127) vs. Control 82.2% (352/428), p=0.043

Table 7. continued

Trial Design Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality %	Preop and/or Postop β-blocker use
Corticosteroid					
P, R, DB, PC N=60[122]	Methylprednisolone (MPD) 30 mg/kg IV x 2 during sternotomy + initiation of cardiopulmonary bypass (CPB) (n=30) vs. Placebo x 2 at same times (n=30)	MPD CABG 100% (30/30) vs. Placebo CABG 100% (30/30)	MPD 26.7% (8/30) vs. Placebo 30% (9/30), p=NR	LOS: MPD 6.9 ± 4.1 vs. Placebo 8.3 ± 5.1, p=NR Mortality: NR	Preop β-blocker: MPD 63.3% (19/30) vs. Placebo 53.3% (16/30), p=NR
P, R, DB, PC N= 294[123]	Dex 4 mg IV x 2 doses (post-induction, then POD 1) (n=147) vs. Placebo (n=147)	Dex CABG 100% (147/147) vs. Placebo 100% (147/147)	Dex 27% (40/147) vs. Placebo 32% (47/147), p=NS	LOS: NR Mortality: Dex 0.7% (1/147) vs. Placebo 0.7% (1/147), p=NS	Preop β-blocker: Dex 88% (130/147) vs. Placebo 84% (123/147), p=NR
P, R, DB, PC N=86[120]	MPD 1 g IV before CPB, then Dex 4 mg IV q6 h x 4 doses (n=43) vs. Placebo (n=43)	MPD + Dex CABG 100% (43/43) vs. Placebo CABG 100% (43/43)	MPD + Dex 20.9% (9/43) vs. Placebo 51.2% (22/43), p=0.003	LOS median: MPD + Dex 6 vs. Placebo 7, p=0.34 Mortality: NR	Postop β-blocker: MPD+ Dex 100% (43/43) vs. Placebo 100% (43/43)
P, R, DB, PC N=241[121]	HCT 100 mg IV eve of surgery, then 1 dose q8 h x 3 d postop (n=120) vs. Placebo (n=121)	HCT CABG 83% (100/120) and valve 9% (11/120) and CABG + valve 8% (9/120) vs. Placebo CABG 79% (96/121) and valve 14% (17/121) and CABG + valve 7% (8/121)	HCT 30% (36/120) vs. Placebo 47.9% (58/121), p=0.01	LOS: NR Mortality: HCT 0.8% (1/120) vs. Placebo 0.8% (1/121), p>0.99	Preop β-blocker: HCT 82.5% (99/120) vs. Placebo 86.6% (103/121), p=0.39 Postop β-blocker: HCT 100% (120/120) vs. Placebo 100% (121/121)

Table 7. continued

Trial Design Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality %	Preop and/or Postop β-blocker use
Thiazolidinedione (TZD)					
Nested study of diabetic pts from AFIST I, II, III N=184[130]	Preop TZD (n=40) vs. Control (n=144)	TZD CABG 97.5% (39/40) and valve 2.5% (1/40) vs. Control CABG 91.7% (132/144) and valve 8.3% (12/144)	TZD 32.5% (13/40) vs. Control 36.8% (53/144), p=0.63	NR	Preop β-blocker: TZD 75% (30/40) vs. Control 75% (108/144), p>0.99 Postop β-blocker: TZD 82.5% (33/40) vs. Control 84.7% (122/144), p=0.73
Omega-3 Fatty Acid					
P, R, OL, C N=160[133]	Polyunsaturated Fatty Acids (PUFA) 2 g PO/NG QD for at least 5 d preop and until DC (n=79) vs. Control (n=81)	PUFA CABG 100%(79/79) vs. Control CABG 100% (81/81)	PUFA 15.2% (12/79) vs. Control 33.3% (27/81), p=0.013	LOS: PUFA 7.3 ± 2.1 vs. Control 8.2 ± 2.6, p=0.017 Mortality: PUFA 1.3% (1/79) vs. Control 2.5% (2/81), p=1.0	Preop β-blocker: PUFA 58.2% (46/79) vs. Control 56.8% (46/81), p=0.98
Ascorbic Acid					
P, OL, retrospective matched controls N=86[135]	Ascorbic acid 2 g PO noc before surgery then 500 mg PO BID x 5 d postop (n=43) vs. Control (n=43)	Ascorbic acid CABG 100% (43/43) vs. Control CABG 100% (43/43)	Ascorbic Acid 16.3% (7/43) vs. Control 34.9% (15/43), p = 0.048	NR	Preop β-blocker: Ascorbic acid 86% (37/43) vs. Control 76% (31/43), p=0.22 Postop β-blocker: Ascorbic acid 84% (36/43) vs. Control 70% (30/43), p=0.13
P, R, OL, C N=100[136]	Ascorbic acid 2 g PO noc before surgery and 1 g PO BID x 5d postop (n=50) vs. Control (n=50)	Ascorbic acid CABG 100% (50/50) vs. Control CABG 100% (50/50)	Ascorbic acid 4% (2/50) vs. Control 26% (13/50), p=0.002	LOS: Ascorbic acid 6.54 ± 3.24 vs. Control 7.08 ± 3.45, p=0.47 Mortality: NR	Preop β-blocker: Ascorbic acid 100% (50/50) vs. Control 100% (50/50) Postop β-blocker: Ascorbic acid 100%(50/50) vs. Control 100% (50/50)
***N*-Acetylcysteine (NAC)**					
P, R, DB, PC N=100[138]	NAC 600 mg PO x 1d preop and AM of surgery, 150 mg/kg IV bolus before skin incision, then perfusion 12.5 mg/kg/h over 24h (n=50) vs. Placebo (n=50)	NAC CABG 100% (50/50) vs. Control CABG 100% (50/50)	NAC 7% (4/50) vs. Control 12% (6/50), p=0.7	LOS: NAC 5.4 ± 2.3 vs. Placebo 5.3 ± 2.5, p=0.7 Mortality: NAC 6% (3/50) vs. Placebo 0%, p=0.1	Preop β-blocker: NAC 88% (44/50) vs. Control 76% (38/50), p=0.1

