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2014 AATS Guidelines for the Prevention and Management of Peri-Operative Atrial Fibrillation and Flutter (POAF) for Thoracic Surgical Procedures

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Preamble

Our mission was to develop evidence-based guidelines for the prevention and treatment of perioperative atrial fibrillation and flutter (POAF) for thoracic surgical procedures. Sixteen experts were invited by the AATS leadership: 7 cardiologists and EP specialists, 3 intensivists/anesthesiologists, 1 clinical pharmacist, joined by 5 thoracic and cardiac surgeons who represented AATS (see E1: list of members and E2: conflict of interest declaration online).

Methods of review

Members were tasked with making recommendations based upon a review of the literature, with grading the quality of the evidence supporting the recommendations, and with assessing the risk benefit profile for each recommendation (table 1). The level of evidence was graded by the task force panel according to standards published by the Institute of Medicine (table 1). For the development of the guidelines we followed the recommendations of The Institute of Medicine (IOM) 2011 "*Clinical Practice Guidelines We Can Trust: Standards for Developing Trustworthy Clinical Practice Guidelines*; www.iom.edu/cpgstandards" [1]. In order to meet these standards most societies (American Heart Association and AATS included) initiated the revision [2], [3] of existing guidelines [4].

For our task force subgroups were formed and tasked with preparing a summary of the available literature for each subtopic. Literature searches were conducted using Pubmed®, focused on articles published since 2000 except in rare circumstances. Both our summaries and original articles were made available to each task force member via a shared electronic folder. The subgroup summaries as well as original literature were presented and discussed at nine scheduled teleconferences. The conferences were recorded. Articles were selected for inclusion based on consensus opinion by task force members. Writing groups were formed to develop the draft guidelines for each subtopic, with 3–7 members and a leader for each group. Group recommendations were submitted prior to, and, subsequently presented for discussion and voting at, a one-day face-to-face conference.

Members were specifically asked to assess the applicability of the available evidence to thoracic surgery patients. All recommendations were subjected to a vote. Acceptance for the final document required >75% approval of each of the recommendations.

A final draft was prepared by the chairman of the task force and made available in a written form to each member for final comments. Subsequently, the recommendations were posted for public comments for AATS members (via REDCap), and then peer reviewed by outside experts selected by AATS Council.

The following recommendations are based on the best available evidence from thoracic surgery. When thoracic surgery specific evidence was not available, we extrapolated from the cardiac surgical literature. In the absence of direct evidence, we present the best expert opinion based on cardiology/cardiac electrophysiology experience and best practices.

An executive summary was prepared for publication in a printed format, while this more extensive guideline was prepared for on-line publication with additional comments, data, and a comprehensive list of references.

AATS member survey

Our survey of the AATS members (results presented in E3 online) indicated the need for a guideline update and identified opportunities for improvement in the areas of prevention, standards for postoperative ECG monitoring and the use of novel oral anticoagulants.

Target audience and patient population

These *guidelines are intended for all non-cardiac intra-thoracic surgeries* and esophagectomies, as well as for patients whose risk factors and comorbidities place them at intermediate to high risk for POAF independent of the procedures. In assessing the patient's risk for POAF it must be noted that the risks posed by the procedure and by patient factors/comorbidities will likely be additive, if not synergistic. Therefore, these factors should be evaluated in combination during the preoperative assessment.

The *target audience* includes not only thoracic surgeons and anesthesiologists but all providers who participate in the care of thoracic surgical patients.

The following *novel information* is included in this 2014 document: (i) standardized definitions for AF and (ii) recommendations for: (a) ECG monitoring, (b) post-discharge management, (c) use of the new-class of novel oral anti-coagulants (NOAC); and (d) obtaining cardiology consultation. Additionally, flow diagrams summarize the strategies for acute and chronic management. Specific drug recommendations and dosing tables are also included.

Epidemiology of perioperative atrial fibrillation and flutter (POAF), its impact on outcomes, cost and morbidity

Atrial fibrillation, the most common sustained arrhythmia after pulmonary and esophageal surgery, is a major, potentially preventable, adverse outcome. POAF peaks on postoperative days 2–4, however, 90–98% of new onset POAF resolves within 4–6 weeks. Post-operative atrial fibrillation has multiple negative implications. In the acute setting, the tachyarrhythmia can lead to hemodynamic instability, necessitating prompt intervention. A sustained elevated

heart rate can result in heart failure, a less common but clinically devastating situation, the incidence of which is not reported in the literature.

The incidence of POAF varies widely based on the intensity of surgical stress (table 2a; Refs:[5]–[17]) and patient characteristics (table 2b; Refs: [5], [6], [8], [10], [18]–[20]). Some of the risk factors for AF like HTN, obesity, and smoking, are modifiable, while others, like older age, Caucasian ancestry, and male sex are not.

Thromboembolic events such as stroke or acute limb ischemia are the most serious and feared consequences of atrial fibrillation. Studies have reported a wide range of the incidence of stroke related to POAF, though the risk appears to be increased by 50–200% for cardiac and thoracic surgical patients over the risk of general surgery [10], [21], [22].

Many studies show an increase in mortality in patients with POAF [6], [10], [15], [16], [23], [24] though some studies have not shown such an effect [13], [25]. Given that patients with other significant comorbidities or who are undergoing more complex operations are more likely to experience POAF, it is unclear to what extent the arrhythmia itself contributes to mortality. It is feasible that the contribution of POAF to mortality is more significant for those patients with fewer other comorbidities however this independent effect is more difficult to measure and has not been well reported in the literature.

POAF is associated with longer intensive care unit and hospital stays, increased morbidity (including strokes/new central neurological events; with incidence of 1.3–1.7 %; [2], [10], [26]–[29] and mortality (up to 5.6–7.5%; RR:1.7–3.4; [5], [26], [28]), as well as higher resource utilization [2], [6], [10], [26]–[30].

Multiple studies have consistently demonstrated an increase in length of hospital stay in patients who develop POAF, generally by a mean of 2 to 4 days [5], [6], [8], [10], [15], [16], [19], [23], [24]. An analysis of the STS database by Onatis *et. al*., demonstrated that in patients undergoing lobectomy or greater resection for lung cancer, the presence of POAF lengthened hospital stay by a median of 3 days [10]. The cost of hospitalization is likewise increased for patients who develop POAF, with an increase reported in the literature anywhere from 30–68% [5], [6], [23]. To some extent, this increase reflects comorbid conditions that occur along with POAF, but POAF itself is associated with an increase in cost. Vaporciyan *et al.* found that for patients who developed POAF without any other complications, the cost of care increased by over $6,000, representing a greater than 30% increase [5].

The possible mechanisms of POAF following thoracic surgery

The mechanisms that initiate and sustain atrial fibrillation (AF), including POAF, are complex and require both a vulnerable atrial substrate [31] and a trigger to initiate AF (table 3). Today they remain incompletely understood. The role of triggers from the pulmonary veins and other atrial sites initiating AF [32] is well appreciated. However, it remains to be understood why they occur and what exact mechanisms are essential for their propagation. The identified risk factors for the development of sustained POAF are mostly identical to those known to make the atrium vulnerable to development of AF in the non-surgical

setting. They include several risk factors that are associated with atrial fibrosis, such as increasing age, atrial dilatation, myocardial ischemia, volume overload, and a history of heart failure [33]–[35]. They also include risk factors like elevated norepinephrine levels and increased vagal tone, both of which shorten atrial wavelength, the latter known to increase atrial vulnerability to AF [36]. Interestingly, both adrenergic and vagal stimulation can promote triggers that initiate AF [37]. In addition, surgical procedures are associated with local or systemic inflammation (like pericarditis), an important risk factor affecting the vulnerability of the atrial substrate to POAF [38]. The extent of pulmonary resection is another important risk factor for development of POAF [7]. The development of POAF is likely to involve some or all of these mechanisms.

We can gain some insight into the mechanism of POAF by examining what prophylactic therapies decrease the rate of POAF occurrence following thoracic surgery. Higher norepinephrine levels were found in patients on preoperative beta-blockers who had their beta-blocker therapy interrupted than in patients not receiving a beta-blockers at all. This was associated with a significantly higher incidence of POAF [34], [39].

Diltiazem therapy initiated in the early postoperative period has been found to significantly reduce the rate of POAF [27]. This is thought to be related to its effects of decreasing pulmonary vascular resistance. It is known that pulmonary hypertension and dilatation of the right side of the heart are associated with an increased incidence of POAF [33]. There is also the possibility that as a systemic vasodilator, diltiazem could reduce preload and left atrial pressures [33]. Of note, the data on use of verapamil have been inconsistent with regard to decreasing the incidence of POAF [40]. Finally, magnesium has been consistently shown to decrease the incidence of POAF after cardiac surgery, and the only prospective, randomized study in thoracic surgery patients also showed a significant decrease in the incidence of POAF [39]. The reason for its effectiveness is uncertain.

In the presence of a vulnerable substrate, additional electrophysiologic abnormalities (drivers) will sustain AF.

RECOMMENDATIONS AND REASONING

1. Recommend the use of the following definitions for the diagnosis of post-operative atrial fibrillation and flutter (POAF) (table 4)

Class I

1.1. *Electro-physiologic definition/diagnosis*: ECG recordings (one or more ECG leads) which demonstrate the presence of characteristic ECG features of AF lasting at least for 30 seconds or for the duration of the ECG recording (if shorter than 30 seconds) [2], [29]. (LOE C)

1.2. *Clinical definition/diagnosis*: Clinically significant POAF is AF in the (intra- and) post-operative setting which requires treatment with rate or rhythm control agents, or requires anticoagulation, and/or extends the duration of hospitalization. (LOE C)

We recommend that both electro-physiologically documented AF and clinically diagnosed AF be included in the clinical documentation and reported in the clinical trials/studies.

