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Strategies for the Prevention of Postoperative Atrial Fibrillation in Cardiac Surgery

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1. Introduction

Atrial fibrillation (AF) occurs in 15% to 50% of patients after cardiac surgery (Bradley et al., 2005; Dunning et al., 2006). 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 (Echahidi et al., 2008; Kaireviciute et al., 2009). The development of POAF is associated with, on average, an additional hospital length of stay (LOS) of 1 to 1.5 days (Kim et al., 2001; Zimmer et al., 2003). Some studies, however, report that POAF increases hospital LOS by almost 5 days (Aranski et al., 1996; Gillespie et al., 2006). POAF is also associated with higher hospital costs with an average increase of $10,000-$12,600 per hospitalization (Gillespie et al., 2006; Aranski et al., 1996).

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 ACCP 2005 Recommendations for the Role of Cardiac Pacing for POAF, 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, the Canadian Cardiovascular Society (CCS) Consensus Conference Statements on AF, and the European Association for Cardio-Thoracic Surgery (EACTS) 2006 POAF Guidelines and updated ESC/EACTS 2010 AF Guidelines (Bradley et al., 2005; Maisel & Epstein 2005; Dunning et al., 2006; Fuster et al., 2006; Eagle et al., 2004; Mitchell et al., 2005; Kerr & Roy, 2004; European Society of Cardiology ([ESC], 2010) (Table 1).

The guidelines are consistent in that they all strongly recommend using beta-blockers to reduce POAF incidence (ACCP 2005 POAF Guidelines Strength A, ACC/AHA/ESC 2006 AF Guidelines and ACC/AHA 2004 CABG Guidelines Class I, Canadian Cardiovascular Society AF/POAF Consensus Class I, and ESC 2010 AF Guidelines Class I). The Surgical Care Improvement Project (SCIP) National Quality Measures also state that all patients undergoing cardiac surgery should receive a beta-blocker during the perioperative period if they were on a beta-blocker prior to arrival (Surgical Care Improvement Project [SCIP] Version 3.0a, 2009). Most institutions have incorporated this requirement into their prospective preoperative order sets for all patients without contraindications to beta-blockers.

Medication or Class	Canadian CV Society Consensus Conference:AF Following Cardiac Surgery (Mitchell et al., 2005a); Canadian CV Society Consensus Conference:AF Executive Summary (Kerr & Roy, 2004)		ACCP 2005 POAF Guidelines (Bradley et al., 2005) ACCP CHEST 2005 Cardiac Pacing (Maisel & Epstein, 2005)			ACC/AHA/ESC 2006 AF Guidelines (Fuster et al., 2006); ACC/AHA 2004 CABG Guidelines (Eagle et al., 2004)		ESC 2010 AF Guidelines (ESC 2010)	
	Class	**Level of Evidence**	**Strength**	**Quality of Evidence**	**Net Benefit**	**Class**	**Level of Evidence**	**Class**	**Level of Evidence**
Pacing	I	C - Temporary ventricular epicardial pacing electrode wires placed at time of cardiac surgery to allow for backup pacing as necessary	B	Good	Biatrial pacing Small/weak	-	-	IIb	A - Biatrial pacing
	IIa	A - Atrial pacing (with or without a ventricular lead) should be considered in pts with symptomatic bradycardia							
	IIa	B - Atrial pacing if not on BB before surgery							
	IIa	B - The proportion of time the ventricles are paced should be minimize in pts with intrinsic AV conduction							

	IIa	B - Temporary atrial pacing should be considered following heart surgery									
	III	B - Atrial pacing for the prevention of AF in the absence of symptomatic bradycardia is not recommended	-	-	-	-	-	-	-	A *(last noted in Dunning et al., 2006)	1a/b *(last noted in Dunning et al., 2006)
Off pump CABG	-	-	-	-	-	-	-	-	-	B *(last noted in Dunning et al., 2006)	1b *(last noted in Dunning et al., 2006)
Posterior Pericardiotomy	-	-	-	-	-	-	-	-	-	Class I	A B - If used, BB are recommended to be continued until day of surgery
Beta-Blockers	I	A - BB before surgery, should be continued through operative period	A	Fair	Substantial	I (Fuster) I (Eagle)	A (Fuster) B (Eagle)			Class IIb	A - May be considered, but associated with risk of proarrhythmia
	IIa	A - If not on BB before surgery	B	Good	Intermediate	IIb	B (Fuster,Eagle)			Class IIa	A - Preoperative amiodarone should be considered for pts at high risk for POAF
Sotalol	-	-	B	Good	Intermediate	- consider if BB contraindicated (Eagle)					
Amiodarone	IIa	A - If not on BB before surgery	B	Good	Intermediate	IIa	A (Fuster)				
						- consider in patients at high risk for POAF					
						IIa	B (Eagle)				
						- consider in patients at high risk for POAF if BB contraindicated					
Magnesium	IIa	B - If not on BB before surgery	D	Low	None	-	-	-	-	-	-
Dexamethasone	-	-	I	Low	Conflicting	-	-	IIb	B - Corticosteroids may be considered, but are associated with risk		

ACCP= American College of Chest Physicians, ACC= American College of Cardiology, AHA= American Heart Association, ESC= European Society of Cardiology AF = atrial fibrillation, BB = beta-blocker, CABG = coronary artery bypass graft, CV = cardiovascular, EACTS = European Association for Cardiothoracic Surgery, POAF= postoperative atrial fibrillation, pts = patients

Table 1. International Guideline Recommendations for Therapies for the Prevention of POAF in Patients Undergoing Cardiac Surgery

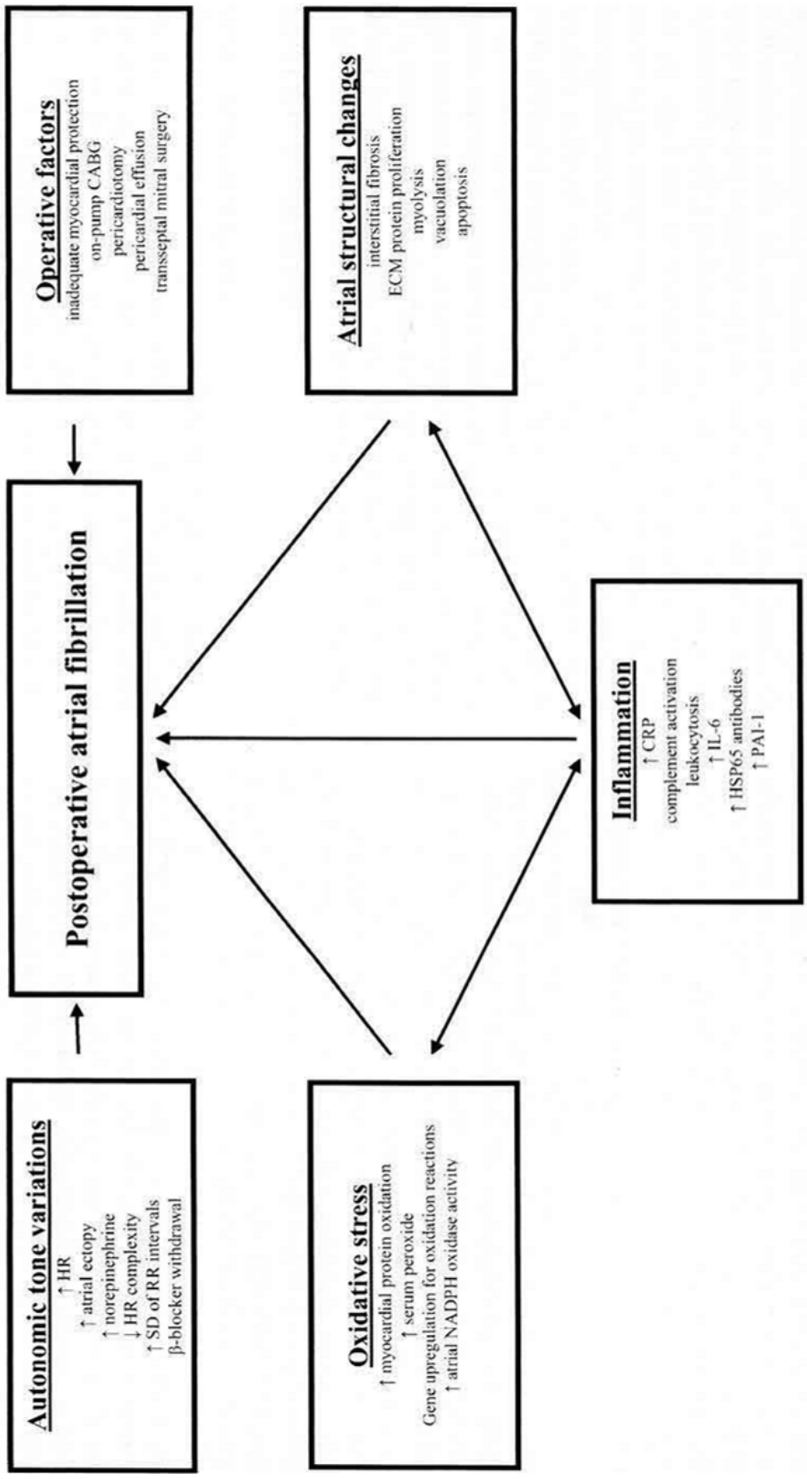
Though there are no studies examining POAF prophylaxis for patients intolerant of beta-blockers, effective alternatives include sotalol and amiodarone, depending upon the contraindication. The guidelines further specify that amiodarone may be given as an alternative or considered in patients at high risk for POAF (Fuster et al., 2006; Eagle et al., 2004; ESC, 2010; Mitchell et al., 2005a; Kerr & Roy, 2004). Only the previous 2006 EACTS and Canadian guidelines support the use of magnesium and state that it may be given in addition to other strategies to reduce POAF(Dunning et al., 2006; Mitchell et al., 2005a; Kerr & Roy, 2004). Additionally, the most recent ESC guidelines include consideration of corticosteroids for the prevention of POAF (ESC, 2010).

The practice guidelines also recommend utilization of non-pharmacologic strategies for the prevention of POAF in cardiac surgery patients (Table 1). The most common strategy referred to in the guidelines is cardiac pacing. The most recent 2010 ESC AF guidelines and ACCP statement from 2005 recommend that biatrial pacing should be considered for prophylaxis (ESC, 2010, Maisel & Epstein, 2005). The CCS statement also recommends that atrial pacing with or without a ventricular lead should be considered in patients with symptomatic bradycardia (Class 2A recommendation based on Level A evidence) and that atrial pacing should be considered if a patient is not on a beta-blocker before surgery (Class 2A recommendation based on Level B evidence) (Mitchell et al., 2005a; Kerr & Roy, 2004). Lastly, the CVS guidelines strongly recommend placing temporary ventricular epicardial pacing electrode wires at the time of surgery to allow for backup pacing as necessary (Class 1 recommendation based on Level C evidence) (Mitchell et al., 2005a; Kerr & Roy, 2004). Other non-pharmacologic strategies mentioned in the guidelines include the use of off-pump CABG, posterior pericardiotomy, and intraoperative maze ablation (Mitchell et al., 2005a; Kerr & Roy, 2004; ESC, 2010).

2. Pathogenesis of POAF

The underlying mechanisms for the development of POAF after cardiac surgery are not precisely known, but are thought to be multifactorial (Figure 1) (Banach et al., 2010). 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 (Baker & White, 2007a). 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 (Baker & White, 2007a; Kalman et al., 1995). Hence, the majority of interventions that reduce the incidence of POAF modulate sympathetic and parasympathetic systems or alter cardiac conduction (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 cardiopulmonary bypass (CPB) with subsequent elevations of C-reactive protein (CRP), interleukin-6 (IL-6), and the complement system (Echahidi et al., 2008; Gaudino et al., 2003; Bruins et al., 1997; Canbaz et al., 2008). Angiotensin II has been



HR= heart rate, SD= standard deviation, NADPH= nicotinomide adenine dinucleotide phosphate, CABG= coronary artery bypass grafting, ECM= extracellular matrix, CRP= C-reactive protein, IL-6= interleukin-6, HSP= heat shock protein, PAI= plasminogen activator inhibitor

Fig. 1. Pathogenesis of postoperative atrial fibrillation (Banach et al., 2010)

shown to increase the production of proinflammatory cytokines, adhesion molecules, and selectins (Erlich et al., 2006; Boos et al., 2006). White blood cell count may also be a predictor of POAF (Lamm et al., 2006). The degree of inflammation postoperatively can negatively affect atrial conduction and duration of atrial fibrillation (Ishii et al., 2005; Tselentakis et al., 2006).

Oxidative stress has also been implicated in the pathogenesis of atrial fibrillation as the atrial tissue undergoes oxidative challenge during CPB (Rodrigo et al., 2008). Patients with POAF have been shown to have increased acute myocardial oxidation when compared to patients that did not experience POAF (Ramlawi et al., 2007). 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 (Kim et al., 2008). This may be due to damage of cardiac myocytes through lipid peroxidation, breakdown of cell membrane, decreased mitochondrial function, calcium overload, and apoptosis (Elahi et al., 2008). Because NADPH is activated by numerous mediators including tumor necrosis factor- α (TNF-α) (Griendling et al., 2000), it has been proposed as a link between inflammation and oxidative stress in POAF.

Based on these newly identified pathways, emerging pharmacologic therapies for the prevention of POAF have been under investigation including HMG Co-A reductase inhibitors (statins), renin-angiotensin-aldosterone-system modulators (including angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)), corticosteroids, omega-3 fatty acids, ascorbic acid, N-acetylcysteine, and sodium nitroprusside.