Table 7. continued

Trial Design Number of Patients	Treatment Strategy	Type of Cardiac Surgery	Incidence POAF	Mean LOS (Days ± SD) and Mortality %	Preop and/or Postop β-blocker use
P, R, DB, PC N=115[139]	NAC 50 mg/kg IV 1h preop, then IV infusion x 48 h postop, 50 mg/kg/d (n=58) vs. Placebo (n=57)	NAC CABG 95% (55/58) and valve ± CABG 5% (3/58) vs. Placebo CABG 91% (52/57) and valve ± CABG 9% (5/57)	NAC 5.1% (3/58) vs. Placebo 21.1% (12/57), p=0.01	LOS: NAC 7.7 ± 3 vs. Placebo 7.9 ± 4.2, p=0.82 Mortality: NAC 0% vs. Placebo 3.5% (2/57), p=NR	Preop and postop β-blocker: NAC 87.9% (51/58) vs. Placebo 93% (53/57), p=NR
Sodium Nitroprusside					
P, R, PC pilot study N=100[140]	Sodium nitroprusside (SNP) 0.5 µg/kg/min IV during rewarming (n=50) vs. Placebo (n=50)	SNP CABG 100% (50/50) vs. Placebo CABG 100% (50/50)	SNP 12% (6/50) vs. Placebo 36% (18/50), p=0.005	LOS: SNP 7.34 ± 0.717 vs. Placebo 9.10 ± 1.22, p=0.000 Mortality: NR	Preop β-blocker: SNP 68% (34/50) vs. Placebo 58% (29/50), p=0.303
Triiodothyronine					
P, R, DB, PC N=142[141, 143]	[141]T3 0.8 µg/kg IV bolus at cross clamp removal then 0.113 µg/kg/h IV infusion x 6 h (n=66) vs. Placebo (n=65)	[143]T3 CABG 100% (66/66) vs. Placebo CABG 100% (65/65)	[141]T3 24% (16/66) vs. Placebo 46% (30/65), p=0.009	[143]Median LOS: T3 8 vs. Placebo 8, p=NS Mortality: T3 6% (4/71) vs. Placebo 4% (3/71), p=NS	[141]Preop β-blocker: T3 54% (36/66) vs. Placebo 65% (42/65), p=NS

P=Prospective, R=Randomized, DB=Double-Blind, SB=Single-Blind, PC=Placebo-Controlled, C=Controlled, OL=Open Label

[a]AFIST III evaluated the impact of epicardial anterior fat pad retention on the incidence of post-cardiothoracic surgery atrial fibrillation incidence.

[b]Authors only state percent of patients receiving valvular surgery, no percentages given for CABG alone, valve alone or CABG + valve

[c]98 patients who were on chronic ACEI > 1 month were randomized to ACEI or ACEI + Candesartan

[d]Supraventricular tachycardia, Atrial fibrillation, Atrial flutter

[e]Supraventricular tachycardia

[f]Interquartile range of 15–75%

[g]Atrial fibrillation occurred either during index hospital admission or at any follow-up visit within 30 d of cardiac surgery