2. Physiologic (ECG) monitoring of patients at risk for POAF (table 5)

Recommendations for the ECG monitoring of the patients at risk for POAF are presented in table 5.

Class I

2.1. Patients should be monitored with continuous ECG telemetry postoperatively for 48–72 hours (or less if their hospitalization is shorter) if:

2.1.1. They are undergoing procedures that pose intermediate (5–15% expected incidence of AF) or high (>15%) risk for the development of postoperative AF or have significant additional risk factors (CHA_2DS_2-VASc ≥ 2) for stroke. (LOE C)

2.1.2. They have a history of preexisting or periodic recurrent AF before their surgery. These patients should also receive ECG monitoring in the immediate pre-operative period if procedures (epidural catheter, regional anesthesia blocks, etc.) are performed. (LOE C)

Class IIa

2.2. Not using routine ECG telemetry is reasonable for patients who undergo low risk (<5% expected incidence of AF) procedures, and have neither prior history of AF, nor significant risk for stroke (based on CHA_2DS_2-VASc score), and have no relevant co-morbidities (such as heart failure or prior stroke). (LOE C)

Class I

2.2.1. If patients exhibit clinical signs of possible AF while not monitored with telemetry ECG recordings to diagnose POAF and ongoing telemetry to monitor the period of AF should be immediately implemented. (LOE C)

3. Rate control and anti-arrhythmic drugs, mechanism of action, side effects and limitations

A detailed description of the drugs used for the management of rate (table 6) or rhythm-control (table 7, [41]) their mechanism of action, side effects, and limitations are discussed here. Dosing information is also presented in tables 6 and 7.

RECOMMENDATION

Class IIa

3.1. To optimize the efficacy and safety of amiodarone, it is reasonable to exercise caution when selecting its doses or intravenous vs. oral route, because cases of ARDS have been reported following pneumonectomy with cumulative intravenous doses above 2,150 mg [42]. (LOE C)

REASONING

3.2. Rate control agents – their mechanisms of action and side effects

3.2.1. β-blockers: β-blockers are Vaughan Williams class II anti arrhythmic agents that inhibit sympathetic nervous system activity and slow the rate of phase IV repolarization, thus slowing the discharge from the sinus node [43]. This antiadrenergic activity inhibits the renin angiotensin aldosterone system, inhibits apoptosis, and reduces hyperphosphorylation of calcium releasing channels [44]. Metoprolol and atenolol are relatively selective β-1 receptor antagonists (primarily affecting cardiac tissue) and in moderate doses have less effect on the β-2 receptors in smooth muscle cells in the vasculature and bronchial tree. Propranolol and esmolol are nonselective, and carvedilol is nonselective and possesses α-receptor blocking activity.

Intravenous administration of metoprolol, propranolol and esmolol reduces ventricular response in patients with atrial fibrillation (AF) within 5 minutes of administration [45], and both intravenous and oral regimens attain resting and exercise rate control, variably defined, in 68–75% of patients [28], [46]–[48]. Rate lowering efficacy varies with acuity and cardiac function and is enhanced with digoxin [46], [47].

The major adverse effects of β-blockers are bronchospasm in patients with asthma, particularly if the asthma is not well controlled; worsening of symptoms in patients with severe peripheral arterial disease; hypotension, and worsening of heart failure symptoms in patients with decompensated heart failure with reduced ejection fraction (HFrEF). Intravenous β-blockers should not be used in patients with suspected accessory conduction pathways [2], [3], [45]. Profound bradycardia can result from acute concomitant administration of β-blockers and diltiazem or verapamil.

3.2.2. Diltiazem: Diltiazem is a nondihydropyridine calcium channel antagonist and class IV Vaughan Williams agent. Diltiazem inhibits L-type calcium channels in vascular and conduction tissue, and especially in nodal tissue [49]. Additionally, diltiazem affects the transient outward and ultrarapid delayed rectifier potassium currents in atrial myocytes {Gao:2005ge}. Intravenous diltiazem administered as a bolus and continuous infusion can control ventricular response in 70–90% of patients with the recent onset of AF. The onset of action of diltiazem is 2–7 minutes [45], [50], [51].

Oral treatment with diltiazem in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial was efficacious in controlling rest and exercise heart rate in approximately 60% of patients, and in 66% and 79% of patients, respectively, when combined with digoxin [46].

Diltiazem can worsen heart failure in patients with HFrEF, and can cause important gastrointestinal adverse effects including ileus. Diltiazem must be used cautiously, especially acutely, in patients concomitantly receiving β-blockers, and is contraindicated in patients with an accessory pathway [45].

3.2.3. Digoxin: Digoxin inhibits sodium potassium adenosine triphosphatase (ATPase), thereby increasing intracellular sodium concentration leading to increased intracellular

calcium concentrations. Additionally, digoxin administration is associated with an increase in baroreceptor sensitivity disproportionate to hemodynamic improvement, and imparts vagomimetic (parasympathetic) effects. The vagomimetic effects of digoxin occur at low serum concentrations and contribute to decreasing sinus and AV nodal conduction. At higher serum concentrations, the parasympathetic effects actually shorten the refractory period of non-nodal specialized conduction tissue [52].

The onset of action of digoxin following intravenous administration of 0.5–0.75 mg bolus doses is 30 minutes to 2 hours [53], [54]. With additional intravenous bolus doses of 0.25 mg every 2–6 hours after the first dose, up to a total dose within 24 hours of 1.25–1.5mg, 75% of patients with AF can achieve rate control at rest [50], [51]. Exercise rate control is achieved much less frequently, except when digoxin is administered concomitantly with a β-blocker or calcium channel blocker [46].

Digoxin should not be administered to patients with suspected accessory pathways or obstructive hypertrophic cardiomyopathy. The potential for digoxin toxicity, including accelerated junctional rhythm, accelerated ventricular escape rhythms (sometimes heralded by regularization of the longest R-R intervals), nausea, and visual symptoms is increased in the presence of hypokalemia, hypomagnesemia, hypercalcemia and concomitant therapy with amiodarone, dronedarone or verapamil [2], [3], [45]. Propensity matched comparisons in the AFFIRM trial do not suggest an increase in mortality associated with chronic digoxin use [55].

3.2.4. Amiodarone: Amiodarone is a Vaughan Williams class III agent that inhibits inward potassium current, prolonging the action potential. However, amiodarone also has properties that could place it in the other three Vaughan Williams classes. It has antisympathetic and calcium blocking activity that lead to important effects on the sinoatrial (SA) and atrioventricular (AV) nodes, and the drug also has sodium channel inhibiting properties that increases the threshold for depolarization ([56] and Sanoski CA, Antiarrhythmic agents. pp: 61–88. In: [57])

Intravenous amiodarone, administered as a bolus and continuous infusion, has an effect on heart rate within 4 hours that is similar to intravenous diltiazem and intravenous digoxin, and improves ventricular rate in 74% of patients with AF by 24 hours [51]. Oral amiodarone can require days for effective rate control to occur. Chronic oral amiodarone therapy for rate control can have effects similar to those of digoxin [2], [3], [58].

Amiodarone is highly lipophilic, and intravenous administration may exert effects that are different from those following oral administration. Intravenous amiodarone can be associated with AV block, vasodilation and hypotension. Intravenous amiodarone should not be used in patients who have a suspected accessory pathway [2], [3]. Pulmonary toxicity associated with high dose intravenous amiodarone is discussed later (in section 3.5.1).

Chronic administration of oral amiodarone can be associated with pulmonary, hepatic, thyroid, neurologic, cutaneous, and ocular toxicities [45]. Amiodarone inhibits the metabolism of warfarin and inhibits elimination of the new oral anticoagulants. Amiodarone

administration can restore sinus rhythm so patients who receive it after 24–48 hours of AF require anticoagulation.

3.3. Antiarrhythmic medications (mechanisms of action, side effects)

3.3.1. Amiodarone (see section 3.2.4. above)

3.3.2. Flecainide: Flecainide is a Vaughan Williams class IC antiarrhythmic agent that is a potent inhibitor of fast sodium conduction [43]. Consequently, flecainide decreases the maximum upstroke velocity and amplitude of atrial, ventricular and Purkinje fiber action potentials [59]. Flecainide may also inhibit I_{Kr} current, and prolongs atrial and ventricular action potential duration. In patients without structural heart disease, oral flecainide is relatively well-tolerated; adverse effects include dizziness (15–20%) and visual abnormalities, including blurred vision and difficulty in focusing (up to 15%), which can usually occur during dose up-titration [60]. However, in patients with structural heart disease, flecainide is associated with more severe adverse effects. Flecainide is associated with ventricular proarrhythmia in this population; this proarrhythmia is not torsades de pointes (TdP), but rather monomorphic ventricular tachycardia. This proarrhythmia was the likely cause of death associated with flecainide (and encainide) in the Cardiac Arrhythmia Suppression Trial (CAST; [61]), in which patients with a history of myocardial infarction and symptomatic or asymptomatic ventricular ectopy [≥ 6 ventricular premature depolarizations (VPDs) per hour] were randomized to receive flecainide, another Vaughan Williams class IC agent encainide, or placebo for VPD suppression. Patients randomized to receive therapy with flecainide or encainide had an increased risk of total mortality and an increased risk of nonfatal cardiac arrest and death from arrhythmia. The risk of proarrhythmia associated with Vaughan Williams class IC antiarrhythmic agents seems to be highest in patients with ventricular conduction delays (QRS duration > 120 ms), structural heart disease, ventricular scar tissue, or left ventricular dysfunction [62]. Consequently, flecainide should be avoided in these patients.

In addition to the risk of proarrhythmia, flecainide has potent negative inotropic activity, and has been associated with worsening heart failure in patients with coronary artery disease or pre-existing heart failure (New York Heart Association class II–IV and/or left ventricular ejection fraction < 30%; [60]). Therefore, flecainide is contraindicated in patients with heart failure and reduced ejection fraction.