The guidelines suggest additive therapies 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 beta-blockers or ACEIs, and increased aortic cross-clamp and CPB time (Mathew et al., 2004; Baker et al., 2007b; Nisanoglu et al., 2007). No simple criteria exist that allow patients to be classified as high risk for the development of POAF. A risk index model (Multicenter Study of Perioperative Ischemia Atrial Fibrillation Risk Index) (Table 2) was developed to identify subjects at high risk for POAF (Mathew et al., 2004). 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 (Barnes et al., 2006).

3. Pharmacologic therapies for the prevention of POAF in cardiac surgery

3.1 Established pharmacologic therapies

3.1.1 Beta-blockers

Beta-blockers work at the myocardium antagonizing the effects of catecholamines and have been studied extensively for the prevention of POAF. Meta-analyses have shown significant reduction in POAF incidence with the use of beta-blocker therapy, resulting in recommendation for their use as first-line therapy (Bradley et al., 2005; Dunning et al.; 2006, Fuster et al., 2006; Eagle et al., 2004, Kerr & Roy, 2004; [ESC], 2010). The largest meta-

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 AF	7
History of COPD	4
Concurrent valve surgery	6
Withdrawal of postoperative treatment	
BB	6
ACEI	5
BB treatment	
Preoperative and postoperative	-7
Postoperative	-11
Preoperative and postoperative ACEI treatment	-5
Postoperative treatment	
Potassium supplementation	-5
NSAIDs	-7
	= [a]Total Points

[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

ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, BB = beta-blocker, CABG = coronary artery bypass graft, COPD = chronic obstructive pulmonary disease, NSAIDs = non-steroidal anti-inflammatory drugs, POAF = postoperative atrial fibrillation

Table 2. Multicenter Study of Perioperative Ischemia Atrial Fibrillation Risk Index (Mathew et al., 2004)

analysis was published in 2002 by Crystal et al. that included 27 randomized controlled trials with 3,840 patients (Crystal et al., 2002). Use of beta-blocker therapy decreased the incidence of POAF from 33% in the control group compared to 19% in the group receiving beta-blockade. This corresponded to a number needed to treat (NNT) of seven patients. A large retrospective analysis of the Society of Thoracic Surgeons (STS) database containing 629,877 patients, demonstrated a reduction in mortality rate with use of peri-operative beta-blockers (Ferguson et al., 2002). It has been shown that patients receiving perioperative beta-blockers have reduced mortality compared to control (3.4% versus 2.8%, OR 0.8, 95% CI 0.78 – 0.82; $p<0.001$). Efficacy of beta-blockade in the prevention of POAF has been theorized to decrease hospital LOS. However, two beta-blocker trials reporting effect on LOS demonstrated a non-significant reduction in LOS (-0.66 days; 95% CI, -2.04-0.72) (Cybulsky et al., 2000; Wenke et al., 1999).

The importance of beta-blockers is also affirmed by the two to five-fold increase in the incidence of POAF when beta-blockers are discontinued postoperatively (Kalman et al., 1995; Jideus et al., 2000; Ali et al., 1997). The increase in POAF is thought to be caused by

beta-blocker withdrawal and mediated by an upregulation of beta adrenergic receptors and sympathetic stimulation (Kalman et al., 1995). Beta-blocker withdrawal is significantly associated with a greater than two-fold risk of developing POAF in cardiac surgery patients (Adjusted OR 2.17, 95% CI 1.11-4.25, p=0.04) (Lertsburapa et al., 2008). Thus, timing of beta-blocker administration appears play an important role and evidence supports the continuation of beta-blocker therapy from the preoperative stage through postoperative management. The guidelines emphasize the importance of reinitiating beta-blockers postoperatively without delay (Bradley et al., 2005).

In addition, the mode of administration of beta-blocker therapy has been evaluated in the prevention of POAF. Intravenous administration of metoprolol has demonstrated superiority to oral administration when accessing for the prevention of POAF. This is theorized to be a result of diminished gastrointestinal absorption with oral administration early after surgery. This phenomenon has been demonstrated by Halonen et al., when a significant reduction (p=0.036) of POAF occurrence by 11.3% was noted to occur in patients assigned to receive intravenous metoprolol therapy compared to patients assigned oral therapy (Halonen et al., 2006).

Controversy exists around selection of the most effective beta-blocker in reducing POAF. Two studies have demonstrated improved efficacy of carvedilol when compared to metoprolol (Acikel et al., 2008; Haghjoo et al., 2007). This was confirmed by approximately 18%-20.4% less episodes of POAF in those patients assigned to receive carvedilol.

Despite the overwhelming evidence to support beta-blocker therapy in the prevention of POAF, contraindications to this therapy exist. Alternative pharmacologic and non-pharmacologic modalities are warranted for patients who cannot tolerate or have the following contraindications to beta-blockers: bradycardia (<45 bpm), heart block, cardiac failure, severe peripheral edema, sick-sinus syndrome, bronchospastic disease (non-selective beta-blockers), and hypotension (SBP < 100 mmHg) with myocardial infarction.

3.1.2 Amiodarone

Amiodarone, a class III antiarrhythmic agent, has shown efficacy in the prevention of POAF. Its activity is demonstrated through blockade of alpha and beta-adrenergic receptors as well as sodium, calcium and potassium channels. Only beta-blockers have more safety and efficacy data to support their effectiveness in the prevention of POAF. Most randomized, controlled trials have supported the efficacy of amiodarone over placebo in the prevention of POAF by showing reduction of occurrence between 12% to 51% (Auer et al., 2004a; Barnes et al., 2006; Daoud et al., 1997; Guarnieri et al., 1999; Giri et al., 2001; White et al., 2002; Yazigi et al., 2002; Tokmakoglu et al., 2002; White et al., 2003; Mitchell et al., 2005a; Budeus et al., 2006; Zebis et al., 2007). Therefore, amiodarone has been granted a class IIa recommendation for POAF prophylaxis, behind beta-blockers, according to the ACC/AHA/ESC 2006 AF Guidelines, ACC/AHA 2004 CABG Guidelines, 2004 CCS AF/POAF Consensus statement, and ESC 2010 (Fuster et al., 2006; Eagle et al., 2004; Kerr & Roy, 2004; ESC, 2010). Additionally, the guidelines support amiodarone as prophylactic therapy in patients unable to tolerate beta-blockers or in high-risk patients with or without beta-blocker therapy (Bradley et al., 2005).

Two trials evaluating amiodarone versus placebo have demonstrated clear reduction of POAF occurrence (Mitchell et al., 2005b; Daoud et al., 1997). Compared to placebo, amiodarone reduced POAF incidence by 13.4%-19%. Effectiveness between amiodarone

versus other pharmacological agents has been established. Two meta-analysis have been conducted evaluating the efficacy of amiodarone in POAF in which a statistically significant decrease in incidence was established (Bagshaw et al., 2006; Haan et al., 2002). Comparisons of amiodarone effectiveness have been made with agents such as beta-blockers (propranolol, metoprolol, and bisoprolol), sotalol, digoxin, and diltiazem. No clear superiority has been established amongst comparative trials. Amiodarone has been given in direct combination with metoprolol, magnesium, and atrial septal pacing in Bachmanns's Bundle (Auer et al., 2004a; Cagli et al.; 2006, White et al., 2003). All of these studies showed amiodarone in direct combination with the previous pharmacologic and non-pharmacologic options to be superior than that of placebo, with absolute reductions in the incidence of POAF by 20% to 24% (Auer et al., 2004a; Cagli et al., 2006; White et al., 2003). Combination therapy with amiodarone and beta-blockers has been well validated. A meta-analysis also found that amiodarone also significantly reduces the LOS by 0.91 days (95% CI, -1.59- -0.24) (Crystal et al., 2002).

Various dosing regimens using IV and/or oral amiodarone with varying administration times have been used in the POAF prevention trials. A meta-analysis evaluating 14 randomized, controlled trials in 2,864 patients, stratified into low (<3 g), medium (3-5 g), or high (>5 g) and timing was divided into preoperative or postoperative administration, found that cumulative doses of >3 g may be more effective than lower doses and preoperative initiation of amiodarone may be unnecessary (Buckley et al., 2007).

Amiodarone is effective for the prevention of POAF, however it has a complex side effect profile that includes QTc interval prolongation, pulmonary and liver toxicity, thyroid abnormalities, and visual disturbances. Patients with any of these pre-existing conditions may be placed at more risk with the addition of amiodarone for the prevention of POAF and the risk versus benefit must be evaluated for each patient. Side effects of amiodarone are typically associated with large cumulative doses and prolonged use. However, dosing regimens for prophylaxis tend to be short in 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. The safety of amiodarone in patients undergoing cardiac surgery has been evaluated in a meta-analysis reviewing 18 randomized controlled trials (Patel et al., 2006). Results showed that amiodarone use was significantly associated with increased risk of hypotension (OR 1.79; 95% CI 1.04-3.09) and bradycardia (OR 2.33; 95% CI 1.41-3.61), especially when the intravenous formulation was utilized in high doses (greater than 1 gram). Therefore, clinicians should be cautious using amiodarone, especially in combination therapy with beta-blockers or other therapies that may cause bradycardia or hypotension. Finally, if amiodarone therapy is added to a patient's medication profile, physical and laboratory exams should be conducted and evaluated for the presence of drug-drug interactions or medication side effects.

3.1.3 Sotalol

Sotalol, a class III antiarrhythmic that possess beta-blocking activity, has been shown to be an effective pharmacological agent for the prevention of POAF. Within the primary literature, sotalol has demonstrated absolute reductions in the incidence of POAF between 13% - 16% (Auer et al., 2004a; Janssen et al., 1986; Suttorp et al., 1991; Weber et al., 1998; Evrard et al., 2000). Despite its demonstrated effectiveness, sotalol is contraindicated in patients with severe renal insufficiency and should be avoided in patients with heart failure. Furthermore, because of its propensity 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. Due to its beta-blocking properties, sotalol is contraindicated in patients intolerant of beta-blockers. Because of the aforementioned limitations of this agent, sotalol has been granted a class IIb recommendation for POAF prophylaxis behind beta-blockers according to the ACC/AHA/ESC 2006 AF Guidelines and the ACC/AHA 2004 CABG Guidelines (Fuster et al., 2006; Eagle et al., 2004). The most recent 2010 ESC guidelines have assigned a Class IIb recommendation for sotalol due to its proarrhythmic risk (ESC, 2010). However, the earlier 2006 EACTS guidelines gave sotalol a stronger grade A recommendation based upon its comparative efficacy trials versus beta-blockers (Dunning et al., 2006) similar to ACC recommendations.

Patel and Dunning evaluated seven different randomized trials comparing sotalol to conventional beta blockers (Patel et al., 2005). Out of the seven trials evaluated, five studies demonstrated a statistically significant reduction in POAF for those patients assigned to sotalol compared to conventional beta-blockade. The number of patients needed to be treated with sotalol to prevent POAF over that of conventional beta-blocker therapy was found to be 10. Conversely, because of the pro-arrythmic properties of sotalol, conventional beta-blocker therapy may be a safer option.

3.1.4 Magnesium

POAF has been associated with decreased postoperative magnesium levels (Kalman et al., 1995). In fact, plasma magnesium concentration levels less that 0.9 mmol have been found to be an independent predictor of POAF (OR 6.7) when using multivariate logistic regression models (Treggiari-Venzi et al., 2000). Multiple large, randomized, controlled trials with magnesium have 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 (Treggiari-Venzi et al., 2000; Serafimovski et al., 2008; Caspie et al., 1995; Bert et al., 2001; Zangrillo et al., 2005), IV infusion based on serum levels (Wilkes et al., 2002), magnesium supplementation in maintenance fluids (Colquhoun et al., 1993) and in supplementation through cardioplegia solution (Shakerinia et al., 1996). Surprising lower cumulative doses of magnesium supplementation (mean cumulative dose 8.2 g) have shown to be more effective in reducing the incidence of POAF (OR 0.36, 95% CI 0.23-0.56), compared to higher doses (mean cumulative dose 15 g) (OR 0.99, 95% CI 0.70-1.41) (Henyan et al., 2005). Results from the same meta-analysis found that preoperative administration of magnesium was more effective at decreasing the incidence of POAF (OR 0.46, 95% CI 0.31-0.67) compared to intraoperative or postoperative administration. Results from several meta-analysis (Woodend et al., 1998; Burgess et al., 2006; Shiga et al., 2004; Miller et al., 2005; Alghamdi et al., 2005; Henyan et al., 2005; Shepard et al., 2008) have shown inconsistent efficacy with magnesium use. A few studies have demonstrated a significant benefit of magnesium when compared to usual care with absolute reductions in the incidence of POAF by 16% to 34% (Nurozler et al., 1996; Maslow et al., 2000; Kohno et al., 2005). However, at this time there is a lack of statistically significant data to support magnesium supplementation as monotherapy compared to that of beta-blocker, amiodarone, or sotalol therapy in the treatment of POAF (Bert et al., 2001; Solomon et al., 2000; Cagli et al., 2006). Only the CCS consensus statement includes magnesium as a Class IIa recommendation, however no other guidelines strongly recommend its use for the prevention POAF (Kerr & Roy, 2004). Magnesium therapy may be considered in combination with amiodarone and/or B-blocker therapy for those patients deemed at high risk or intolerant to the latter

medications. If magnesium is utilized in the prevention of POAF, doses of 2.5-5 g have been most commonly utilized (Nurozler et al., 1996; Maslow et al., 2000; Kohno et al., 2005). When utilized in combination with B-blockers, clinicians should monitor for hypotension as combination therapy has been shown to significantly increase the risk of hypotension compared to B-blocker therapy alone (24.4% versus 43.5%, p=0.01) (Solomon et al., 2000). Finally, it should be noted that magnesium levels need to be monitored carefully throughout cardiac surgery and postoperatively regardless if magnesium is being utilized as a pharmacological agent for the prophylaxis of POAF.

4. Emerging pharmacologic therapies for the prevention of POAF in cardiac surgery

4.1 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, up-regulate antioxidant enzymes, and enhance nitric oxide bioavailability (Paraskevas, 2008). It is also proposed that they possess direct antiarrhythmic effects mediated through cell membrane stabilization, down-regulation of the renin-angiotensin-aldosterone-system (RAAS), and protection of ischemic myocardium (Howard & Barnes, 2008). They also have been shown to reduce the expression of inflammatory mediators (i.e. interleukin-6 **(**IL-6), interleukin-8 **(**IL-8), tumor necrosis factor- α (TNF-α), C-reactive protein (CRP), cyclooxygenase 2) and decrease the expression of CD11b with consequential decreased adherence to endothelial cells of vein grafts (Chello et al., 2006; Patel et al., 2007). 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.

Many trials have evaluated the effect of statins on the incidence of POAF in cardiac surgery patients. Prospective, randomized trials found an absolute reduction in the incidence of POAF of 14% to 22% with statins compared to placebo or usual care (Chello et al., 2006; Patti et al, 2006; Song et al., 2008; Ji et al., 2009). 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 (Patti et al., 2006). This study enrolled only patients who had no previous history of statin use and these patients could have less risk of pre-existing atherosclerotic disease and subsequently been at lower risk for developing POAF.

Other statin trials in CABG patients are observational, cohort studies with conflicting results of no benefit (Thielmann et al., 2007; Mithani et al., 2009) or a significant reduction in the incidence of POAF (Lertsburapa et al., 2008; Subramaniam et al., Mariscalco et al., Ozaydin et al., 2007; Miceli et al., 2009a; Kinoshita et al., 2010).

One study evaluated the combination of a statin and beta-blocker on the incidence of POAF. Monotherapy with atorvastatin or a beta-blocker reduced the risk of POAF by 61% (OR 0.39; 95% CI 0.18-0.85) and 82% (OR 0.19; 95% CI 0.08-0.44), respectively. However, the combination of atorvastatin plus a beta-blocker performed better by reducing the risk of POAF by 90% (OR 0.10; 95% CI 0.02-0.25) (Patti et al., 2006). The combination of preoperative and postoperative beta-blocker and amiodarone prophylaxis in 40% of patients may have also influenced the positive results in the statin group (Lertsburapa et al., 2008).

A few studies have been conducted to determine the optimal prophylactic dose of statins. Kourlioros et al found that simvastatin 40 mg and atorvastatin 40 mg had the greatest effect on POAF (Kourlioros et al., 2008). Simvastatin 20 mg and atorvastatin 20 mg maintained efficacy compared to control, but no difference was found at 10 mg or 80 mg of either drug. Lertsburapa et al analyzed patients by converting their statin dose to atorvastatin equivalents. Relative statin doses ≥40 mg of atorvastatin resulted in the greatest reduction in POAF by 55% (OR 0.45; 95% CI 0.21-0.99) (Lertsburapa et al., 2008). 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). Mithani et al found in their multivariate analysis that POAF was less common among patients taking higher doses of statins compared to those taking simvastatin < 20 mg/day (28% versus 34%, p=0.03). (Mithani et al., 2009) Comparing statins, only one prospective, observational study found that POAF was less frequent in patients receiving pravastatin compared to atorvastatin (9.5% versus 34.9%, p=0.0257) or no statins (9.5% versus 34.2%, p=0.0025). (Tamura et al., 2010)

A long-term study found that statins' benefit may extend beyond the immediate postoperative period and in outcomes other than POAF. 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) (Dotani et al., 2000). Kaplan-Meier 30 day atrial fibrillation-free survival curves also indicated benefit with statins (Patti et al., 2006; Mariscalco et al., 2007; Ozaydin et al., 2007; Song et al., 2008). 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) (Laikopoulos et al., 2008, Chen et al., 2010). While statins appear to reduce POAF in the short term setting in cardiac surgery patients, a recent meta-analysis found that longer term (≥ 6 months of follow-up) use of statins in cardiac patients was not associated with a significant reduction in AF (OR 0.95; 95% CI 0.88-1.03, p=0.24), however only one of the 22 studies was in CABG patients (Rahimi et al., 2011).

Statins have shown benefit in reducing the risk of POAF, LOS, mortality, 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 and standard beta-blocker therapy is safe, certain statins, such as simvastatin, should only be used in reduced doses with the combination of amiodarone due to risk of myalgias or rhabdomyolysis (FDA Alert 2008). Larger, prospective, randomized control trials are necessary to confirm that statins are effective in reducing the occurrence of POAF in addition to beta-blockers.

4.2 Renin-angiotensin-aldosterone-system (RAAS) modulators

An increasing number of investigations are being conducted to evaluate the association between the RAAS, the inflammatory process, and atrial fibrillation. Interruption of the RAAS by angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers 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 (Boos et al., 2006). 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 (Boos et al., 2006). Histologic evidence exists that persistent and paroxysmal atrial fibrillation leads to altered angiotensin II receptor expression (Erlich et al., 2006; Boos et al., 2006). Genetic polymorphisms in the angiotensinogen gene are also two to three times more likely to have

non-familial atrial fibrillation (Tsai et al., 2004), 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, hypertension, or post MI (Makkar et al., 2009).

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 (Erlich et al., 2006).

Few prospective, controlled studies have been conducted to assess the efficacy of ACEIs or ARBs in reducing the incidence of POAF in cardiac surgery patients (White et al., 2007a; Ozaydin et al., 2008a). 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 beta-blockers preoperatively and 97% of patients in the historical control group were on beta-blockers (Ozaydin et al., 2008a). Despite the high percentage of preoperative beta-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 (White et al., 2007a). 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 beta-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 beta-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 (White et al., 2007a).

Cohort studies conducted to evaluate the risk factors associated with the development of POAF in cardiac surgery patients 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 increases the risk of POAF by 1.7 times (OR 1.69; 95% CI 1.38-2.08; $p<0.001$) (Mathew et al., 2004) while another study in cardiac surgery patients with EF ≤ 50% confirmed this association that both ACEIs decreased the risk of POAF by 73% (OR 0.27, 95% CI 0.12-0.62, p=0.002) and ARBs by 79% (OR 0.21; 95% CI 0.07-0.62, p=0.005) (Ozaydin et al., 2010). Unfortunately, three other cohort studies did not confirm a protective effect of ACEIs or ARBs with no significant reduction in the risk of POAF compared to controls (Coleman et al., 2007; Miceli et al., 2009b; Rader et al., 2010). The largest of these cohort studies, evaluating over 10,000 patients, found that preoperative ACEI doubled the risk of death (OR 2.00, 95% CI 1.17-3.42; p= 0.013) and that preoperative ACEIs were an independent predictor of mortality ($p = 0.04$), postoperative renal dysfunction (p= 0.0002), use of inotropic drugs ($p < 0.0001$), and new onset POAF ($p < 0.0001$). (Miceli et al., 2009b) A

significant reduction may not have been observed in these studies as patients were propensity score matched for common predictors of atrial fibrillation. Thus groups could have been at high risk for the development of POAF (Coleman et al., 2007; Rader et al., 2010).

Further prospective, controlled trials are needed evaluate the impact of ACEIs or ARBs on the development of POAF. These studies will provide more definitive evidence concerning the effectiveness of ACEIs and ARBs in the prevention of POAF following cardiac surgical procedures. If ACIEs or ARBs are used in combination with standard therapies for the prevention of POAF, they must be used with caution or avoided in patients with renal dysfunction or electrolyte abnormalties, specifically hyperkalemia.

4.3 Corticosteroids

Corticosteroids have been traditionally utilized in cardiac surgeries to reduce inflammation in an effort 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 have used various types of intravenous (IV) steroids, doses, and regimens. Two studies used beta-blockers postoperatively in all of their patients found that corticosteroids were superior to placebo with absolute reductions in the incidence of POAF of 18% to 30% (Prasongsukarn et al., 2005; Halonen et al., 2007). However other trials failed to show a significant benefit (Chaney et al., 1998; Halvorsen et al., 2003) 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 (Halonen et al., 2007). The authors further performed a meta-analysis combining results from their trial with two other similar trials for a total of 621 patients (Prasongsukarn et al., 2005; Halvorsen et al., 2003). They found that corticosteroid therapy significantly reduced the risk of POAF by 33% (OR 0.67; 95% CI 0.54-0.84) (Halonen et al., 2007). 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 (Whitlock et al., 2008; Baker et al., 2007b).

At this time, specific dosing of corticosteroids that may confer optimal protection against POAF is unkown. 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 (Baker et al., 2007b). The most recent meta-analysis by Ho et al converted steroid dosing to hydrocortisone equivalence and found a significant reduction of POAF in patients receiving low (< 1,000 mg hydrocortisone equivalent) and intermediate (1,000-10,000 mg hydrocortisone equivalent) doses of steroids (Ho & Tan, 2009).

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 have received

corticosteroids have been shown to have peak white blood cell counts were higher up to 14 days postoperatively, higher blood glucose and larger insulin requirements (Sano et al., 2006), greater risk of wound and infectious complications (Whitlock et al., 2008). Therefore it may be necessary to avoid corticosteroids in patients with uncontrolled hyperglycemia, infection, or edema.

Corticosteroids can target the inflammatory process for the prevention of POAF in patients undergoing cardiac surgery. While some studies found a reduction in the incidence of POAF using corticosteroids as prophylaxis in cardiac surgery patients receiving standard beta-blocker therapy, there is no consensus on which steroid, dose, and duration has the greatest benefit. Only the 2010 European guidelines recommend corticosteroids for prophylaxis of POAF in cardiac surgery patients and include suggested dosing in dexamethasone equivalent for the prevention of POAF with a Class 2B recommendation, stating however that there is risk associated with using them (ESC, 2010). The most relevant risk in hospitalized patients after cardiac surgery includes steroid-induced hyperglycemia or leukocytosis. 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 beta-blockers.

4.4 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 (Kris-Etherton et al., 2002; Korantzopoulos et al., 2006). Calo et al performed a prospective, randomized, open label study in 160 patients assessing the impact of N-3 polyunsaturated fatty acids (PUFA) 2 g/day on the incidence of POAF in cardiac surgery patients (Calo et al., 2005). Approximately 60% of patients in both groups were on preoperative beta-blockers. They found a significant reduction in incidence of POAF (15.2% versus 33.3%, respectively, p=0.013) and mean LOS (7.3 $\pm$ 2.1 days versus 8.2 $\pm$ 2.6 days, respectively, p=0.017) in patients receiving PUFA compared to control patients. Another small prospective, randomized study found that administration of IV PUFA at 100 mg fish oil/kg/day significantly reduced the incidence of POAF compared to control (17.3% vs. 30.6%, $p<0.05$) however this study did not mention the percentage of patients on beta-blocker therapy (Heidt, et al., 2009). Similar to other new agents showing studies with conflicting results for the prevention of POAF in cardiac surgery patients, two small, prospective, randomized, double blind, placebo controlled studies found no benefit using PUFA ~ 2 g/day therapy (Heidarsdottir et al., 2010; Saravanan et al., 2010). Further studies are warranted to determine if omega-3 fatty acids are viable add-on prophylactic therapy or alternative for patients unable to take beta-blockers.

4.5 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 (Korantzopoulos et al., 2005). Vitamin C has been studied in prospective trials for the prevention of POAF in cardiac surgery patients (Carnes et al., 2001; Eslami et al., 2007). Both studies demonstrated significant benefit using vitamin C compared to usual care with an absolute reduction in POAF between 19-22%, but no reduction in mean LOS. Both studies also had substantial rates of both pre- and postoperative beta-blocker utilization. Due to the low cost and relative safety of this drug, larger placebo-controlled trials appear to be warranted.

4.6 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 (Carnes et al., 2007). Two recent studies, which were randomized and placebo-controlled, found conflicting results with NAC in the prophylaxis of POAF (El-Hamamsy et al, 2007; Ozaydin et al., 2008b). 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, did show a significant benefit with NAC compared to placebo (5% versus 21%, p=0.01). After controlling for perioperative beta-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 beta-blocker use while Ozaydin et al also reported substantial postoperative beta-blocker utilization. Two conflicting meta-analyses have been recently published, one that found a statistically significant reduction in POAF with NAC use (36%, 95% CI 2-58%, total n=1,338) and one larger one that did not (OR 0.67, 95% CI 0.37-1.22, p=0.19, total n=1,407) (Baker et al., 2009; Wang et al., 2011). Large, prospective, randomized clinical trials are necessary to determine if NAC is effective in reducing the occurrence of POAF in addition to beta-blockers.

4.7 Sodium nitroprusside

One pilot study evaluated sodium nitroprusside as an agent for POAF prophylaxis compared to placebo (Cavolli et al., 2008). This study demonstrated a significant reduction in the incidence of POAF when compared to placebo (12% versus 36%, p=0.005) and a significant reduction in mean LOS (7.3 $\pm$ 0.7 days versus 9.1 $\pm$ 1.2 days, p<0.001). The authors suggest that nitric oxide (NO) function may be disrupted due to ischemia-reperfusion injury and that administration of NO donors such as nSNP could recover this function. SNP may also reduce POAF by reducing left atrial stretching due to preload and afterload reduction. 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 beta-blockers when compared to the placebo group (68% versus 58% p=0.303). Postoperative beta-blocker use was not addressed. Likewise, patients in this study had relative preserved ejection fractions (60-61%). 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.

4.8 Dofetilide

Dofetilide has been compared to placebo for postoperative atrial tachycardia (POAT) prophylaxis in one study (Serafimovski et al., 2008). 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 beta-blockers was not reported, the authors conclude that the dofetilide group experienced a significant decrease in POAT independent of concomitant beta-blocker use based on multivariate logistic regression accounting for preoperative beta-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 POAF prophylaxis. Like sotalol,

it also carries a greater risk of Torsades 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 beta-blockers but should first be compared to other traditional class III antiarrhythmics such as amiodarone or sotalol in head to head trials.