Intravenous flecainide is not available in the US, but is available in other countries. In addition to the potential for ventricular proarrhythmia in patients with structural heart disease and worsening of heart failure in patients with left ventricular dysfunction, intravenous flecainide may be associated with hypotension.

3.3.3. Magnesium: Intravenous magnesium is often referred to as a “physiologic” calcium channel blocker, owing to its antagonism of L- and T-type calcium channels [63]. Intravenous magnesium diminishes atrial automaticity [64]) and inhibits atrioventricular (AV) node conduction [65]. Intravenous magnesium is well-tolerated; sinus bradycardia or AV block have been reported with an incidence of approximately 3% [66]. Intravenous magnesium may also cause hypotension (approximate incidence 4%; [66]). Transient

adverse effects including flushing, tingling, and dizziness may occur in up to 17% of patients [66].

3.3.4. Dofetilide: Dofetilide is a Vaughan Williams class III antiarrhythmic agent that inhibits I_{Kr} current [67], and prolongs atrial and ventricular action potential duration [68]. While dofetilide has been shown to be effective for converting nonsurgical AF to sinus rhythm [69] and for maintenance of sinus rhythm in patients with nonoperative AF [70], it has not been studied specifically for prevention or management of AF following noncardiac thoracic surgery. As a result of its propensity to inhibit I_{Kr} and prolong ventricular repolarization, dofetilide may cause TdP, with an incidence of approximately 1% in patients with normal left ventricular function [68]. However, the incidence increases to 3.3% in patients with heart failure with reduced left ventricular ejection fraction [71]. To minimize the risk of TdP, dofetilide doses must be appropriately adjusted for kidney disease [2], [3].

3.3.5. Dronedarone: Dronedarone is a Vaughan Williams class III antiarrhythmic agent that was developed as a potentially safer congener of amiodarone. Dronedarone is similar to amiodarone with respect to the fact that it inhibits multiple ion currents, including fast Na^+ current, I_{Kr}, acetylcholine-activated K^+ current, and L-type calcium current [72]. Dronedarone is also a noncompetitive β-adrenergic inhibitor. Unlike amiodarone, however, which possesses two iodine atoms that compose 37% of its molecular weight, dronedarone's structure does not include iodine atoms. In addition, the half-life of dronedarone (13–31 hours) is much shorter than that of amiodarone (10–40 days; [72]). Dronedarone's primary adverse effects include gastrointestinal distress (16%), dizziness (9%), and bradycardia (3%; [72]). Dronedarone was associated with an increased incidence of mortality in a randomized, double-blind, placebo-controlled study [73], and therefore is contraindicated in patients with New York Heart Association (NYHA) class III–IV heart failure, and in those patients with unstable NYHA class II heart failure.

Dronedarone has been shown to be effective for maintenance of sinus rhythm in patients with nonsurgical paroxysmal AF. Dronedarone is contraindicated in patients with permanent AF, due to increased mortality associated with dronedarone in that patient population [74]. The efficacy of dronedarone for maintenance of sinus rhythm in patients with nonsurgical AF has not been investigated.

3.3.6. Ibutilide: Ibutilide is a Vaughan Williams class III antiarrhythmic agent that exerts its antiarrhythmic activity via activation of slow inward sodium current [75] and inhibition of I_{Kr} [76]. Ibutilide is effective for conversion of atrial flutter and fibrillation to sinus rhythm [77]. Ibutilide is not available in an oral dosage form, and therefore is not used for maintenance of sinus rhythm. Ibutilide has been shown to be effective for conversion to sinus rhythm of AF occurring following coronary artery bypass graft surgery [78]. The efficacy of ibutilide for conversion to sinus rhythm of AF following noncardiac surgery has not been investigated.

The primary adverse effect associated with ibutilide is TdP, which occurs in 1–3% of patients. The incidence of TdP is 2–3-fold higher in patients with heart failure due to

reduced ejection fraction, which is a known risk factor for TdP. Ibutilide may also cause non-sustained monomorphic ventricular tachycardia in up to 8% of patients.

3.3.7. Procainamide: Procainamide is a Vaughan Williams class IA antiarrhythmic agent that exerts its antiarrhythmic effects through inhibition of fast sodium current as well as inhibition of I_{Kr}. In addition, a primary metabolite of procainamide, N-acetylprocainamide (NAPA), inhibits I_{Kr} current and contributes to the overall antiarrhythmic activity of procainamide. Procainamide is effective for conversion of nonoperative AF to sinus rhythm [79]. The efficacy of procainamide for conversion to sinus rhythm of AF following noncardiac thoracic surgery has not been investigated. Procainamide is no longer available in an oral dosage form, and therefore is no longer indicated for maintenance of sinus rhythm in patients with nonsurgical AF.

The primary adverse effects associated with intravenous procainamide are hypotension, QT interval prolongation and TdP, and lengthening of the QRS complex.

3.3.8. Propafenone: Propafenone is a Vaughan Williams class IC antiarrhythmic agent that is a potent inhibitor of sodium conductance [80]. Propafenone may also inhibit the transient outward potassium current (I_{to}) and the ultra-rapid delayed rectifier potassium (I_{kur}) current in atrial myocytes [81]. Propafenone is effective for maintenance of sinus rhythm in patients with nonoperative AF [82]. In addition, single-oral dose propafenone is effective for conversion of nonsurgical AF to sinus rhythm [83]. The efficacy of propafenone for prophylaxis or management of AF following noncardiac thoracic surgery has not been investigated.

Oral propafenone is well tolerated overall. Adverse effects include dizziness and blurred vision. However, propafenone possesses negative inotropic activity, and is contraindicated in patients with heart failure due to reduced ejection fraction [2], [3]. In addition, propafenone is contraindicated in patients with coronary artery disease or a history of myocardial infarction. Although propafenone was not studied in the CAST trial, the effects of flecainide and encainide in that study are believe to be due to potent sodium channel inhibition, and contraindications in patients with structural heart disease have been applied to propafenone.

3.3.9. Sotalol: Sotalol is an adrenergic β-receptor blocking agent [84] that also prolongs atrial and ventricular action potential duration via inhibition of I_{Kr} [85]. Sotalol is effective for reducing the incidence of recurrent AF in patients with paroxysmal AF [86] and after conversion to sinus rhythm [87]. Sotalol has not been shown to be effective for conversion of AF to sinus rhythm. Sotalol has been used to reduce the risk of AF following CABG surgery [88]. However, the efficacy of sotalol for prophylaxis of AF after noncardiac thoracic surgery has not been investigated.

3.3.10. Quinidine: Quinidine is a Vaughan Williams class IA antiarrhythmic agent that inhibits sodium conduction [89] as well as conductance of a variety of potassium currents, including I_{Kr}, I_{KI} and I_{to} [90]. The use of oral quinidine for management of AF has largely been discontinued, due to evidence that quinidine may increase mortality [2], [3], [91].

Quinidine may prolong the QT interval and cause TdP. The efficacy of quinidine for prevention or management of AF after noncardiac thoracic surgery has not been evaluated.

3.4. Serum drug concentration monitoring

3.4.1. Digoxin – serum drug concentration monitoring maybe warranted only if toxicity is of concern: Digoxin has a narrow therapeutic index, meaning that serum concentrations required for efficacy are similar to those that may cause toxicity. When used for heart failure, the desired therapeutic range is 0.5–0.9 ng/mL [92]. The optimal therapeutic range for digoxin for management of AF has not been established. The incidence of adverse effects associated with digoxin increases with serum concentrations > 2 ng/mL [93].

During management of AF following noncardiac thoracic surgery, monitoring of serum digoxin concentrations for assessment of efficacy is not necessary, as a strong relationship between rate control efficacy and serum digoxin concentration has not been established. Determination of serum digoxin concentration may be warranted if patients exhibit symptoms of digoxin toxicity, including nausea, vomiting, anorexia, or ventricular arrhythmias. If a serum concentration is thought to be necessary, the blood sample should be obtained at least 12 hours, and preferably 24 hours following the previous digoxin dose, as a result of the prolonged tissue distribution phase (Schentag JJ *et al.*, Digoxin. pp 410–439 In: [94]); if the blood sample is obtained < 12 hours following the dose, the serum concentration may be falsely elevated, due to incomplete distribution of digoxin from serum to tissue.

To reduce the risk of digoxin toxicity in patients receiving the drug for AF after noncardiac thoracic surgery, serum digoxin concentration monitoring may be warranted if digoxin therapy must be continued for longer than one week, for those patients who remain in AF following hospital discharge. For patient with normal kidney function, the half-life of digoxin is approximately 36 hours; therefore, steady state serum concentrations require approximately one week. Routine determination of a steady state serum digoxin concentration after one week of therapy is not required in all patients. However, determination of a serum digoxin concentration after one week of therapy may be warranted in patients with chronic kidney disease or acute kidney injury, or in patients who are treated concomitantly with a drug that inhibits digoxin elimination, such as amiodarone, dronedarone, propafenone, quinidine, and verapamil (Schentag JJ *et al.*, Digoxin. pp 410–439 In: [94]).

3.4.2. Procainamide – serum drug concentration monitoring is not warranted: The suggested therapeutic range for procainamide efficacy is 4–10 mg/L (Bauman JL *et al.*, Clinical pharmacokinetics of oral antiarrhythmic drugs. pp 440–462 In: [94]). However, this therapeutic range was determined using suppression of ventricular premature depolarizations and prevention of episodes of ventricular tachycardia. Serum procainamide concentrations have not been correlated with efficacy in AF, and therefore, desired serum procainamide concentrations for efficacy in AF are unknown. Serum concentration monitoring for intravenous procainamide for management of AF after noncardiac thoracic surgery is not warranted. The risk of adverse effects associated with intravenous procainamide can be minimized by terminating the loading dose of 20–50 mg/min continuous infusion if

hypotension occurs, QRS duration is prolonged by 50%, or a cumulative intravenous dose of 17 mg/kg has been administered [41].

3.4.3. Amiodarone – serum drug concentration monitoring is not warranted: Serum amiodarone concentration monitoring has been performed during therapy for ventricular arrhythmias. However, a relationship between serum amiodarone concentrations and efficacy for prevention or management of AF has not been established. Similarly, a relationship between serum amiodarone concentrations and the majority of amiodarone's adverse effects, particularly those that occur during short-term therapy, has not been established. Therefore, monitoring of serum amiodarone concentrations during prophylaxis or management of AF following noncardiac thoracic surgery is not warranted. However, to minimize the risk of pulmonary toxicity it is recommended to keep total cumulative intravenous amiodarone doses below 2,150mg.

3.4.4. Flecainide – serum drug concentration monitoring is not warranted: The therapeutic range for serum flecainide concentrations is often cited as 0.3–2.5 mg/L (Bauman JL *et al.*, Clinical pharmacokinetics of oral antiarrhythmic drugs. pp 440–462 In: [94]). However, this therapeutic range was developed using suppression of ventricular premature depolarizations as an endpoint, rather than efficacy for the management of AF. A relationship between serum flecainide concentrations and efficacy for prophylaxis or management of AF, particularly that occurring after noncardiac thoracic surgery, has not been established. Serum flecainide concentration monitoring for prophylaxis or treatment of AF after noncardiac thoracic surgery is not warranted.

3.5. Key limitations of drugs

3.5.1. Pulmonary toxicity: A primary concern regarding the administration of intravenous amiodarone following lung resection is pulmonary toxicity, specifically adult respiratory distress syndrome (ARDS). This concern was prominently identified by Van Mieghem *et. al.* [42], who initiated a study to determine the comparative effectiveness of amiodarone, verapamil, or placebo for prevention of AF after pulmonary resection. The study was terminated prematurely due a high incidence of ARDS in amiodarone-treated patients, specifically in patients who had undergone pneumonectomy. At the time of discontinuation of the amiodarone arm, the drug had been administered to 32 patients, of whom 21 had undergone lobectomy and 11 had undergone pneumonectomy. No patients who underwent lobectomy developed amiodarone-associated ARDS associated. In contrast, 3 of 11 patients (27%) in the amiodarone group who underwent pneumonectomy developed ARDS. The investigators recommended avoiding amiodarone administration for patients undergoing pulmonary resection.

Other investigators have administered intravenous amiodarone to patients undergoing lung surgery without adverse effects. In a prospective, randomized, unblinded amiodarone prophylaxis [95], the incidence of ARDS among the 65 amiodarone-treated patients (of whom n =40 underwent lobectomy, n=8 underwent bilobectomy, and n=17 underwent pneumonectomy) was 0%. Barbetakis *et. al.* [96] administered intravenous amiodarone to 43 patients for treatment of AF after lung resection. No patients developed ARDS; n=21 of

these patients underwent pneumonectomy. Riber *et. al*. [97] conducted a randomized, prospective, double-blind placebo-controlled study of amiodarone for prevention of AF following lung resection. Only 2 patients of the 122 who received amiodarone underwent pneumonectomy; the remainder underwent right side lobectomy or bilobectomy. No patients in this study developed ARDS or any pulmonary toxicity.

One potential difference in patients undergoing pneumonectomy in the Van Miegham study ([42] compared to these more recent trials [95]–[97] include the cumulative intravenous amiodarone dose administered. In the Van Mieghem study, intravenous amiodarone was administered as a bolus of 150 mg over 2 minutes, followed by a continuous infusion of 1200 mg over 24 hours for 3 consecutive days, for a possible cumulative intravenous amiodarone dose of 3750 mg. The three patients who developed amiodarone-induced ARDS received cumulative intravenous amiodarone doses of 2150, 3750, and 3350 mg before discontinuation of therapy. In the more recent studies, patients received a cumulative intravenous amiodarone dose of 1050 mg, after which oral amiodarone was initiated [95], or a loading dose of 300 mg intravenous amiodarone before switching to oral amiodarone [97]. In the Barbetakis study [96], intravenous amiodarone was administered as a loading dose of 5 mg/kg over 5 minutes, followed by 15 mg/kg for an undefined time period. In addition, in the Van Miegham study, the three patients who developed amiodarone-associated ARDS underwent right-sided pneumonectomy, which is associated with a higher risk of postoperative ARDS than other types of lung surgery.

Overall, administration of amiodarone at the dose shown to be effective by Riber *et al.* (300 mg intravenous loading dose followed by 600 mg orally twice daily for 5 days) appears to be safe and effective for prevention of AF following pulmonary resection [97].

3.5.2. QT interval prolongation/torsades de pointes: A number of drugs that may be used for prophylaxis or management of postoperative AF may cause QT interval prolongation, and therefore pose a risk for the life-threatening polymorphic ventricular arrhythmia known as torsades de pointes (TdP) (Tisdale JE. Ventricular arrhythmias. pp 485–515 – In: [98]). Drugs that prolong the QT interval are generally those that inhibit I_{Kr}, and include amiodarone, procainamide, dofetilide, dronedarone, ibutilide, sotalol, and quinidine. A Bazett's-corrected QT (QT_c) interval > 500 ms markedly increases the risk for drug-induced TdP [99]. Patients receiving a drug that prolongs the QT_c interval should have a QT_c interval measured from a rhythm strip or 12-lead ECG at least once daily during therapy. In addition, since the occurrence of TdP is highly dependent on the presence of other risk factors (female sex, hypokalemia, hypomagnesemia, hypocalcemia, bradycardia, heart failure, elevated serum drug concentrations) (Tisdale JE. Ventricular arrhythmias. pp485–515 In: [98]; [99]), modifiable risk factors should be corrected. Serum potassium, magnesium and calcium concentrations should be maintained in the normal range. Drug interactions leading to elevated concentrations of a QT interval-prolonging drug should be avoided. Doses of renally eliminated QT interval prolonging drugs (dofetilide, procainamide, sotalol) should be appropriately adjusted for declining kidney function. In addition, concomitant therapy with other QT interval-prolonging drugs, particularly noncardiovascular QT interval-prolonging drugs (fluoroquinolone and macrolide antibiotics,

azole antifungal agents, antidepressants, antipsychotics, many others) (Tisdale JE. Ventricular arrhythmias. pp 485–515 In: [98]) should be avoided or performed cautiously.

3.5.3. Hypotension: Several drugs administered intravenously for prophylaxis or management of postoperative AF may cause hypotension, including diltiazem, esmolol, metoprolol, procainamide, and amiodarone. Drug-associated hypotension is more likely to occur when patients are volume-depleted, which is often the case following thoracic surgery. In the post-coronary artery bypass graft population with AF, hypotension associated with intravenous diltiazem was more likely when the pretreatment systolic blood pressure was < 115 mm Hg [100].

3.5.4. Bradycardia: Drugs used for ventricular rate control can also result in bradycardia through inhibition of sinus node function or AV nodal conduction. These drugs include amiodarone, propafenone, flecainide, esmolol, metoprolol, sotalol, and diltiazem (Tisdale JE. Supraventricular arrhythmias. pp 485–515 In: [98]). The risk is higher when combinations of sinus node or AV node-inhibiting drugs are used.

3.5.5. Exacerbation of heart failure with reduced left ventricular ejection fraction: Several drugs used for prophylaxis or treatment of postoperative AF possess negative inotropic activity and are contraindicated in patients with heart failure with reduced left ventricular ejection fraction. These drugs include diltiazem, procainamide, propafenone, and flecainide.

4. Prevention strategies and their efficacy (figure 1)

Recent evidence suggest that some prevention strategies (avoiding beta blockade withdrawal for those chronically on those medications, correction of serum magnesium when abnormal) maybe effective for all patients for reducing the incidence of POAF. By surveying the AATS membership, we also found that many of these strategies are currently underutilized.

RECOMMENDATIONS

4.1. Recommended prevention strategies for all patients

Class I

4.1.1. Patients taking β-blockers prior to thoracic surgery should continue them in the postoperative period to avoid β-blockade withdrawal [3], [26], [29], [101]–[106]. (LOE A)

Class IIb

4.1.2. Intravenous magnesium supplementation may be considered to prevent postoperative AF when serum magnesium level is low or it is suspected that total body magnesium is depleted [29], [35], [100], [106], [107]. (LOE C)

Class III

4.1.3. Digoxin should not be used for prophylaxis against AF [2], [29], [108]–[110]. (LOE A)

4.1.4. Catheter or surgical pulmonary vein isolation (at the time of surgery) is not recommended for prevention of POAF for patients who have no prior history of AF [111]. (LOE C)

4.1.5. Complete or partial pulmonary vein isolation at the time of (even bilateral) lung surgery should not be considered for prevention of POAF, as it is unlikely to be effective [15], [26], [96], [104], [106], [111]–[114]. (LOE B)

For those patients at elevated risk for the development of POAF, preventive administration of medications (diltiazem or amiodarone) may be reasonable. However, these strategies may not be useful for all thoracic surgical patients.