4.9 Levosimendan

Levosimendan is an intravenous calcium sensitizer agent that is used for the treatment of acute decompensated heart failure. It increases myocardial contraction without increasing myocardial oxygen consumption and produces coronary and peripheral vasodilation (Lilleberg et al., 1998). While the drug is not approved and will not be pursued for FDA approval in the US, it has been shown in one study to significantly reduce the incidence of POAF and increase stroke volume in patients with ejection fraction $\leq$30% when compared to milrinone (50% for milrinone, 5% for levosimendan started post anesthesia, and 35% for levosimendan started after cross clamp release, $p<0.01$) (De Hert et al., 2008). Very few patients in this study, however, were taking preoperative beta-blockers (~13-14%) and all patients received dobutamine after the release of the cross clamp.

5. Unestablished pharmacologic therapies for the prevention of POAF in cardiac surgery

5.1 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 for POAF prophylaxis (Bradley et al., 2005; Dunning et al., 2006; Fuster et al., 2006; Eagle et al., 2004). 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 (Bradley et al., 2005). 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 (Wijeysundera et al., 2003). However, two other meta-analyses found a non-significant reduction (Andrews et al., 1991) and even an increase in the risk of POAF (Woodend et al., 1998) with the CCBs. Because of this and the risk of atrioventricular block and low-output syndrome, especially in combination with beta-blockers, 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 (Bradley et al., 2005; Eagle et al., 2004).

5.2 Thiazolidinediones

Thiazolidinediones (TZDs) may affect POAF through pleiotropic anti-inflammatory activity against macrophage activation and pro-inflammatory cytokines (Consoli & Devangelio, 2005; Ricote et al., 1998). One study evaluated a nested cohort study of diabetic patients from the AFIST I, II, and III trials (Giri et al., 2001; White et al., 2003; White et al., 2007a) assessed whether the use of TZDs affected the incidence of POAF in diabetic patients who were also receiving beta- blockers and amiodarone (Anglade et al., 2007). In addition to substantial pre- and postoperative beta-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 beta-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%, $p<0.05$). 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 (Lertsburapa K, 2008). At this time, TZDs can not be recommended as an option for POAF prophylaxis, either alone or in combination with beta-blockers.

5.3 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 (Klemperer et al., 1996). The mechanism by which T3 may prevent POAF is unknown (Reichert & Verzino, 2001). Interestingly, it has been shown that POAF is more common in patients with subclinical hypothyroidism when compared to those with normal thyroid function, after adjustments for other variables (Park et al., 2009). One demonstrated that intravenous administration of T3 starting at the time of cross clamp removal significantly decreases the incidence of POAF when compared to placebo (24% versus 46%, $p=0.009$) (Klemperer et al., 1996). 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 (Klemperer et al., 1995). The authors previously reported data from this same study but included those patients with a history of preoperative atrial fibrillation (Klemperer et al., 1995). 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 beta-blocker use but suggest that because the study population was more ill (ejection fraction <40%), beta-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 (Bradley et al., 2005). Until more data becomes available supporting its for POAF prophylaxis, it should not be routinely utilized.

6. Non-pharmacologic strategies for the prevention of POAF in cardiac surgery

6.1 Pacing

The use of right atrial, left atrial, bi-atrial and pacing of the Bachman's bundle all have been evaluated in their merit in reducing post-operative supraventricular arrhythmias. The mechanism of atrial fibrillation is in part believed to be related to changes in the substrate on a temporary basis which causes lengthening of the P-R interval thereby allowing re-entrant POAF (Fan et al., 2003). There is evidence that bi-atrial pacing is beneficial especially in the age group over 70 (Gerstenfeld et al., 2001). While bi-atrial pacing has demonstrated some success it is noted the right atrial pacing alone is less favorable (Chung et al., 1996). Pacing thresholds and stability of the pacing wire has become problematic and alternate sources of pacing locations have been sought out (Goette et al., 2002). Bachman's bundle, a thick fibrous strip of muscle at the roof of both atria that crosses the intra-atrial septum has been demonstrated to have low pacing thresholds for at least five days post-operatively. This site may reduce intra-atrial conduction times thus reducing POAF (Goette et al., 2002).

In a meta-analysis of 10 clinical trials it was demonstrated that atrial pacing at the right atrium, left atrium or Bachman's bundle produced a decrease in atrial fibrillation (Fan et al., 2003). These 10 studies are limited by multiple pacing protocols, including using complex algorithms, fixed pacing and flexible algorithms. Eight of these studies demonstrated that bi-atrial pacing reduced the odds of POAF by 54% (OR=0.46; 95% CI 0.3-0.71). There was a significant lack of use of beta-adrenergic blocking drugs used in the post-operative phase in the meta-analysis at 56%. In a small group of patients (n=80) who underwent valvular surgery it was found that bi-atrial synchronous pacing for 72 hours decreased atrial fibrillation from 45% in the control group to 20% in the paced group (p=0.02) (Debrunner et al., 2004). It is noted that only 30% of this small group were exposed to pre-operative beta-adrenergic blockade, and post-operative use was not collected.

Pacing of the atria is not without risk. In a randomized trial of 100 patients it was found that atrial fibrillation occurred in 27.5% of the paced patients and 28.6% of the control group (Chung, 2003). There was an increase in atrial ectopy (10 fold increase) in the group of patients whom developed atrial fibrillation (Chung, 2003). It was hypothesized that inconsistent pacing in the atria, under sensing and intermittent loss of capture were factors in the increase in ectopy (Chung, 2003). A sub-analysis of patients paced at a lower rate (80 bpm) and use of an algorithm that maintained the atrial rate 50 ms above the intrinsic rate, demonstrated no difference in atrial fibrillation rates (Chung, 2003).

The most recent 2010 European AF guidelines recommend that biatrial pacing should be considered for prophylaxis (Class 2B recommendation based on Level A evidence) (ESC, 2010). Earlier publication in 2006 by EACTS for the guidelines for POAF after cardiothoracic surgery in 2006 (Grade A recommendation based on Level 1B studies) and in 2005 by the American College of Chest Physicians (ACCP) (Strength: B, Evidence: good, Net Benefit: small/weak) both similarly recommend biatrial pacing for prophylaxis (Dunning et al., 2006; Maisel & Epstein, 2005). (Table 1) Specifically, the 2005 ACCP guideline specifically recommends not using unilateral pacing of the right or left atrium. (Strength: I, Evidence: fair, Net Benefit: small/weak) (Maisel & Epstein, 2005). Furthermore, the 2006 EACTS guidelines recommend that temporary pacing should be used in high risk patients receiving beta-blockers and amiodarone for prophylaxis as protection from complications of bradycardia (Grade A recommendation based of Level 1B studies). The CCS guideline also recommends considering atrial pacing with or without a ventricular lead in patients with symptomatic bradycardia (Class 2A recommendation based on Level A evidence) and those patients who are not on a beta-blocker before surgery (Class 2A recommendation based on Level B evidence) (Mitchell et al., 2005a; Kerr & Roy, 2004). Last, the CCS guidelines strongly recommend placing temporary ventricular epicardial pacing electrode wires at the time of surgery to allow for backup pacing as necessary (Class 1 recommendation based on Level C evidence) (Mitchell et al., 2005a; Kerr & Roy, 2004).

6.2 Posterior pericardiotomy

The pathophysiology of posterior pericardiotomy is based upon adequate drainage of the pericardial space thereby reducing pericardial effusion (Biancari, 2010). Only the earlier European guidelines do include posterior pericardiotomy as a non-pharmacologic option for the prevention of POAF (Grade B recommendation based on Level 1B studies) (Dunning et al., 2006). A recent meta-analysis evaluating 763 patients found that patients who had a posterior pericardiotomy significantly reduced POAF (10.8% versus 28.1%, p=0.003; OR. 0.33, 95% CI 0.16–0.69) and early (6.9% versus 46.2% p<.0001) or late (0% versus 11.3%,

p=0.0001) pleural effusion (Biancari & Mahar, 2010). The authors noted several limitations to the studies favoring pericardiotomy, including no data regarding hemodynamic instability, re-operation for bleeding and use of drugs for prevention of POAF (Biancari & Mahar, 2010). Posterior pericardiotomy however is not risk free. Potential risks include cardiac herniation as well as compromise of grafts protruding thought the pericardiotomy (Biancari & Mahar, 2010).

6.3 Coronary bypass surgery without the use of cardiopulmonary bypass ("Off-pump" CABG)

The introduction of cardiac surgery without the use of cardiopulmonary bypass, also referred to as "off-pump", has been hypothesized to lower the incidence of POAF. The multiple mechanisms hypothesized to cause POAF may all be avoided when coronary bypass surgery is completed without the use of the cardiopulmonary bypass circuit. Salamon et al evaluated a series of over 2500 patients with 252 undergoing "off-pump" coronary bypass surgery (Salamon et al., 2003). Patient on cardiopulmonary bypass had higher rates of atrial fibrillation and concluded that avoiding cardiopulmonary bypass did not aid in the reduction of AF. Another retrospective analysis by Enc and colleagues in 670 patients undergoing conventional compared to "off-pump" coronary bypass surgery, found a lower, but non-significant reduction in POAF respectively (16.1% versus 14.6%) (Enc et al., 2004).

Elimination of the use of cardiopulmonary bypass in cardiac surgery has shown inconsistent results from meta-analyses and studies. Only the European EACTS 2006 guidelines supports its use as a non-pharmacologic option are the 2006 EACTS guidelines and include earlier meta-analysis that show conflicting results (Dunning et al., 2006). Focus for the prevention of POAF in cardiac surgery patients should focus on the use more standard prophylactic regimens including beta-blockers, rather than explicit avoidance of cardiopulmonary bypass.

6.4 Pericardial fat pad

Two other novel non-pharmacologic options that have been studied include preservation of pericardial fat pad and regulation of body temperature during cardiac surgery which targets disruption of AV node and inflammation, respectively. The anterior fat pad is commonly disrupted to provide clear field of view while applying the cross clamp during cardiac surgery. The anterior fat pad is known to possess parasympathetic ganglia as well as vagal pathways (Singh et al., 1996). The fat pads located at the superior vena cava-atrial junction contain post ganglionic fibers that lead to the sino-atrial node (Carlson et al., 1992). The fat pads located at the pulmonary vein-left atrium contain post ganglionic fibers that innervate the atrio-ventricular node (Quan et al., 2001). These fat pads are analogous to dog physiology and has been determined that ablation of these fibers in dogs reduces susceptibility of POAF. In a study of 55 patients where the fat pad was preserved, a significant reduction of POAF was observed (Cummings et al., 2004). A significant limitation of this research includes a small sample size and not accounting for the use of beta-adrenergic blocking drugs. Secondarily the rate of atrial fibrillation in "off-pump" cardiac surgery remains a significant problem despite no manipulation of the epicardial fat pads (Salamon et al., 2003).

6.5 Regulation of body temperature during surgery

The other novel non-pharmacologic strategy is to regulate body temperature to limit systemic effects of the inflammatory cascade during cardiac surgery. Adams and colleagues

identified that hypothermia decreases sympathetic activation which lowers plasma norepinephrine levels and neuropeptide Y levels (Adams et al., 2000). A study randomized patients into two groups including mild hypothermia (34° C) and moderate hypothermia (28° C) and found no difference in the incidence of POAF between the groups, thus did not validate this pathophysiologic basis of POAF (Adams et al., 2000). The study was completed without benefit of knowledge regarding use of beta blockers or other adjunct measures to prevent POAF which could influence the outcome of that study.. It should be noted that POAF is still common in beating heart surgery with normothermia, therefore negating the use of hypothermia as a valid tool in prevention of POAF.

6.6 Maze procedure during open-heart surgery

The surgical maze procedure, or Cox-maze procedure, uses surgical incisions in the atria to form scar tissue to interrupt possible macroreentrant circuits (Cox et al., 1991). Alternative energy sources including radiofrequency or cryothermia have been incorporated to create lesions blocking atrial conduction without surgical incision into the atria. These procedures can be effective in restoring sinus rhythm, however when it is combined with other open heart operations to treat chronic AF, operative morbidity is consistently increased (Banach, et al., 2010). It is usually only performed on patients needing open-heart surgery for other issues, such as valve replacement or repair or CABG. The Canadian and most recent European guidelines both mention surgical ablation, however it should only be considered in patients with symptomatic AF already undergoing cardiac surgery (Kerr & Roy, 2004; ESC, 2010). The Canadian guidelines additionally mention that it should be considered in patients with previous AF who are undergoing mitral valve surgery, who may be at higher risk of POAF (Kerr & Roy, 2004)

7. Conclusion

For the prevention of postoperative atrial fibrillation in patients undergoing cardiac surgery, pharmacologic prophylaxis with beta-blockers and amiodarone are widely utilized. Evidence based guidelines also support the use of sotalol, magnesium, and atrial pacing. While these agents reduce the incidence of POAF, they do not eliminate it. Thus, there is a need for additional effective therapies. Other strategies that may be beneficial for prophylaxis include dofetilide, renin-angiotensin-aldosterone-system modulators, statins, corticosteroids, omega-3 fatty acids, ascorbic acid, N-acetylcysteine, sodium nitroprusside, levosimendan or intraoperative maze procedure in symptomatic AF patients undergoing cardiac surgery. For most of these strategies, there is a need for additional large scale, adequately powered, clinical studies to determine the benefit before they can be considered for routine use. Identification of high risk patients undergoing cardiac surgery and use of appropriate pharmacologic and non-pharmacologic therapies may further reduce the incidence of POAF and lead to improvements in the overall morbidity and burden to the health care system.