4.2. Recommended prevention strategies for intermediate to high-risk patients

Class IIa

4.2.1. It is reasonable to administer diltiazem to those patients with preserved cardiac function who are not taking β-blockers preoperatively in order to prevent POAF [2], [17], [95], [97], [115], [116]. (LOE B)

4.2.2. It is reasonable to consider the postoperative administration of amiodarone to reduce the incidence of POAF for intermediate and high risk patients undergoing pulmonary resection [2], [27], [42], [110], [117]. (LOE A)

Class IIb

4.2.3. Postoperative administration of intravenous amiodarone may be considered to prevent POAF in patients undergoing esophagectomy [3], [15], [17], [26], [29], [42], [95], [97], [104], [106], [116], [118], [119]. (LOE B)

4.2.4. Atorvastatin may be considered to prevent POAF for statin naïve patients scheduled for intermediate and high risk thoracic surgical procedures [3], [26], [29], [104], [106], [120]–[122]. (LOE C)

4.3. Recommended prevention strategies for the highest-risk patients

Class IIb

4.3.1. Left atrial appendage excision may be considered at the time of extensive left lung surgery for patients with preexisting AF who are considered too high of a risk for anticoagulation in the perioperative period [2], [29], [123]. (LOE C)

REASONING

4.4. Prevention of postoperative AF: Atrial fibrillation, the most common sustained arrhythmia after pulmonary and esophageal surgery, is associated with longer intensive care unit and hospital stays, increased morbidity and mortality and higher utilization of healthcare resources [6], [30]. POAF also represents a major potentially preventable adverse outcome. A number of randomized controlled studies and meta-analyses have examined the efficacy of a variety of agents including antiarrhythmics, β-blockers and novel agents such as magnesium and statins, to prevent the development of POAF in patients undergoing thoracic surgery. However, it should be appreciated that there is a dearth of data indicating

that prophylactic therapy for AF improves outcomes after thoracic surgery, e.g., stroke and reduces length of hospital stay and many of the recommendations are extrapolated from the cardiac surgery arena.

The recommendation to avoid withdrawal of β-blockers in all patients undergoing thoracic surgery is mainly derived from the cardiac surgery literature. Nattel *et al.* [101] showed that abrupt propranolol withdrawal was associated with increased sensitivity to isoproterenol, and a large meta-analysis of randomized studies confirmed that acute withdrawal of β-blockers prior to cardiac surgery increases the risk of developing POAF [105]. There are only limited data supporting the role of prophylactic β-blockers in patients undergoing thoracic surgery [102], [103]. While both of these randomized studies showed a reduction in POAF, there was a high incidence of hypotension and bradycardia that limited the use of β-blockers in the perioperative setting [124]. There remains controversy in the recent literature as to whether to initiate perioperative β-blockade in patients who are not already taking them. At recommended doses aimed at achieving a target heart rate, β-blockers may cause significant postoperative hypotension and stroke related mortality [124]. In randomized controlled trials diltiazem has not been associated with perioperative hypotension. The ability of diltiazem to reduce AF after thoracic surgery is moderate [27].

To date the best evidence for efficacy of AF prevention in general thoracic surgery patients has been with amiodarone. An important issue with any prevention efforts is the acceptance of a recommended medication by the responsible surgical team, particularly with a drug like amiodarone that has potential for side effects. The antiarrhythmic mechanism of amiodarone combines varying degrees of class III antiarrhythmic activity, β-blockade and calcium channel antagonism. Slower postoperative heart rates with short term-use and greater than moderate efficacy in reducing AF may result in wider physician acceptance of amiodarone, although concerns regarding rare reports of pulmonary toxicity with right lung resection or lung transplantation may moderate its use (discussed in more detail in Section 3 above).

4.5. Pharmacological Therapies to Prevent POAF

4.5.1. Amiodarone

Efficacy: Tisdale *et al.* [95] showed that amiodarone 1.05 gm given by continuous IV infusion over the first 24h after pulmonary resection and then 400 mg orally twice daily for up to 6 days, reduced the rate of POAF requiring treatment, 9/65 (14%) in comparison to 21/65 (32%), in an untreated control group. The same investigators in a similar study [17] showed that continuous infusion of amiodarone 43.75 mg/h for 96 hours (total dose 4200 mg) was associated with a lower POAF rate of 6/40 (15%) in patients undergoing esophagectomy when compared to 16/40 (40%) in an untreated control group. The largest trial to date by Riber *et al.* [97] used a randomized, double-blind, placebo-controlled design of amiodarone given by loading 300 mg IV immediately when stable after surgery followed by 600 mg orally twice daily for up to 5 days. They showed that amiodarone-treated patients had a rate of POAF (lasting > 5 min) of 9% (11/122), compared to placebo controls who had a rate of 32% (38/120). A final study of patients undergoing pulmonary resection randomized 2 groups of patients in a prospective, double-blind design to either amiodarone (postoperative IV loading 5 mg/kg, then 15 mg/kg for 48 h IV infusion) or magnesium

sulfate (preoperative loading of 80 mg/kg and then 8 mg/kg/h for 48 h IV infusion after surgery) [116]. This study showed that the incidence of POAF (lasting >30 sec) was 10% (21/219) with amiodarone and 13% (27/219) with magnesium. None of these studies reported any serious adverse effects due to amiodarone except occasional bradycardia.

Safety: In the non-surgical population it is commonly accepted that amiodarone-related pulmonary toxicity does not occur with short-term (<1 month) exposure. Concerns over amiodarone-related perioperative pulmonary toxicity were raised two decades ago in a small randomized study that was interrupted early because 3 right-sided pneumonectomy patients out of a total of 11 patients that received amiodarone for prevention of POAF developed acute respiratory distress syndrome (ARDS), whereas none of the 21 patients undergoing lobectomy and exposed to amiodarone developed this complication [42]. The authors acknowledged that right-sided pneumonectomy in itself was a well-established risk for ARDS, but nevertheless cautioned on the use of amiodarone for AF prevention after pulmonary resection. Since then a number of observational and more recent prospective randomized trials failed to find a link between use of amiodarone for AF prevention and ARDS immediately after pulmonary resection [17], [95], [97], [116], [118]. A number of other studies used amiodarone for acute treatment of AF following general thoracic surgery, and none of these reported amiodarone-related pulmonary toxicity. Of 3 retrospective studies describing risk and treatment of AF after lung transplant, only 1 study [119] reported an association of pulmonary toxicity with amiodarone use and cautioned on the routine use of amiodarone after lung and heart-lung transplants [15], [119].

4.5.2. Diltiazem

Efficacy: A meta-analysis of randomized controlled trials that evaluated calcium channel blockers given immediately before, during or after coronary artery bypass (CABG) surgery or valve surgery showed that these drugs reduced rates of myocardial injury, and supraventricular tachycardia (SVT) [117]. In patients undergoing thoracic surgery there have been 3 prospective randomized trials of nondihydropyridine calcium channel antagonists for the prevention of AF. Verapamil prophylaxis was used in a large, randomized, open-label study of patients undergoing lobectomy or pneumonectomy using somewhat aggressive loading (started within 1 hour of arrival in recovery, 10 mg over 10 minutes followed by 0.375 mg/min over 30 minutes) and then by continuous infusion (0.125 mg/min for 3 days) dosing [40]. This regimen was associated with a non-significant reduction of AF from 15% (15/99) in placebo patients to 8% (8/100) respectively. In a small randomized, open-label study of patients undergoing standard or intrapericardial pneumonectomy diltiazem prophylaxis was associated with reduced overall incidence of SVT in comparison to digoxin treated patients (0/21 vs. 8/25, P<0.005, respectively [110]). In a larger follow-up, randomized, double-blind, placebo controlled study of patients undergoing lobectomy or pneumonectomy, diltiazem started within 1 hour of arrival in recovery, 0.15 mg/kg (loading while patient was fasting then 120 mg orally twice a day for 14 days) reduced the rates of postoperative atrial arrhythmias in comparison to placebo, (25/167 [15%] vs. 40/163 [25%] respectively, P=0.03) [27].

Safety: With the doses described in a randomized open-label study of verapamil given early after lobectomy or pneumonectomy, 14% of the patients experienced hypotension and 9% had bradycardia requiring temporary interruption of the drug infusion [40]. In contrast, mild transient hypotension was reported in 4% (6/163) of diltiazem treated patients especially early after surgery with resumption of diltiazem therapy soon thereafter [27].

4.5.3. Novel Therapies to Prevent Postoperative AF: Inflammation and oxidative stress play an important role in the pathogenesis of AF [125]. A number of studies have examined the role of statin therapy in preventing POAF. One of the largest (n=200) randomized studies evaluated the role of atorvastatin, given 7 days before and 7 days after cardiac surgery. Those patients who received the statin demonstrated a 22% reduction in incidence of POAF. Amar *et al.* [120] conducted a prospective study of 131 patients undergoing major lung or esophageal surgery to evaluate the relationship of C-reactive protein (CRP) and POAF. A secondary analysis in this study showed that in the subset of patients receiving preoperative statins the risk of developing AF was almost three-fold lower than in those not taking them. Two meta-analyses of randomized studies examining prophylactic statin therapy was performed that involved over 2200 patients [121], [122]. These studies supported the role of statins in preventing POAF in statin-naïve patients undergoing high-risk cardiac and non-cardiac surgery or after acute coronary syndromes. Additional randomized placebo controlled studies will be required before statin therapy can be recommended as a Class I or IIa indication to prevent POAF in statin-naïve patients undergoing moderate to high-risk lung surgery. As in other patients undergoing non-cardiac surgery, most physicians continue statin therapy preoperatively to avoid withdrawal.

There is strong evidence supporting the use of magnesium supplementation to prevent POAF in patients undergoing cardiac surgery [107]. In the only prospective, unblinded randomized controlled trial (n = 200) in patients undergoing thoracic surgery, Terzi *et al.* [35] demonstrated that the incidence of postoperative atrial tachyarrhythmias, mainly AF, was reduced from 23% to 11% in those patients treated with an IV infusion of magnesium during the perioperative period.

Three large randomized clinical trials have clearly demonstrated that prophylaxis with digoxin does not prevent and may in fact increase the incidence of POAF in patients undergoing all types of thoracic surgery [108]–[110]. While, acute digoxin loading may be beneficial in controlling rapid ventricular rates during AF in patients with hypotension, there is no place for digoxin prophylaxis in patients undergoing thoracic surgery.

4.5.4. Surgical Prevention Strategies: Cardiac surgery patients with pre-existing AF who undergo surgical pulmonary vein isolation (PVI) and receive additional biatral linear lines of block may achieve a 75–85% freedom from AF at 6–12 months, and the procedure adds on average an additional 9 minutes to the surgery, without perceptible safety risks, though possibly the patients have a slightly higher risk of needing a pacemaker during the early postoperative period [126]. Patients who undergo the equivalent of near complete PVI associated with bilateral lung transplantation have a very low incidence of AF 3–6 six months post procedure [111]. For patients with preexisting AF, who are known to tolerate poorly the arrhythmia or who have an increased bleeding risk on anticoagulants, two

questions arise: would PVI, bilateral or unilateral, help prevent perioperative AF, and would operative left atrial appendage exclusion lower perioperative thrombotic risk?

Multiple studies [111], [113], [114] have shown that the incidence of POAF is in the 20–40% range even following double lung transplant, confirming the fact that this form of AF is related to inflammatory, mechanical, and autonomic factors, in addition to pulmonary vein triggers. Unilateral pulmonary vein isolation is not likely to be any more beneficial, and has a distinct disadvantage beyond the perioperative period [112].

Excision of the left atrial appendage can be performed safely, with efficacy rates approaching 87%, following a learning curve [123], but there are no studies that show a reduction in perioperative thrombotic events. The Left Atrial Appendage Occlusion Study is ongoing. Data from the Watchman [127] and Prevail trials cannot necessarily be extrapolated to operative left atrial appendage exclusion, and neither of these studies involved thoracotomy patients. Though the alteration in left atrial compliance and filling pressures following appendage exclusion may be small, the effects may be different in a lung population that may have a smaller atrial size, than in a cardiac valve surgery population.

5. Treatment strategies for POAF and their efficacy

The management of patients presenting with POAF requires different strategies depending on their hemodynamic stability. While some interventions are likely to benefit all patients (see 5.1), hemodynamically unstable patients will require urgent efforts for the restitution of sinus rhythm (section 5.2). However, for stable patients with POAF the emphasis shifts to rate control strategies (see detailed in 5.3) [2].

RECOMMENDATIONS

5.1. Management strategies recommended for all patients with new onset POAF (figure 2)

Class I

5.1.1. Reduce or stop catecholaminergic inotropic agents if hemodynamics allow. (LOE C)

5.1.2. Optimize fluid balance and maintain normal electrolyte levels. (LOE C)

5.1.3. Evaluate the presence of and treat all possible correctable triggering factors. These may include bleeding, pulmonary embolism, pneumothorax, pericardial processes, airway issues, myocardial ischemia, or infection/sepsis. (LOE C)

Class IIb

5.1.4. Cardiology consultation may be useful for those patients (LOE C) who:

5.1.4.1. Develop recurrent or refractory POAF.

5.1.4.2. Develop a hemodynamically unstable condition.

5.1.4.3. Are at high risk for stroke based on CHA_2DS_2-VASc score and will likely require longer-term anticoagulation.

5.1.4.4. Require a *second-line* anti-arrhythmic medication for stabilization.

5.1.4.5. Also develop acute kidney injury.

REASONING—For all patients with new onset POAF after thoracic surgery, consideration should be given to triggering causes. Although inflammation provoked by surgical procedures, patient risk factors for AF, and mechanical proximity of thoracic surgery procedures to cardiac structures are often sufficient to explain the occurrence of POAF, other triggers may need to be identified in patients with recurring, symptomatic, or refractory AF. These include bleeding, pulmonary embolism, pneumothorax, pericardial processes, airway issues, myocardial ischemia, or infection/sepsis. Minimization, weaning or discontinuation of catecholaminergic inotropic agents, if possible, optimization of fluid status, and correction of any electrolyte/metabolic disturbances may also facilitate restoration and maintenance of sinus rhythm.

As a general rule, although much, if not most, POAF is transient and largely limited to the postoperative period (2–6 weeks), consultation with a cardiologist or cardiac electrophysiologist may be useful, especially for patients with recurrent or refractory POAF. This is usually for three issues: management of rate control during AF; consideration of whether, when, and how to restore sinus rhythm; and consideration of anticoagulation. The first issue is usually not difficult to accomplish, and standard prophylactic use of diltiazem or β blockers usually insures that should POAF occur, ventricular rate control may be as simple as maintaining this therapy. However, tachy-brady syndrome may complicate efforts at rate control that may require alternative medical options, rhythm control strategies, or anti-bradycardic pacing. The second issue may be more complex, but decisions about if, when, and how to restore sinus rhythm often benefits from direct, nuanced cardiology and/or cardiac electrophysiology (EP) involvement. Such consultation can be useful in the selection and management of antiarrhythmic medications or in determining a need for permanent pacing. The third issue is probably the most important and a challenge particularly for patients at high risk for bleeding. Cardiologists may assist with management of patients at high risk for stroke needing longer term anticoagulation, unstable patients, or patients with acute kidney injury, which can worsen outcomes, including stroke, and limit antiarrhythmic and anticoagulant choices. Close interaction between the surgical team and the cardiology team should provide excellent, well considered anticoagulation decisions. In the end, the patient and thoracic surgical team will be well served by a close consultative relationship with the cardiologist.

RECOMMENDATIONS

5.2. Recommendations for the management of the hemodynamically unstable patient with new onset POAF (figure 3)

Class I

5.2.1. Emergent R-wave synchronized direct-current electrical cardioversion (DCC) is recommended for hemodynamically unstable patients and for patients with evidence of

acute myocardial ischemia or infarction. Signs of hemodynamic instability include: severe symptomatic hypotension, shock, or pulmonary edema. [2]–[4], [29]. (LOE C)

5.2.1.1. For unstable patients with new onset POAF of less than 48-hour duration, emergent DC cardioversion is indicated and is acceptable to be performed prior to initiation of anticoagulation. [2], [3], [73]. (LOE C)

5.2.1.2. For unstable patients who undergo cardioversion more than 48 hours after the onset of AF, and who do not have an excessive bleeding risk or other contraindication, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks [2], [3], [45]. (LOE C)

Class IIa

5.2.2. If initial DC cardioversion is unsuccessful or hemodynamically unstable AF recurs, the following steps can be useful:

5.2.2.1. Initiate rate and possible rhythm control therapy with intravenous esmolol, diltiazem, digoxin, or amiodarone while preparing for repeat DC cardioversion. (LOE C)

5.2.2.2. Repeat DC cardioversion (more likely to be successful after initiating a rhythm control agent). (LOE C)

REASONING—Some patients with new onset AF are hemodynamically unstable, defined as AF associated with symptomatic severe hypotension, evidence of acute myocardial ischemia or infarction, or pulmonary edema/heart failure. For such patients, immediate electrical direct current (DC) cardioversion is recommended [2], [3]. Electrical cardioversion should be performed under deep conscious sedation with R-wave synchronized shocks. Cardioversion can be performed with biphasic or monophasic waveforms. However biphasic waveform shocks are preferred over monophasic waveforms, as the latter can require higher defibrillation energies for success. Anterior-posterior electrode patch positioning (e.g. R parasternal – L posterior or mid-low sternal -posterior) may produce a more successful defibrillation vector for cardioversion of AF than anterior only (e.g. R parasternal to anterior or anterolateral apex) positions. If DC cardioversion using one defibrillator patch location fails, the alternate patch position should be used.

If AF duration in the unstable patient is less than 48 hours, cardioversion can be performed prior to initiation of anticoagulation [2], [3], [45]. However, for patients with AF of more than 48 hours duration who become hemodynamically unstable, there is a higher risk of left atrial or atrial appendage thrombus that could dislodge at the time of or in the days following cardioversion in the absence of anticoagulation. Thus, it is recommended that for these patients, in the absence of contraindications (such as excessive bleeding risk or known heparin sensitivity) heparin be administered concurrently with the cardioversion, and used during transition to an oral anticoagulant. The oral anticoagulant should be provided for at least 4 weeks after cardioversion, as for patients undergoing elective cardioversion [2], [3], [45].

Should initial cardioversion be unsuccessful or should hemodynamically unstable AF recur, repeat cardioversion can be attempted. To facilitate this, and while preparing for repeat cardioversion, attempts at pharmacologic rate or rhythm control may be considered with such drugs as IV amiodarone, esmolol, diltiazem, or digoxin. When hypotension is a problem, IV digoxin may be considered. However, should pharmacologic management fail, repeat electrical cardioversion is recommended.

RECOMMENDATIONS

5.3. Recommendations for the management of the hemodynamically stable patient with new onset AF (figure 4 and 5): Primary treatment goal is rate control with rhythm control as secondary option.

Class IIa

5.3.1. It is reasonable to manage stable, well-tolerated new onset POAF with a rate control strategy. [2], [26], [106], [128]–[130]. (LOE C)

5.3.2. Rhythm control with antiarrhythmic drugs and/or DC cardioversion can be useful for patients with hemodynamically stable new onset POAF who have recurrent or refractory POAF, continued symptoms, intolerance to rate control medications, or ventricular rates that cannot be adequately controlled. [2], [128], [130]. (LOE C)

5.3.3. A rhythm control approach with pharmacologic or DC cardioversion is reasonable for patients with new onset POAF nearing 48 hours in duration, who are at high risk for bleeding, in order to avoid anticoagulation that would be otherwise indicated for AF persisting longer than 48 hrs. (LOE C)

REASONING—Similar to AF occurring after cardiac surgery, new onset POAF after thoracic surgery is often self-limited with patients returning to sinus rhythm within 4–6 weeks after surgery regardless of a rate or rhythm control strategy. An observational study of 30 patients with new onset AF after lung resection and no history of heart rhythm disease reported that sinus rhythm was restored within the first 24 hours in 70% of patients treated with diltiazem, and in 67% of patients treated with amiodarone; after 48 hrs, 80% in both groups were in sinus rhythm [26]. AF recurred in 11 (37%), but 10 converted after IV treatment. In a retrospective review of 41 patients who developed POAF after lung resection, 98% of AF disappeared within a day of discharge and 85.4% required pharmacologic management, but none required electrical cardioversion [106]. Sinus rhythm was restored after loading with digoxin in 80%, 11.5% after amiodarone, and 8.5% with both. All patients except one were discharged in sinus rhythm. In another study of aortic surgery in 211 patients, 22 developed POAF; 16 spontaneously converted to sinus rhythm, 2 converted chemically and 1 electrically, and 3 continued in AF at discharge, but all were in sinus rhythm documented with an ECG a mean of 14 months after discharge [129]. Thus, most patients with new POAF after thoracic surgery can be expected to return to sinus rhythm regardless of a rate or rhythm control strategy.