8. References

Acikel, S.; Bozbas, H.; Gultekin, B.; Aydinalp, A.; Saritas, B.; Bal, U.; Yildirir, A.; Muderrisoglu, H.; Sezgin, A. & Ozin, B. (2008). Comparison of efficacy of

metoprolol and carvedilol for preventing atrial fibrillation after coronary bypass surgery. *International Journal of Cardiology*, Vol.126, pp. 108-113, ISSN 0167-5273

Adams, D.; Heyer, E.; Simon, A.; Delphin, E.; Rose, E.; Oz, M.; McMahon, D. & Sun, L. (2000). Incidence of atrial fibrillation after mild or moderate hypothermic cardiopulmonary bypass. *Critical Care Medicine*, Vol.28, No.2, pp. 309-311, ISSN 0090-3493

Alghamdi, A.; Al-Radi, O. & Latter, D. (2005). Intravenous magnesium for prevention of atrial fibrillation after coronary artery bypass surgery a systemic review and meta-analysis. *Journal of Cardiac Surgery,* Vol.20, pp. 293-299, ISSN 1540-8191

Ali, I.; Sanalla, A. & Clark, V. (1997). Beta-blocker effects on post-operative atrial fibrillation. European Journal of Cardiothoracic Surgery, Vol.11, pp. 1154-115-7, ISSN 1010-7940

Andrews, T.; Reimold, S.; Berlin, J. & Antman, E. (1991). Prevention of supraventricular arrhythmias after coronary artery bypass surgery. *Circulation*, Vol.84, Suppl. III, pp. 236-244, ISSN 0009-7322

Anglade, M.; Kluger, J.; White, M.; Aberle, J. & Coleman, C. (2007). Thiazolidinedione use and post-operative atrial fibrillation a US nested case-control study. *Current Medical Research and Opinion*, Vol.23, No.11, pp. 2849-2855, ISSN 0300-7995

Aranski, S.; Shaw, D.; Adams, D.; Rizzo, R.; Couper, G.; VanderVliet, M.; Collins, J.; Cohn, L. & Burstin, H. (1996) Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. *Circulation,* Vol.94, pp. 390-397, ISSN 0009-7322

Auer, J.; Weber, T.; Berent, R. Puschmann, R.; Hartl, P.; Ng, C.; Schwarz, C.; Lehner, E.; Strasser, U.; Lassnig, E.; Lamm, G. & Eber, B. (2004a). A comparison between oral antiarrhythmic drugs in the prevention of atrial fibrillation after cardiac surgery: the pilot study of prevention of postoperative atrial fibrillation (SPPAF), a randomized, placebo-controlled trial. *The American Heart Journal*, Vol.147, pp. 636-643, ISSN 0002-8703

Auer, J.; Weber, T.; Berent, R.; Lamm, G.; Ng, C.; Hartl, P; Strasser, U. & Eber, B. (2004b). Use of Hmg-coenzyme a-reductase inhibitors (statins) and risk reduction of atrial fibrillation after cardiac surgery: results of the SPPAF study: a randomized placebo-controlled trial. *European Heart Journal*, Vol.25, Suppl.353, Abstract 2045, ISSN 1522-9645

Bagshaw, S.; Galbraith, P.; Mitchell, L.; Sauve, R.; Exner, D. & Ghali, W. (2006). Prophylactic amiodarone for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. *The Annals of Thoracic Surgery,* Vol.82, pp. 1927-1937, ISSN 0003-4975

Banach, M.; Kourliouros, A.; Reinhart, K.; Benussi, S.; Mikhailidis, D.; Jahangiri, M.; Baker, W.; Galanti, A.; Rysz, J.;Camm, J.; White, C. & Alfieri, O. (2010). Postoperative atrial fibrillation - what do we really know? *Current Vascular Pharmacology*, Vol.8, No. 4, pp. 553-572, ISSN 1875-6212

Barnes, B.; Kirkland, E.; Howard, P.; Grauer, D.; Gorton, M.; Kramer, J.; Muehlebach, G. & Reed, W. (2006). Risk-stratified evaluation of amiodarone to prevent atrial fibrillation after cardiac surgery. *The Annals of Thoracic Surgery*, Vol.82, pp. 1332-1337, ISSN 0003-4975

Baker, W. & White, C. (2007a). Post-cardiothoracic surgery atrial fibrillation: a review of preventive strategies. *The Annals of Pharmacotherapy*, Vol.41, pp.587-598, ISSN 1060-0280

Baker, W.; White, C.; Kluger, J.; Denowitz, A.; Konecny, C. & Coleman, C. (2007b). Effect of perioperative corticosteroid use on the incidence of postcardiothoracic surgery atrial fibrillation and length of stay. *Heart Rhythm*, Vol.4, pp.461-468, ISSN 1547-5271

Baker, W.; Anglade, M.; Baker, E.; White, C.; Kluger, J. & Coleman, C. (2009). Use of N-acetylcysteine to reduce post-cardiothoracic surgery complications: a meta-analysis. *European Journal of Cardiothoracic Surgery,* Vol.35, pp. 521-527, ISSN 1873-734X

Barnes, B.; Kirkland, E.; Howard, P.; Grauer, D.; Gorton, M.; Kramer, J.; Muehlebach, G. & Reed W. (2006). Risk-stratified evaluation of amiodarone to prevent atrial fibrillation after cardiac surgery. *Annals of Thoracic Surgery*, Vol.82, pp. 1332-1337, ISSN 0003-4975

Bert, A.; Reinert, S. & Singh, A. (2001). A beta-blocker, not magnesium, is effective prophylaxis for atrial tachyarrhythmias after coronary artery bypass graft surgery. *Journal of Cardiothoracic and Vascular Anesthesia*, Vol.15, No.2, pp. 204-209, ISSN 1532-8422

Biancari, F. & *Mahar, M.* (2010). Meta-analysis of randomized trials on the efficacay of posterior pericardiotomy in preventing atrial fiibrillation after coronary bypass surgery. *The Journal of Thoracic and Cardiovascular Surgery*, Vol.139, pp. 1158-1161, ISSN 0022-5223

Boos, C.; Anderson, R. & Lip, G. (2006). Is atrial fibrillation an inflammatory disorder? *European Heart Journal*, Vol.27, pp. 136-149, ISSN 1522-9645

Bradley, D.; Creswell, L.; Hogue, C.; Epstein, A.; Prystowsky, E. & Daoud, E. (2005). American college of chest physicians guidelines for the prevention and management of Postoperative atrial fibrillation after cardiac surgery. *Chest*, Vol.128, No.2, pp. 39S-47S, ISSN 1931-3543

Bruins, P.; Velthuis, H.; Yazdanbakhsh, A.; Jansen, P.; van Hardevelt, F.; de Beaumont, E.; Wildevuur, C.; Eijsman, L,.; Trouwborst, A. & Hack, C. (1997). Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation*, Vol.96, No.10, pp. 3542-3548, ISSN 0009-7322

Buckley, M.; Nolan, P.; Slack, M.; Tisdale, J.; Hilleman, D. & Copeland, J. (2007). Amiodarone prophylaxis for atrial fibrillation after cardiac surgery: meta-analysis of dose response and timing of initiation. *Pharmacotherapy*, Vol.27, pp. 360-368, ISSN 1060-0280

Budeus, M.; Hennersdorf, M.; Perings, S.; Rohlen, S.; Schnitzler, S.; Felix, O.; Reimert, K.; Feindt, P.; Gams, E.; Lehmann, N.; Weineke, H.; Sak, S.; Erbel, R. & Perings, C. (2006). Amiodarone prophylaxis for atrial fibrillation of high-risk patients after coronary bypass grafting: a prospective, double-blinded, placebo-controlled, randomized study. *European Heart Journal* Vol.27, pp.1584-1591, ISSN 1522-9645

Burgess, D.; Kilborn, M. & Keech, A. (2006). Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. *European Heart Journal,* Vol.27, pp. 2846-2857, ISSN 1522-9645

Cagli, K.; Ozeke, O.; Ergun, K.; Ergun, K.; Budak, B.; Demirtas, E.; Birincioglu, C. & Pac, M. (2006). Effect of low-dose amiodarone and magnesium combination on atrial fibrillation after coronary surgery. *Journal of Cardiac Surgery*, Vol.21, pp. 458-464, ISSN 1540-8191

Calo, L.; Bianconi, L.; Colivicchi, F.; Lamberti, F.; Loricchio, M.; de Ruvo, E.; Meo, A.; Pandozi, C.; Staibano, M. & Santini, M. (2005). N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *Journal of the American College of Cardiology*, Vol.45, pp. 1723-1728, ISSN 1936-8798

Canbaz, S.; Erbas, H.; Huseyin, S. & Duran, E. (2008). The role of inflammation in atrial fibrillation following open heart surgery. *The Journal of International Medical Research,* Vol.36, pp. 1070-1077, ISSN 1473-2300

Carlson, M.; Geha, A.; Hsu, J.; Martin, P.; Levy, M.; Jacobs, G. & Waldo, A. (1992). Selective stimulation in of parasympathetic nerve fibers in the human sinoatrial node. *Circulation*, Vol.85, pp. 1311-1317, ISSN 0009-7322

Carnes, C.; Ching, M.; Nakayama, T.; Nakayama, H.; Baliga, R.; Piao, S.; Kanderian, A.; Pavia, S.; Hamlin, R.; McCarthy, P.; Bauer, J. & Van Wagoner, D. (2001). Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. *Circulation Research*, Vol.89, pp. e32-38, ISSN 0009-7330

Carnes, C.; Janssen, P.; Ruehr, M.; Nakayama, H.; Nakayama, T.; Haase, H.; Bauer, J.; Chung, M.; Fearon, I.; Gillinov, A.; Hamlin, R. & Van Wagoner, D. (2007). Atrial glutathione content, calcium current, and contractility. *The Journal of Biological Chemistry*, Vol.282, pp. 28063-28073, ISSN 0021-9258

Caspie, J.; Rudis, E.; Bar, I.; Safadi, T. & Saute, M. (1995). Effects of magnesium on myocardial function after coronary artery bypass grafting. *The Annals of Thoracic Surgery*. Vol.59, pp. 942-947, ISSN 0003-4975

Cavolli, R.; Kaya, K.; Aslan, A.; Emiroglu, O.; Erturk, S.; Korkmaz, O.; Oguz, M.; Tasoz, R. & Ozyurda, U. (2008). Does sodium nitroprusside decrease the incidence of atrial fibrillation after myocardial revascularization? A pilot study. *Circulation*, Col.118, pp.476-481, ISSN 0009-7322

Chaney, M.; Nikolov, M.; Blakeman, B.; Bakhos, M. & Slogoff, S. (1998). Pulmonary effects of methylprednisolone in patients undergoing coronary artery bypass grafting and early tracheal extubation. *Anesthesia and Analgesia*, Vol.87, pp. 27-33, ISSN 0003-2999

Chen, W.; Krishnan G.; Sood, N.; Kluger, J. & Coleman, C. (2010). Effect of statins on atrial fibrillation after cardiac surgery: a duration- and dose-response meta-analysis. *The Journal of Thoracic and Cardiovascular Surgery*, Vol.140, pp. 364-72, ISSN 0022-5223

Chung, M.; Augostini, R.; Asher, C.; Pool, D.; Grady, T.; Zikri, M.; Buehner, S.; Weinstock, M. & McCarthy, P. (1996). A randomized, controlled study of atrial overdrive pacing for the prevention of atrial fibrillation after coronary bypass surgery [Abstract]. *Circulation*, Vol.94, Supplement I, pp. I-90, ISSN 0009-7322

Chung, M. (2003). Proarrhythmic effects of post-operative pacing intended to prevent atrial fibrillation: evidence from a clinical trial. *Cardiac Electrophysiology Review*, Vol.7, No. 2, pp. 143-146, ISSN 1385-2264

Coleman, C.; Makanji, S.; Kluger, J. & White, C. (2007). Effect of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on the frequency of post-cardiothoracic surgery atrial fibrillation. *The Annals of Pharmacotherapy*, Vol.41, pp. 433-437, ISSN 1060-0280

Colquhoun, I.; Berg, G.; El-Fiky, M.; Hurle, A.; Fell, G. & Wheatley, D. (1993). Arrhythmia prophylaxis after coronary artery surgery. *European Journal of Cardiothoracic Surgery,* Vol.7, pp. 520-523, ISSN 1010-7940

Consoli, A. & Devangelio, E. (2005). Thiazolidinediones and inflammation. *Lupus*, Vol.14, No.9, pp. 794-797, ISSN 0961-2033

Cox, J.; Schuessler, R.; D'Agostino, H.; Stone, C.; Chang, B.; Cain, M.; Corr, P. & Boineau, J. (1991). The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *Journal of Thoracic and Cardiovascular Surgery, Vol.*101, No.4, pp. 569–83, ISSN 0022-5223

Crystal, E.; Connolly, S.; Sleik, K.; Ginger, T.; & Yusuf, S. (2002). Interventions on prevention of postoperative atrial fibrillation in patients undergoing heart surgery: a meta-analysis. *Circulation*, Vol.106, pp. 75-80, ISSN 0009-7322

Cummings, J.; Akhrass, R.; Dery, M.; Biblo, L. & Quan, K. (2004). Preservation of the anterior fat pad paradoxically decreases the incidence of post-operative atrial fibrillation in humans. *Journal of American College of Cardiology*, Vol.43, No.6, pp. 994-1000, ISSN 1936-8798

Cybulsky, I.; Connolly, S.; Lamy, A.; Roberts, R.; O'brien, B.; Carroll, S.; Crystal, E.; Thorpe, K. & Gent M. (2000). Beta-blocker length of stay study (BLOSS): a randomized trial of metoprolol for reduction of post-operative length of stay. *The Canadian Journal of Cardiology*, Vol.16, Abstract, pp. 238F, ISSN 0828-282X

Daoud, E.; Strickberger, S.; Man, K.; Goyal, R.; Deeb, G.; Bolling, S.; Pagani, F.; Bitar, C.; Meissner, M.; & Morady, F. (1997). Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. *The New England Journal of Medicine*, Vol.337, pp. 1785-1791, ISSN 0028-4793