Rate vs. rhythm control strategies have been studied in randomized trials for non-POAF [131]–[135]. The largest of these, the Atrial Fibrillation Follow-Up Investigation of Rhythm

Management (AFFIRM) study [131], was powered to detect a difference in overall mortality, but showed no difference between a strategy of rhythm vs. rate control in the primary endpoint of all-cause mortality, with a slight trend toward better survival in the rate control arm. Secondary analyses demonstrated no differences in quality of life [136], although other sub-analyses demonstrated better mortality in patients in sinus rhythm or on warfarin [137], and a functional status sub-study demonstrated better NYHA functional class in the rhythm control arm and longer 6 minute walk test distances in patients in sinus rhythm [138].

However, there are no randomized trials studying rate vs. rhythm control strategies for POAF after thoracic surgery, and there have been only small, randomized pilot trials performed after cardiac surgery. In a randomized pilot study by Lee, et al, of 50 patients with POAF after cardiac surgery, 27 were randomized to antiarrhythmic drug therapy ± electrical cardioversion and 23 to a rate control approach [128]. The endpoints were length of stay and incidence of recurrent AF. There was no significant difference in time to conversion to sinus rhythm. With multivariable Cox analyses, adjusting for other covariates, there was a trend toward a reduction in time from treatment to sinus rhythm in the antiarrhythmic arm (P=0.08), as well as a lower length of stay (P=0.05). At termination, in the rate control arm, 91% were in sinus rhythm, and in the antiarrhythmic arm 96% were in sinus rhythm. The majority were in sinus rhythm after 2 months. In a randomized pilot study by Soucier, *et al*. [130], in stable patients with new AF after cardiac surgery, 42 patients were randomized to propafenone 600 mg dose (N=20) vs. ibutilide 1 mg IV up to 2 doses (N=10) vs rate control (N=12). At 24 hours 0, 65 and 34% of patients in the ibutilide (P=0.01), propafenone (P>0.05), and rate control arms remained in AF. Ibutilide decreased AF duration, but recurrence rates were 90%, 41%, and 58% in the three arms (P>0.05). The 3 patients who did not convert all received propafenone. There were no differences in length of stay or rhythm at discharge. These two small prospective randomized pilot studies thus showed few differences between rate and rhythm control strategies.

The absence of significant differences in the small rate vs. rhythm control studies of AF after cardiac surgery justifies use of either rate or rhythm control strategies in patients with new onset POAF who are hemodynamically stable. However, the high rate of spontaneous conversion to sinus rhythm in the first 24 hours after onset of POAF makes it reasonable to opt for an initial rate control approach in stable patients, especially over the first 24 hours. Since anticoagulation is generally recommended in patients with AF lasting longer than 48 hours, the higher risks of postoperative bleeding with anticoagulation can also justify a rhythm control approach in patients with new postoperative AF that persists longer than 24 hrs despite a rate control approach. A rhythm control approach with pharmacologic or electrical cardioversion may also be reasonable in patients whose ventricular rates cannot be adequately controlled, or in patients who either do not tolerate AV nodal blockers to control ventricular rate or who remain symptomatic or hemodynamically compromised despite control of the ventricular rate.

For the patient with stable hemodynamics and minimal symptoms, a trial of rate control for the first 24 hours is generally recommended, as a high proportion will convert to sinus rhythm within 24 hours using rate control or rhythm control agents. Inotropes should be

stopped or reduced, if clinically acceptable, fluid balance optimized, and normal electrolyte balance maintained. Rate control may be achieved with IV esmolol or metoprolol, IV diltiazem, IV verapamil (though this carries more risk for hypotension than diltiazem), digoxin (especially if there is hypotension or heart failure), or IV amiodarone. If AF persists, DC cardioversion may be considered within 48 hrs of onset; anticoagulation would be indicated for AF persisting >48 hrs. Alternatively, if the AF is well tolerated, the patient could be started on anticoagulation and rate control with plans for elective cardioversion in 4–6 weeks. If AF is recurrent after cardioversion, antiarrhythmic therapy with repeat DC cardioversion can be continued with maintenance oral therapy for 4–6 weeks, or a rate control approach can be adopted with anticoagulation and plans for elective cardioversion if AF persists after 4–6 weeks (see figures 2, 4 and 5).

RECOMMENDATIONS

5.4. Medical management of patients with new onset POAF (figure 4 and 5)

5.4.1. Rate Control Recommendations

5.4.1.1. Intravenous administration of beta-blockers (e.g. esmolol or metoprolol) or nondihydropyridine calcium channel blockers (diltiazem or verapamil) is recommended to achieve rate control (heart rate ≤110 bpm) for patients who develop POAF with rapid ventricular response [2], [26], [28]. (LOE B)

5.4.1.2. Caution should be used with patients with hypotension, LV dysfunction, or heart failure [2], [26], [28], [29]. (LOE B)

5.4.1.3. Combination use of AV nodal blocking agents, such as beta-blockers (e.g. esmolol or metoprolol), nondihydropyridine calcium channel antagonists (e.g. diltiazem or verapamil), or digoxin, can be useful to control heart rates when a single agent fails to control rates of POAF. The choice should be individualized and doses modified to avoid bradycardia [2], [29]. (LOE B)

5.4.1.4. For patients with *hypotension, heart failure or LV dysfunction*, or when other measures are unsuccessful or contraindicated, intravenous amiodarone can be useful for control of heart rate. Amiodarone could result in conversion to sinus rhythm, and if it is initiated after 48 hours of AF, both a TEE when possible, to rule out LA/LAA thrombus, and full anticoagulation should be considered [3], [26], [29], [104], [106]. (LOE B)

5.4.1.5. For patients with *heart failure, LV dysfunction or hypotension*, intravenous digoxin may be considered for rate control of POAF [29], [100], [106]. (LOE B)

5.4.1.6. For patients with ventricular preexcitation (i.e. Wolff-Parkinson-White syndrome) and POAF, use of AV nodal blocking agents, such as beta-blockers (e.g. esmolol or metoprolol), intravenous amiodarone, nondihydropyridine calcium channel antagonists (e.g. diltiazem or verapamil), or digoxin, should be avoided [2], [29]. (LOE C)

REASONING—Achieving control of ventricular rates in AF is a first line approach to patients with POAF after thoracic surgery. This may be achieved with use of intravenous or

oral AV nodal blocking agents, but intravenous beta-blockers or nondihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) can often achieve more rapid rate control than use of oral agents. Choice of agents is usually based on comorbidities. Beta-blockers have often been first line therapy for ventricular rate control after cardiac surgery, and may be preferred over calcium channel blockers in patients with coronary disease. Calcium channel blockers are preferred in patients with bronchospasm limiting consideration of beta-blockers, but should be avoided in patients with heart failure or severe LV dysfunction. Diltiazem is often as effective as beta-blockers with less hypotension, can be titrated as a continuous infusion, and has a greater margin of safety than verapamil, which may be limited by hypotension.

The use of digoxin is generally less effective in the acute postoperative high catecholaminergic state, and it has a slower onset of action. But in the face of hypotension, digoxin may be the treatment of choice. Beta-blockers and calcium channel blockers have been shown to be more effective at controlling ventricular rates with shorter times to effect than digoxin. Tisdale, *et al.* [100] compared intravenous diltiazem (N=20) vs. digoxin (N=20). The endpoints included ventricular rate control, defined as a ≥20% decrease from in pretreatment ventricular rate, and postoperative length of stay. Intravenous diltiazem achieved rate control within a mean of 10 mins, compared to 352 mins with digoxin ($P<0.0001$). At 2 and 6 hours, successful rate control was higher in the diltiazem group, but by 24 hrs there was no difference, as conversion to sinus rhythm occurred in 55% on diltiazem and 65% on digoxin. There was no difference in postoperative length of stay. However, digoxin may be particularly useful in patients with heart failure, LV dysfunction, or hypotension, or in combination with other agents. The addition of digoxin might also facilitate a lower dose of beta-blockers or calcium channel blockers in patients with hypotension. Combination use of beta-blockers, calcium channel blockers, or digoxin can be attempted in patients with rapid rates refractory to monotherapy, but caution should be exercised with dosage modification to avoid hypotension and bradycardia, including pauses upon termination of AF.

It should be noted that in the presence of ventricular preexcitation (Wolff-Parkinson-White syndrome), AV nodal blocking agents, such as calcium channel blockers, beta-blockers, digoxin and intravenous amiodarone may potentiate rapid conduction through the accessory atrioventricular pathway due to removal of concealed conduction from the AV node. Digoxin may also shorten the AV node effective refractory period within the accessory pathway. For these patients AV nodal blocking agents should be avoided, and antiarrhythmic medication (intravenous ibutilide, amiodarone, or procainamide) considered.