Debrunner, M.; Naegeli, B.; Genoni, M.; Turina, M. & Bertel, O. (2004). Prevention of atrial fibrillation after cardiac valvular surgery by epicardial, biatrial synchronous pacing. *European Journal of Cardio-Thoracic Surgery, Vol.*25, pp. 16-20, ISSN 1010-7940

DeHert, S.; Lorsomradee, S.; Eede, H.; Cromheecke, S. & Van der Linden, P. A randomized trial evaluating different modalities of levosimendan administration in cardiac surgery patients with myocardial dysfunction. (2008). *Journal of Cardiothoracic and Vascular Anesthesia* Vol.22, No.5, pp. 699-705, ISSN 1532-8422

Dotani, M.; Elnicki, D.; Jain, A. & Gibson, C. (2000). Effect of preoperative statin therapy and cardiac outcomes after coronary artery bypass grafting. *The American Journal of Cardiology*, Vol.86, pp. 1128-1130, ISSN 1879-1913

Dunning, J.; Treasure, T.; Versteegh, M.; Samer, A. & the EACTS Audit and Guidelines Committee. (2006.) Guidelines on the prevention and management of de novo atrial fibrillation after cardiac and thoracic surgery. *European Journal of Cardiothoracic Surgery*, Vol.30, pp. 852-872, ISSN 1010-7940

Eagle, K.; Guyton, R.; Davidoff, R.; Edwards, F.; Ewy, G.; Gardner, T.; Hart, J.; Herrmann, H.; Hillis, L.; Hutter, A.; Lytle, B.; Marlow, R.; Nugent, W.; Orszulak, T.; Antman, E.; Smith, S.; Alpert, J.; Anderson, J.; Faxon, D.; Fuster, V.; Gibbons, R.; Gregoratos, G.; Halperin, J.; Hiratzka, L.; Hunt, S.; Jacobs, A. & Ornato, J. (2004). ACC/AHA 2004 Guideline update for coronary artery bypass graft surgery: summary article. A report of the American college of cardiology/American heart association task force on practice guidelines (Committee to update the 1999 guidelines for coronary artery bypass graft surgery). *Journal of the American College of Cardiology*, Vol.44, pp. e213-310, ISSN 1936-8798

Echahidi, N.; Pibarot, P.; O'Hara, G. & Mathieu, P. (2008). Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. *Journal of American College of Cardiology*, Vol.51, No.8, pp. 793-801, ISSN 1936-8798

Elahi, M.; Flatman, S. & Matata, B. (2008). Tracing the origins of postoperative atrial fibrillation: the concept ofoxidative stress-mediated myocardial injury phenomenon. *European Journal of Cardiovascular Prevention and Rehabilitation*, Vol.15, pp.735-741, ISSN 1741-8275

El-Hamamsy, I.; Stevens, L.; Carrier, M.; Pellerin, M.; Bouchard, D.; Demers, P.; Cartier, R.; Page, P. & Perrault, L. (2007). Effect of intravenous N-acetylcysteine on outcomes after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial. *Journal of Thoracic and Cardiovascular Surgery*, Vol.133, No.1, pp. 7-12, ISSN 0022-5223

Enc, Y.; Ketenci, B.; Ozsoy, D.; Camur, G.; Kayacioglu, I.; Terzi, S. & Cicek, S. (2004). Atrial fibrillation after surgical revascularization: is there any difference between on-pump and off-pump? *European Journal of Cardiothoracic Surgery*, Vol.26, pp. 1129-1133, ISSN 1010-7940

Erlich, J.; Hohnloser, S. & Nattel, S. (2006). Role of angiotensin system and effects of its inhibition in atrial fibrillation: clinical and experimental evidence. *European Heart Journal*, Vol.27, pp. 512-518, ISSN 1522-9645

Eslami, M.; Badkoubeh, R.; Mousavi, M.; Radmehr, H.; Salehi, M.; Tavakoli, N. & Avadi, M. (2007). Oral ascorbic acid in combination with beta-blockers. *Texas Heart Institute Journal*, Vol.34, pp. 268-274, ISSN 0730-2347

European Society of Cardiology. (2010). Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *European Heart Journal,* Vol.31, No.19, pp. 2369-2429, ISSN 1522-9645

Evrard, P.; Gonzalez, M.; Jamar, J.; et al. (2000). Prophylaxis of supraventricular arrhythmias after coronary artery bypass grafting with low-dose sotalol. *The Annals of Thoracic Surgery,* Vol.70, pp. 151-156, ISSN 0003-4975

Fan, K.; Lee, K. & Lau, CP. (2003). Mechanisms of biatrial pacing for prevention of postoperative atrial fibrillation-insights from a clinical trail. *Cardiac Electrophysiology Review*, Vol.7, No.2, pp. 147-153, ISSN 1573-725X

FDA Alert 8/8/2008. Information for Healthcare Professionals - Simvastatin (marketed as Zocor and generics), Ezetimibe/Simvastatin (marketed as Vytorin), Niacin extended-release /Simvastatin (marketed as Simcor), used with Amiodarone (Cordarone, Pacerone) Available from

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm118869.htm.

Ferguson, J.; Coombs, L. & Peterson, E. (2002). Society of thoracic surgeons national adult cardiac surgery database: pre-operative beta-blocker use and mortality and morbidity following CABG surgery in north america. *Journal of the American Medical Association*, Vol.287, pp. 2221-2227, ISSN 0098-7484

Fuster, V.; Ryden, L.; Cannom, D.; Crijns, H.; Curtis, A.; Crijns, H.; Curtis, A.; Ellenbogen, K.; Halperin, J.; Le Heuzey, J.; Kay, G.; Lowe, J.; Olsson, S.; Prystowsky, E.; Tamargo, J.; Wann, S.; Smith, S.; Jacobs, A.; Adams, C.; Anderson, J.; Antman, E.; Halperin, J.; Hunt, S.; Nishimura, R.; Ornato, J.; Page, R.; Riegel, B.; Priori, S.; Blanc, J.; Budaj, A.; Camm, A.; Dean, V.; Deckers, J.; Despres, C.; Dickstein, K.; Lekakis, J.; McGregor, K.; Metra, M.; Morais, J,.; Osterspey, A.; Tamargo, J. & Zamorano, J. (2006). ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation – executive summary: a report of the American college of cardiology/American heart association task force on practice guidelines and the European society of cardiology committee for practice guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): developed in collaboration with the European heart rhythm society. *Circulation,* Vol.114, pp.700-752, ISSN 0009-7322

Gerstenfeld, E.; Khoo, M.; Cook, J.; Lancey, R.; Rofino, K.; Vander Salm, T. & Mittleman, R. (2001). Effectiveness of bi-atrial pacing for reducing atrial fibrillation after coronary artery bypass graft surgery. *Journal of Interventional Cardiac Electrophysiology*, Vol.5, No.3, pp. 275-283, ISSN 1572-8595

Gillespie, E.; White, C.; Kluger, J.; Rancourt, J.; Gallagher, R. & Coleman, C.(2006). Cost-effectiveness of amiodarone for prophylaxis of atrial fibrillation after cardiothoracic surgery. *Pharmacotherapy*, Vol.26, pp. 499-504, ISSN 0277-0008

Giri, S.; White, C.; Dunn, A.; Felton, K.; Freeman-Bosco, L.; Reddy, P.; Tsikouris, J.; Wilcox, H. & Kluger, J. (2001). Oral amiodarone for the prevention of atrial fibrillation after open heart surgery, the Atrial Fibrillation Suppression Trial (AFIST): a randomized placebo-controlled trial. *The Lancet*, Vol.357, pp. 830-836, ISSN 0099-5355

Goette, A.; Mittag, J.; Friedl, A.; Busk, H.; Jepsen, M.; Hartung, W.; Huth, C. & Klein H. (2002). Pacing of Bachmann's bundle after coronary artery bypass grafting. *Pacing and Clinical Electrophysiology: PACE*, Vol.25, No.7, pp. 1072-1078, ISSN 1540-8159

Griendling, K.; Sorescu, D. & Ushio Fukai, M. (2000). NAD(P)H oxidase: role in cardiovascular biology and disease. *Circulation Research*, Vol.86, pp. 494-501, ISSN 0009-7330

Gaudino, M.; Andreotti, F.; Zamparelli, R.; Di Castelnuovo, A.; Nasso, G.; Burzotta, F.; Iacoviello, L.; Donati, M.; Schiavello, R.; Maseri, A. & Possati, G. (2003). The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? *Circulation* 2003;Vol.108, Suppl 1:II, pp. 195-199, ISSN 0009-7322

Guarnieri, T.; Nolan, S.; Gottlieb, S.; Dudeck, A. & Lowry, D. (1999). Intravenous amiodarone for the prevention of atrial fibrillation after open heart surgery: the amiodarone reduction in coronary heart (ARCH) trial. *Journal of the American College of Cardiology*, Vol.34, pp. 343-347, ISSN 1936-8798

Haan, C. & Geraci, S. (2002). Role of amiodarone in reducing atrial fibrillation after cardiac surgery in adults. *The Annals of Thoracic Surgery*, Vol.73, pp. 1665-1669, ISSN 0003-4975

Haghjoo, M.; Saravi, M.; Hashemi, M.; Hosseini, S.; Givtaj, N.; Ghafarinejad, M.; Khamoushi, J.; Emkanjoo, Z.; Fazelifar, A.; Alizadeh, A. & Sadr-Ameli, M. (2007). Optimal beta-blocker for prevention of atrial fibrillation after on-pump coronary artery bypass graft surgery. *Heart Rhythm*, Vol.4, pp. 1170-1174, ISSN 1547-5271

Halonen, J.; Hakala, T.; Auvinen, T., Karjalainen, J.; Turpeinen, A.; Uusaro, A.; Halonen, P.; Hartikainen, J. & Hippelaeinen, M. (2006). Intravenous administration of metoprolol is more effective than oral administration in the prevention of atrial fibrillation after cardiac surgery. *Circulation*, Vol.114, pp. 1-4, ISSN 0009-7322

Halonen, J.; Halonen, P.; Jarvinen, O.; Taskinen, P.; Auvinen, T.; Tarkka, M.; Hippeläinen, M.; Juvonen, T.; Hartikainen, J. &

Hakala, T. (2007). Corticosteroids for the prevention of atrial fibrillation after cardiac surgery- a randomized controlled trial. *Journal of the American Medical Association*, Vol.297, pp. 1562-1567, ISSN 0098-7484

Halvorsen, P.; Raeder, J.; White, P.; White, P.; Almdahl, S.; Nordstrand, K.; Saatvedt, K. & Veel, T. (2003). The effect of dexamethasone on side effects after coronary revascularization procedures. *Anesthesia and Analgesia*, Vol.96, pp. 1578-1583, ISSN 0003-2999

Heidarsdottir, R.; Arnar, D.; Skuladottir, G.; Torfason, B.; Edvardsson, V.; Gottskalksson, G.; Palsson, R. &

Indridason, O. (2010). Does treatment with n-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery? *Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology: Journal Of The Working Groups On Cardiac Pacing, Arrhythmias, And Cardiac Cellular Electrophysiology Of The European Society Of Cardiology*, Vol.12, No.3, pp. 356-363, ISSN 1532-2092

Heidt, M.; Vician, M.; Stracke, K.; Grebe, M.; Boening, A.; Vogt, P. & Erdogan, A. (2009). Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. *The Journal of Thoracic and Cardiovascular Surgery*, Vol.57, pp. 276-280, ISSN 1097-685X

Henyan, N.; Gillespie, E.; White, C.; Kluger, J. & Coleman, C. (2005). Impact of intravenous magnesium on post-cardiothoracic surgery atrial fibrillation and length of hospital stay: a meta-analysis. *The Annals of Thoracic Surgery,* Vol.80, pp. 2402-2406, ISSN 0003-4975

Ho, K. & Tan, J. (2009). Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose–response meta-analysis. *Circulation*, Vol.119, pp. 1853–1866, ISSN 0009-7322

Howard, P. & Barnes, B. (2008). Potential use of statins to prevent atrial fibrillation after coronary artery bypass surgery. *Annals of Pharmacotherapy*, Vol.42, pp. 253-258, ISSN 1060-0280

Ishii, T.; Schuessler, R.; Gaynor, S.; Yamada, K.; Fu, A.; Boineau, J. & Damiano, R. (2005). Inflammation of atrium after cardiac surgery is associated with in homogeneity of atrial conduction and atrial fibrillation. *Circulation*, Vol.111, No.22, pp. 2881-2888, ISSN 0009-7322

Janssen, J.; Loomans, L.; Harink, J.; Taams, M.; Brunninkhuis, L.; van der Starre, P. & Kootstra, G. (1986). Prevention and treatment of supraventricular tachycardia shortly after coronary artery bypass grafting: a randomized open trial. *Angiology*, Vol.37, No.1, pp. 601-609, ISSN 0003-3197

Ji, Q.; Mei, Y.; Wang, X.; Sun, Y.; Feng, J.; Cai, J.; Xie, S. & Chi, L. (2009). Effect of preoperative atorvastatin therapy on atrial fibrillation following off-pump coronary artery bypass grafting. *Circulation Journal: Official Journal Of The Japanese Circulation Society*, Vol.73, No.12, pp. 2244-2249, ISSN 1347-4839

Jideus, L.; Blomstrom, P.; Nilsson, L.; Stridsberg, M.; Hansell, P. & Blomström-Lundqvist, C. (2000). Tachyarrhythmias and triggering factors for atrial fibrillation after coronary artery bypass operations. *Annals of Thoracic Surgery*, Vol.69, pp. 1064-9, ISSN 0003-4975

Kaireviciute, D.; Aidietis, A. & Lip, G. (2009). Atrial fibrillation following cardiac surgery: clinical features and preventive strategies. *European Heart Journal*, Vol.30, pp. 410-425, ISSN 1522-9645

Kalman, J.; Munawar, M.; Howes, L.; Louis, W.; Buxton, B.; Gutteridge, G. & Tonkin, A. (1995). Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation. *The Annals of Thoracic Surgery,* Vol.52, pp. 529-533, ISSN 0003-4975

Kerr, C. & Roy, D. Canadian Cardiovascular Society Consensus Conference: Atrial fibrillation 2004, Executive summary. Available at : http://www.ccs.ca/download/consensus_conference/consensus_conference_archives/2004_Atrial_Fib_full.pdf

Kim, Y.; Kattach, H.; Ratnatunga, C.; Pillai, R.; Channon, K. & Casadei, B. (2008). Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. *Journal of the American College of Cardiology*, Vol.51, pp. 68-74, ISSN 1936-8798

Kim M.; Deeb G.; Morady, F.; Bruckman, D.; Hallock, L.; Smith, K.; Karavite, D.; Bolling, S.; Pagani, F.; Wahr, J.; Sonnad, S.; Kazanjian, P.; Watts, C.; Williams, M. & Eagle, K. (2001). Effect of postoperative atrial fibrillation on length of stay after cardiac surgery (The Postoperative Atrial Fibrillation in Cardiac Surgery Study [PACS]). *The American Journal of Cardiology*, Vol.87, pp. 881-885, ISSN 1879-1913

Kinoshita, T.; Asai, T.; Nishimura, O.; Hiramatsu, N.; Suzuki, T.; Kambara, A. & Matsubayashi, K. (2010). Statin for prevention of atrial fibrillation after off-pump coronary artery bypass grafting in Japanese patients. *Circulation Journal: Official Journal Of The Japanese Circulation Society*. 2010. Vol.74, No.9, pp. 1846-1851, ISSN 1347-4839

Klemperer, J.; Klein, I.; Gomez, M.; Helm, R.; Ojamaa, K.; Thomas, S.; Isom, O. & Krieger, K. (1995).Thyroid hormone treatment after coronary-artery bypass surgery. *The New England Journal of Medicine,* Vol.333, pp. 1522-1527, ISSN 0028-4793

Klemperer, J.; Klein, I.; Ojamaa, K.; Helm, R.; Gomez, M.; Isom, O. & Krieger; H. (1996). Triiodothyronine therapy lowers the incidence of atrial fibrillation after cardiac operations. *The Annals of Thoracic Surgery,* Vol.61, No.5, pp. 1323-1327, ISSN 0003-4975

Kohno, H.; Koyanagi, T.; Kasegawa, H. & Miyazaki, M. (2005). Three day magnesium administration prevents atrial fibrillation after coronary artery bypass grafting. *Annals of Thoracic Surgery*, Vol.79, pp. 117-126, ISSN 0003-4975

Korantzopoulos, P.; Kolettis, T.; Kountouris, E.; Dimitroula, V.; Karanikis, P.; Pappa, E.; Siogas, K.; Goudevenos, J. (2005). Oral vitamin C administration reduces early recurrences rates after electrical cardioversion of persistent atrial fibrillation and attenuates associated inflammation. *International Journal of Cardiology*, Vol.102, pp. 321-326, ISSN 0167-5273

Korantzopoulos, P.; Kolettis, T. & Goudevenos, J. (2006). Effects of N-3 fatty acids on postoperative atrial fibrillation following coronary artery bypass surgery. *Journal of the American College of Cardiology*, Vol.47, No.2, pp. 467(Letter), ISSN 1936-8798

Kourlioros, A.; DeSouza, A.; Roberts, N.; Marciniak, A.; Tsiouris, A.; Valencia, O.; Camm, J. & Jahangiri, M. (2008). Dose-related effects of statins on atrial fibrillation after cardiac surgery. *The Annals of Thoracic Surgery*, Vol.85, pp. 1515-1520, ISSN 0003-4975

Kris-Etherton, P.; Harris, W. & Appel, L. (2002). Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease, *Arteriosclerosis, Thrombosis and Vascular Biology,* Vol.106, pp. 2747-2757, ISSN 1524-4636

Laikopoulos, O.; Choi, Y.; Haldenwang, P.; Strauch, J.; Wittwer, T.; Dörge, H.; Stamm, C.; Wassmer, G. & Wahlers, T. (2008). Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30000 patients. *European Heart Journal*, Vol.29, pp. 1548-1559, ISSN 1522-9645

Lamm, G.; Auer, J.; Weber, T.; Berent, R.; Ng, C. & Eber, B. (2006). Postoperative white blood cell count predicts atrial fibrillation after cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia*, Vol.20, pp. 51-56, ISSN 1532-8422

Lertsburapa, K.; White, C.; Kluger, J.; Faheem, O.; Hammond, J. & Coleman, C. (2008). Preoperative statins for the prevention of atrial fibrillation after cardiothoracic surgery. *Journal of Thoracic and Cardiovascular Surgery*, Vol.135, pp. 405-411, ISSN 0022-5223

Lilleberg, J.; Nieminen, M.; Akkila, J.; Heikkilä, L.; Kuitunen, A.; Lehtonen, L.; Verkkala, K.; Mattila, S. & Salmenperä, M. (1998). Effects of a new calcium sensitizer, levosimendan, on haemodynamic, coornar blood flow, and myocardial substrate utilization early after coronary artery bypass grafting. *European Heart Journal* Vol.19, pp.660-668, ISSN 1522-9645

Maisel, W. & Epstein, A. (2005). The role of cardiac pacing. *Chest*, Vol.128, pp. 36S-38S, ISSN 1931-3543

Makkar, K.; Sanoski, C. & Spinler, S. (2009). Role of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone antagonists in the prevention of atrial and ventricular arrhythmias. *Pharmacotherapy*, Vol.29, pp. 31-48, ISSN 0277-0008

Mariscalco, G.; Lorusso, R.; Klersy, C.; Ferrarese, S.; Tozzi, M.; Vanoli, D.; Domenico, B. & Sala, A. (2007). Observational study on the beneficial effect of preoperative statins in reducing atrial fibrillation after coronary surgery. *The Annals of Thoracic Surgery*, Vol.84, pp. 1158-1165,ISSN 0003-4975

Maslow, A.; Regan, M.; Heindle, S.; Panzica, P.; Cohn, W. & Johnson, R. (2000). Postoperative atrial tachyarrhythmias in patients undergoing coronary artery bypass graft surgery without cardiopulmonary bypass: a role for intraoperative magnesium supplementation. *Journal of Cardiothoracic and Vascular Anesthesia*, Vol.14, No.5, pp. 524-530, ISSN 1532-8422

Mathew, J.; Fontes, M.; Tudor, J.; Ramsay, J.; Duke, P.; Mazer, C.; Barash, P.; Hsu, P. & Mangano, D. (2004). A multicenter risk index for atrial fibrillation after cardiac surgery. *Journal of the American Medical Association*, Vol.291, pp. 1720-1729, ISSN 0098-7484

Miceli, A.; Fino, C.; Fiorani, B.; Yeatman, M.; Narayan, P.; Angelini, G. & Caputo, M. (2009a). Effects of preoperative statin treatment on the incidence of postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. *The Annals of Thoracic Surgery*, Vol.87, No.6, pp. 1853-1858, ISSN 0003-4975

Miceli, A.; Capoun, R.; Fino, C.; Narayan, P.; Bryan, A.; Angelini, G. & Caputo, M. (2009b). Effects of angiotensin-converting enzyme inhibitor therapy on clinical outcome in patients undergoing coronary artery bypass grafting. *Journal of the American College of Cardiology*, Vol.54, No.19, pp. 1778–84, ISSN 1936-8798

Miller, S.; Crystal, E.; Garfinkle, M.; Lau, C.; Lashevsky, I. & Connolly, S. (2005). Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis. *Heart*, Vol.91, pp. 618-623, ISSN 1355-6037

Mitchell, L.; Crystal, E.; Heilbron, B. & Page, P. (2005a). Atrial fibrillation following cardiac surgery. *The Canadian Journal of Cardiology*, Vol.21, Suppl B, pp. 45B-50B, ISSN 0828-282X

Mitchell, L.; Exner, D.; Wyse, D.; Connolly, C.; Prystai, G.; Bayes, A.; Kidd, W.; Kieser, T.; Burgess, J.; Ferland, A.; MacAdams, C. & Maitland, A. (2005b). Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair. PAPABEAR: A randomized controlled trial. *Journal of the American Medical Association*, Vol.294, pp. 3093-3100, ISSN 0098-7484

Mithani, S.; Akbar, M.; Johnson, D.; Kuskowski, M.; Apple, K.; Bonawitz-Conlin, J.; Ward, H.; Kelly, R.; McFalls, E.; Bloomfield, H.; Li, J.; Adabag, S. (2009). Dose dependent effect of statins on postoperative atrial fibrillation after cardiac surgery among patients treated with beta blockers. *Journal of Cardiothoracic Surgery*, Vol.4, pp. 61-61, ISSN 1749-8090

Nisanoglu, V.; Erdil, N.; Aldemir, M.; Ozgur, B.; Berat Cihan, H.; Yologlu, S. & Battaloglu, B. (2007). Atrial fibrillation after coronary artery bypass grafting in elderly patients: incidence and risk factor analysis. *Journal of Thoracic and Cardiovascular Surgery*, Vol.55, pp. 32-38, ISSN 0022-5223

Nurozler, F.; Tokgozoglu, L.; Pasaoglu, I.; Boke, E.; Ersoy, U. & Bozer, A. (1996). Atrial fibrillation after coronary artery bypass surgery: predictors and the role of MgSO4 replacement. *Journal of Cardiothoracic and Vascular Anesthesia*, Vol.11, pp. 421-427, ISSN 1532-8422

Ozaydin, M.; Dogan, A.; Varol, E.; Kapan, S.; Tuzun, N.; Peker, O.; Aslan, S.; Altinbas, A.; Ocal, A. & Ibrisim, E (2007). Statin use before by-pass surgery decreases the

incidence and shortens the duration of postoperative atrial fibrillation. *Cardiology*, Vol.107, pp. 117-121, ISSN 0008-6312

Ozaydin, M.; Dede, O.; Varol, E.; Kapan, S.; Turker, Y.; Peker, O.; Duver, H. & Ibrisim, E. (2008a). Effect of renin-angiotensin aldosterone system blockers on postoperative atrial fibrillation. *International Journal of Cardiology*, Vol.127, pp. 362-367, ISSN 0167-5273

Ozaydin, M.; Peker, O.; Erdogan, D.; Kapan, S.; Turker, Y.; Varol, E.; Ozguner, F.; Dogan, A. & Ibrisim, E. (2008b). N-acetylcysteine for the prevention of postoperative atrial fibrillation: a prospective, randomized, placebo-controlled pilot study. *EuropeanHeart Journal*, Vol.29, pp. 625-631, ISSN 1522-9645

Ozaydin M.; Varol, E.; Türker, Y.; Peker, O.; Erdoğan, D.; Doğan, A. & Ibrişim, E. (2010). Association between renin-angiotensin-aldosterone system blockers and postoperative atrial fibrillation in patients with mild and moderate left ventricular dysfunction. *Anadolu Kardiyoloji Dergisi: AKD = Anatolian Journal Of Cardiology*, Vol.10, No.2, pp. 137-142, ISSN 1308-0032

Paraskevas, K. (2008). Applications of statins in cardiothoracic surgery: more than just lipid lowering. *European Journal of Cardiothoracic Surgery*, Vol.33, pp. 377-390, ISSN 1010-7940

Park, Y.; Yoon, J.; Kim, K.; Lee, Y.; Kim, K.; Choi, S.; Lim, S.; Choi, D.; Park, K.; Choh, J.; Jang, H.; Kim, S.; Cho, B. & Lim, C. (2009). Subclinical hypothyroidism might increase the risk of transient atrial fibrillation after coronary artery bypass grafting. *The Annals of Thoracic Surgery*, Vol.87, pp. 1846-1852, ISSN 0003-4975

Patel, A. & Dunning, J. (2005). Is sotalol more effective than standard beta-blockers for prophylaxis of atrial fibrillation during cardiac surgery? *Interactive Cardiovascular and Thoracic Surgery,* Vol.4, pp.147-150, ISSN 1569-9285

Patel, A.; White, C.; Gillespie, E.; Kluger, J. & Coleman, C. (2006). Safety of amiodarone in prevention of postoperative atrial fibrillation: a meta-analysis. *The American Journal of Health-System Pharmacy,* Vol.63, pp. 829-839, ISSN 1079-2082

Patel, A.; White, C.; Shah, S.; Dale, K.; Kluker, J. & Coleman, C. (2007). The relationship between statin use and atrial fibrillation. *Current Medical Research and Opinion*, Vol.23, pp. 1177-1185, ISSN 0300-7995

Patti, G.; Chello, M.; Candura, D.; Pasceri, V.; D'Ambrosio, A.; Covino, E. & Di Sciascio, G. (2006). Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery- results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) Study. *Circulation*, Vol.114, pp. 1455-1461, ISSN 0009-7322

Prasongsukarn, K.; Abel, J.; Jamieson, E.; Cheung, A.; Russell, J.; Walley, K. & Lichtenstein, S. (2005). The effects of steroids on the occurrence of postoperative atrial fibrillation after coronary artery bypass grafting surgery: a prospective randomized trial. *Journal of Thoracic and Cardiovascular Surgery*, Vol.130, pp. 193-198, ISSN 0022-5223

Quan, K.; Lee, J.; Van Hare, G.; Biblo, L.; Mackall, J. & Carlson, M. (2001). Identification and characterization of atrioventricular parasympathetic innervation in humans. *Journal of Cardiovascular Electrophysiology*, Vol.13, No.8, pp. 737-739, ISSN 1540-8167

Rader, F.; Van Wagoner, D.; Gillinov, A. & Blackstone, E. (2010). Preoperative angiotensin-blocking drug therapy is not associated with atrial fibrillation after cardiac surgery. *American Heart Journal,* Vol.160, No.2, pp. 329-336.e1, ISSN 0002-8703

Rahimi, K.; Martin, J.; Emberson, J.; McGale, P.; Majoni, W.; Merhi, A.; Asselbergs, F.; Krane, V. & Macfarlane, P. (2011). Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomized controlled trials. *British Medical Journal*, Vol.342,d1250, pp. 1-11, ISSN 0267-0623

Ramlawi, B.; Out, H.; Mieno, S.; Boodhwani, M.; Sodha, N.; Clements, R.; Bianchi, C. & Sellke, F. (2007). Oxidative stress and atrial fibrillation after cardiac surgery: a case control study. *The Annals of Thoracic Surgery*, Vol.84, pp. 1166-1173, ISSN 0003-4975

Reichert, M. & Verzino, K. (2001). Triiodothyronine supplementation in patients undergoing cardiopulmonary bypass. *Pharmacotherapy*, Vol.21, No.11, pp. 1368-1374, ISSN 0277-0008

Ricote, M.; Li, A.; Willson, T.; Kelly, C. & Glass, C. (1998). The peroxisome proliferators-activated receptor-gamma is a negative regulator of macrophage activation. *Nature*, Vol.391, pp. 79-82, ISSN 0028-0836

Rodrigo, R.; Cereceda, M.; Castillo, R.; Asenjo, R.; Zamorano, J.; Araya, J.; Castillo-Koch, R.; Espinoza, J. & Larraín, E. (2008). Prevention of atrial fibrillation following cardiac surgery: basis for a novel therapeutic strategy based on non-hypoxic myocardial preconditioning. *Pharmacology and Therapeutics*, Vol.118, pp. 104-127, ISSN 0163-7258

Salamon, T.; Michler, R.; Knott, K. & Brown, D. (2003). Off pump coronary artery bypass grafting does not decrease the incidence of atrial fibrillation . *The Annals of Thoracic Surgery*, Vol.73, pp. 505-507, ISSN 0003-4975

Sano, T.; Morita, S.; Masuda, M. & Yasui, H. (2006). Minor infection encouraged by steroid administration during cardiac surgery. *Asian Cardiovascular Thoracic Annals*, Vol.14, pp. 505-510, ISSN 1816-5370

Saravanan, P.; Bridgewater, B.; West, O'Neill, S.; Calder, P. & Davidson, N. (2010). Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial. *Circulation. Arrhythmia and Electrophysiology*, Vol.3, No.1, pp. 46-53, ISSN 1941-3084

Serafimovski, N.; Burke, P.; Khawaja, O.; Sekulic, M. & Machado, C. (2008). Usefulness of dofetilide for the prevention of atrial tachyarrhythmias (atrial fibrillation or flutter) after coronary artery bypass grafting. *The American Journal of Cardiology,* Vol.101, pp.1574-1579, ISSN 1879-1913

Shakerinia, T.; Ali, I. & Sullivan, J. (1996). Magnesium in cardioplegia: is it necessary? *Canadian Journal of Surgery*, Vol.39, No.5, pp. 397-400, ISSN 1488-2310

Shepherd, J.; Jones, J.; Framptom, G.; Tanajewske, L.; Turner, D. & Price, A. (2008). Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systemic review and economic evaluation. *International Journal of Technology Assessment in Health Care,* Vol.12, No.28, pp. 1-95, ISSN 1471-6348

Shiga, T.; Wajima, Z.; Inoue, T. & Ogawa, R. (2004). Magnesium prophylaxis for arrhythmias after cardiac surgery: a meta-analysis of randomized controlled trials. *The American Journal of Medicine*, Vol.117, pp. 325-333, ISSN 0002-9343

Singh, S.; Johnson, P.; Lee, R.; Orfei, E.; Lonchyna, V.; Sullivan, H.; Montoya, A.; Tran, H.; Wehrmacher, W. & Wurster, R. (1996). Topography of cardiac ganglia in the adult human heart. *The Journal of Thoracic and Cardiovascular Surgery*, Vol.112, pp. 943-953, ISSN 0022-5223

Solomon, A.; Berger, A.; Trivedi, K.; Hannan, R. & Katz, N. (2000). The combination of propranolol and magnesium does not prevent postoperative atrial fibrillation. *The Annals of Thoracic Surgery*, Vol.69. pp. 126-129, ISSN 0003-4975

Song, Y.; On, Y.; Kim, J.; Shin, D.; Kim, J.; Sung, J.; Lee, S.; Kim, W. & Lee, Y. (2008). The effects of atorvastatin on the occurrence of postoperative atrial fibrillation after off-pump coronary artery bypass grafting surgery. *American Heart Journal*, Vol.156, pp. 373e379-373e316, ISSN 0002-8703

Subramaniam, K.; Koch, C. & Allen, B. (2005). Preoperative statin use is associated with a reduction in postoperative atrial arrhythmias in isolated coronary artery bypass grafting. *Anesthesia and Analgesia*, Vol.100, SCA1-116 (Abstract SCA110), ISSN 0003-2999

Surgical Care Improvement Project (SCIP) National Hospital Inpatient Quality Measures. (2009) Version 3.0a. Set Measure ID#: SCIP-Card-2. Specifications Manual for National Hospital Inpatient Quality Measures. Available from qualitynet.org

Suttorp, M.; Kingma, Koomen, E.; Tijssen, G.; van Hemel, N.; Defauw, J. & Ernst, S. (1991). Effectiveness of sotalol in preventing supraventricular tachyarrhythmias shortly after coronary artery byp J.; Peels, H.; ass grafting. *The American Journal of Cardiology,* Vol.68, pp.1163-1169, ISSN 1879-1913

Tamura, K.; Ito, F. & Ushiyama, T. (2010). Pravastatin treatment before coronary artery bypass grafting for reduction of postoperative atrial fibrillation. *General Thoracic and Cardiovsacular Surgery*, Vol.58, pp. 120-125, ISSN 1863-6713

Thielmann, M.; Neuhauser, M.; Marr, A.; Jaeger, B.; Wendt, D.; Schuetze, B.; Kamler, M.; Massoudy, P.; Erbel, R. & Jakob, H. (2007). Lipid-lowering effect of preoperative statin therapy on postoperative major adverse cardiac events after coronary artery bypass surgery. *Journal of Thoracic and Cardiovascular Surgery*, Vol.134, pp. 1143-1149, ISSN 0022-5223

Tokmakoglu, H.; Kandemir, O.; Gunaydin, S.; Catav, Z.; Yorgancioglu, C. & Zorlutuna, Y. (2002). Amiodarone versus digoxin and metoprolol combination for the prevention for post coronary bypass atrial fibrillation. *European Journal of Cardio-Thoracic Surgery*, Vol.21, pp. 401-405, ISSN 1873-734X

Treggiari-Venzi, M.; Waeber, J.; Perneger, T.; Suter, P.; Adamec, R. & Romand, J. (2000). Intravenous amiodarone or magnesium sulphate is not cost-beneficial prophylaxis for atrial fibrillation after coronary artery bypass surgery. *British Journal of Anaesthesia,* Vol.85, pp. 690-695, ISSN 0007-0912

Tsai, C.; Lai,I.; & Lin, J. (2004). Renin-angiotensin system gene polymorphisms and atrial fibrillation. *Circulation*, Vol.109, pp. 1640-1646, ISSN 0009-7322

Tselentakis, E.; Woodford, E.; Chandy, J.; Gaudette, G. & Saltman, A. (2006). Inflammation effects on the electrical properties of atrial tissue and inducibility of postoperative atrial fibrillation. *Journal of Surgical Research*, Vol.135, No.1, pp. 68-75, ISSN1095-8673

Wang, G.; Bainbridge, D.; Martin, J. & Cheng, D. N-acetylcysteine in cardiac surgery: do the benefits outweight the risks? A meta-analytic reappraisal. (2011). *Journal of Cardiothoracic and Vascular Anesthesia,* Vol.25, No.2, pp. 268-275, ISSN 1532-8422

Weber, U.; Osswald, S.; Huber, M.; Buser, P.; Skarvan, K.; Stulz, P.; Schmidhauser, C. & Pfisterer, M. (1998). Selective versus non-selective antiarrhythmic approach for prevention of atrial fibrillation after coronary surgery: is there a need for pre-operative risk stratification? *European Heart Journal,* Vol.19, pp.794-800, ISSN 1522-9645

Wenke, K.; Parsa, M.; Imhof, M. & Kemkes, B. (1999). Efficacy of metoprolol in prevention of supraventricular arrhythmias after coronary artery bypass grafting. *Zeitschrift für Kardiologie*, Vol.88, pp. 647-652, ISSN 1861-0692

White, C.; Caron, M.; Kalus, J.; Rose, H.; Song, J.; Reddy, P.; Gallagher, R. & Kluger, J. (2003). Intravenous plus oral amiodarone, atrial septal pacing, or both strategies to prevent post-cardiothoracis surgery atrial fibrillation: The Atrial Fibrillation Suppression Trial II (AFIST II). *Circulation*, Vol.108, Suppl II, pp. II200-II206, ISSN 0009-7322

White, C.; Kluger, J.; Lertsburapa, K.; Faheem, O. & Coleman, C. (2007a). Effect of preoperative angiotensin converting enzyme inhibitor or angiotensin receptor blocker use on the frequency of atrial fibrillation after cardiac surgery: a cohort study from the atrial fibrillation suppression trials II and III. *European Journal of Cardiothoracic Surgery*, Vol.31, pp. 817-820, ISSN 1010-7940

White, C.; Sander, S.; Coleman, C.; Gallagher, R.; Takata, H.; Humphrey, C.; Henyan, N.; Gillespie, E. & Kluger, J. (2007b). Impact of epicardial anterior fat pad retention on post-cardiothoracic surgery atrial fibrillation incidence: the atrial fibrillation suppression trial III. *Journal of the American College of Cardiology*, Vol.49, pp. 298-303, ISSN 1936-8798

White, D.; Giri, S.; Tsikouris, J.; Dunn, A.; Felton, K.; Reddy, P, & Kluger, J. (2002). A comparison of two individual amiodarone regimens to placebo in open heart patients. *The Annals of Thoracic Surgery*, Vol.74, pp. 69-74, ISSN 0003-4975

Whitlock, R.; Chan, S.; Devereaux, P.; Sun, J.; Rubens, F.; Thorlund, K. & Teoh, K. (2008). Clinical benefit of steroid use in patients undergoing cardiopulmonarybypass: a meta-analysis of randomized trials. *European Heart Journal*, Vol.29, pp. 2952-2960, ISSN 1522-9645

Wijeysundera, D.; Beattie, W.; Rao, V. & Karski, J. (2003).Calcium antagonists reduce cardiovascular complications after cardiac surgery. *Journal of the American College of Cardiology*, Vol.41, pp. 1496-1505, ISSN 1936-8798

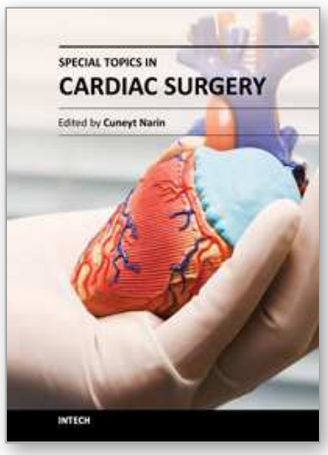
Wilkes, N.; Mallett, S.; Peachey, T.; DiSalvo, C. & Walesby, R. (2002). Correction of ionized plasma magnesium during cardiopulmonary bypass reduces the risk of postoperative cardiac arrhythmia. *Anesthesia & Analgesia*, Vol.95, pp. 828-834, ISSN 1526-7598Yazigi, A.; Rahbani, P.; Zeid, H.; Madi-Jebara, S.; Haddad, F. & Hayek, G. (2002). Postoperative oral amiodarone as prophylaxis against atrial fibrillation after coronary artery surgery. *Journal of Cardiothoracic and Vascular Anesthesia,* Vol.16, pp. 603-606, ISSN 1532-8422

Woodend, A.; Nichol, G.; Carey, C. & Tang, L. (1998). Sotalol confers no additional benefit over beta-blockers in post-coronary artery bypass atrial fibrillation. *Journal of the American College of Cardiology*, Vol.31, p. 383 (Abstract), ISSN 1936-8798

Zangrillo, A.; Londoni, G.; Sparicio, D.; Pappalardo, F.; Bove, T.; Cerchierini, E.; Sottocoma, O.; Aletti, G. & Crescenzi, G. (2005). Perioperative magnesium supplementation to prevent atrial fibrillation after off-pump coronary artery surgery: a randomized controlled study. *Journal of Cardiothoracic and Vascular Anesthesia,* Vol.19, No.6, pp. 723-728, ISSN 1532-8422

Zebis, L.; Christensen, T.; Thomsen, H.; Mikkelsen, M.; Folkersen, L.; Sørensen, H. & Hjortdal, V. (2007). Practical regimen for amiodarone use in preventing postoperative atrial fibrillation. *The Annals of Thoracic Surgery*, Vol.83, pp. 1326-1331, ISSN 0003-4975

Zimmer, J.; Pezzullo, J.; Choucair, W.; Southard, J.; Kokkinos, P.; Karasik, P.; Greenberg, M. & Singh S. (2003). Meta-analysis of antiarrhythmic therapy in the prevention of postoperative atrial fibrillation and the effect on hospital length of stay, costs, cerebrovascular accidents, and mortality in patients undergoing cardiac surgery. *The American Journal of Cardiology*, Vol.91, pp. 1137-1140, ISSN 1879-1913



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This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

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