Amiodarone has also been used for ventricular rate control. However, as its antiarrhythmic properties could lead to conversion of AF to sinus rhythm, caution should be exercised if amiodarone is initiated after 24–48 hours after the onset of AF, as there is a possibility that the AF could convert to sinus rhythm with the attendant risk of thromboembolism. In these circumstances, a TEE should be considered to exclude left atrial or left atrial appendage thrombi prior to initiation of amiodarone.

Parameters for optimal control of ventricular rates during AF remain controversial. The RACE II study [28] evaluated a lenient (resting heart rate <110 bpm) versus strict (resting heart rate <80 bpm) rate control strategy in 614 patients with permanent AF. There was no difference in cardiovascular death, hospitalization for heart failure, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. It should be noted that the mean ventricular rate in the lenient-control group was 85 bpm and in the strict-control group 76 bpm at the end of the follow-up period. Although this population is quite different from patients with new onset POAF, more lenient rate control (to HR ≤ 110 bpm) may be preferable to strict rate control in the postoperative setting when patients are prone to hemodynamic instability or hypotension. The normal metabolic response to surgery is associated with an increase in catecholamines, often manifested in sinus tachycardia in the early perioperative period and reflected in higher ventricular rates in AF.

There are no data to suggest efficacy for adding magnesium or potassium to facilitate conversion to sinus rhythm or to improve rate control after thoracic surgery. However, it seems reasonable to recommend maintaining normal levels.

RECOMMENDATIONS

5.4.2. Recommendations for the use of antiarrhythmic drugs (figure 6a and 6b)

Class IIa

5.4.2.1. Restoration of sinus rhythm with pharmacologic cardioversion is reasonable in patients with symptomatic, hemodynamically stable POAF [5], [139]–[141]. (LOE C)

5.4.2.1.1. Intravenous amiodarone can be useful for pharmacologic cardioversion of POAF [15], [26], [96], [104], [106]. (LOE B)

5.4.2.2. It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm for patients with recurrent or refractory POAF [2], [115]. (LOE B)

5.4.2.2.1. Amiodarone, sotalol, flecainide, propafenone, or dofetilide can be useful to maintain sinus rhythm in patients with POAF, depending on underlying heart disease, renal status and other comorbidities (see below) [2]. (LOE B)

Class IIb

5.4.2.3. Flecainide or propafenone may be considered for pharmacologic cardioversion of POAF and maintenance of sinus rhythm if the patient has had no prior history of myocardial infarction, coronary artery disease, impaired LV function, significant LVH, or valvular heart disease that is considered moderate or greater. These agents may need to be combined with an AV nodal blocking agent [3], [26], [29], [104], [106]. (LOE C)

5.4.2.4. Intravenous ibutilide or procainamide may be considered for pharmacologic conversion of POAF for patients with structural heart disease and new onset POAF, but no hypotension or manifestations of congestive heart failure. Serum electrolytes and QTc interval must be within a normal range and patients must be closely monitored

during and for at least 6 hours after the infusion if either ibutilide or procainamide [3], [26], [29], [104], [106]. (LOE B)

5.4.2.5. Intravenous ibutilide or procainamide may be considered for patients with POAF and an accessory pathway [2], [29]. (LOE B)

Class III

5.4.2.6. Flecainide and propafenone should not be used to treat POAF in patients with a history of a prior myocardial infarction, coronary artery disease, and/or severe structural heart disease, including severe left ventricular hypertrophy, or significantly reduced left ventricular ejection fraction [3], [29]. (LOE B)

5.4.2.7. Dronedarone should not be used for treatment of POAF in patients with heart failure [2], [73]. (LOE B)

REASONING—For patients with symptomatic but hemodynamically stable AF after thoracic surgery, consideration should be given to restoring sinus rhythm with pharmacological cardioversion [139], Faniel:1983vl. [141]. While one study demonstrated a cardioversion rate of 86% with intravenous amiodarone in patients undergoing pulmonary resection for lung carcinoma [26], [96], a meta-analysis that included both medical and POAF suggested a slightly lower rate of conversion of 76% [15], [26], [96], [104], [106], [142]. The class IC antiarrhythmic drugs (flecainide, propafenone) may also be considered to restore and maintain sinus rhythm. Reisinger *et al.* [143] compared the efficacy and safety of intravenous flecainide vs. intravenous ibutilide in patients with recent onset AF and showed that the rate of cardioversion was similar (56% vs. 50%, $P>0.05$). However, it should be appreciated that the intravenous form of flecainide is not available in the U.S. and an oral loading dose of flecainide (and propafenone) would be required to restore sinus rhythm [96], [142]–[146]. It is usually customary to combine flecainide and propafenone with AV nodal blocking agents to prevent 1:1 atrial flutter and rapid ventricular conduction. Ibutilide is another antiarrhythmic drug that has moderate efficacy at restoring sinus rhythm [143]. However, it is only available in an intravenous form and it necessitates close monitoring of serum electrolytes and QTc. Patients must be monitored during and after intravenous ibutilide for at least 6 hours [2], [147].

For patients with recurrent symptomatic POAF, it is reasonable to not only restore sinus rhythm but also consider maintaining sinus rhythm with antiarrhythmic drugs. While many membrane active drugs (amiodarone, sotalol, flecainide, propafenone, dofetilide or dronedarone) have been shown to prevent recurrences of AF in both POAF and in the non-operative setting with variable efficacy, the choice of antiarrhythmic drug is very much governed by associated comorbidities, such as structural heart disease and impaired renal function. Overall, the selection of antiarrhythmic drugs to maintain sinus rhythm after thoracic surgery is similar to that outlined in the recently published AF guidelines for the management of non-operative AF [2], [3]. A review of antiarrhythmic drugs, their side effects and interactions are outlined in Section 3 and in tables 6 and 7.

RECOMMENDATIONS

5.5. Non-pharmacologic management of POAF

5.5.1. Recommendations for DC cardioversion for stable patients with POAF

5.5.1.1. DC cardioversion is recommended for symptomatic or relatively hemodynamically compromised patients with POAF if they do not respond promptly to pharmacological attempts to control rapid ventricular rates [2], [3], [45]. (LOE C)

5.5.1.2. DC cardioversion is recommended for patients without hemodynamic instability when symptoms of AF are unacceptable to the patient or when rapid ventricular rates do not respond to pharmacological measures [2], [6], [30]. (LOE C)

5.5.1.3. DC cardioversion can be a reasonable alternative to pharmacological cardioversion [139]–[141]. (LOE C)

5.5.1.4. Pretreatment with an antiarrhythmic drug can be useful to enhance the success of DC cardioversion (as described in 5.2.2.1.1.) and to prevent recurrent AF [2]. (LOE B)

5.5.1.5. Caution is advised for patients with preoperative or unknown sinus node dysfunction or with patients receiving significant doses of rate controlling medications, as significant pauses can occur after DC cardioversion. For those patients external pacing may be required and should be readily available. (LOE C)

5.5.1.6. It is reasonable to repeat DC cardioversion, following administration of an antiarrhythmic medication, for patients who relapse to AF after successful cardioversion [2], [45]. (LOE C)

5.5.1.7. Patient and physician preference are reasonable considerations for selecting DC cardioversion [2], [101]–[103], [105]. (LOE C)

5.6. Recommendations for prevention of thromboembolism for patients with stable atrial fibrillation/flutter undergoing DC cardioversion

Class I

5.6.1. For stable patients with POAF of 48-hours duration or longer, anticoagulation (with warfarin for INR 2.0 to 3.0, a novel oral anti-coagulant [NOAC] or LMWH) is recommended for at least 3 weeks prior to and 4 weeks after cardioversion, regardless of the method (electrical or pharmacological) used to restore sinus rhythm [2], [35], [107]. (LOE B)

Class IIa

5.6.2. During the first 48 hours after the onset of POAF, the need for anticoagulation before and after DC cardioversion may be based on the patient's risk of thromboembolism (CHA_2DS_2-VASc score; figures 9 and 10) *balanced by the risk of postoperative bleeding* [2], [108]–[110]. (LOE C)

5.6.3. For POAF lasting longer than 48 hrs, as an alternative to 3 weeks of therapeutic anticoagulation prior to cardioversion of POAF, it is reasonable to perform TEE in

search of thrombus in the LA or LA appendage, preferably with full anticoagulation at the time of TEE in anticipation of DC cardioversion after the TEE [111], [148], [149]. (LOE B)

5.6.3.1. For patients with no identifiable thrombus, DC cardioversion is reasonable immediately after the TEE exam if therapeutic anticoagulation is achieved. Anticoagulation should continue for at least 4 additional week though the benefits must be weighed against the risk of bleeding [2], [111]–[114]. (LOE C)

5.6.4. For POAF lasting longer than 48 hrs in patients who are not candidates for TEE (e.g. post-esophageal surgery), an initial rate control strategy combined with therapeutic anticoagulation using warfarin (aiming for INR 2.0 to 3.0), a direct thrombin inhibitor (e.g. dabigatran), factor Xa inhibitor (e.g. rivaroxaban, apixaban), or LMWH is recommended for at least 3 weeks prior to and 4 weeks after cardioversion. (LOE C).

5.6.5. Anticoagulation recommendations for cardioversion of atrial flutter are similar to those for atrial fibrillation [2], [17], [95], [97], [116]. (LOE C)

Class III

5.6.6. For patients with an identified thrombus, cardioversion should not be performed until a longer period of anticoagulation is achieved (usually at least 3 weeks) and in accordance with established AF guidelines [2], [27], [42], [110], [117], [148], [149]. (LOE B)

REASONING—Electrical DC cardioversion is recommended for new onset POAF that is associated with unstable hemodynamics. DC cardioversion should be performed under deep conscious sedation with R-wave synchronized shocks. Biphasic waveform shocks are preferred over monophasic waveforms, which can require higher defibrillation energies for success.

Commonly, rate control is attempted for at least the first 24 hours, as up to 80% of patients may spontaneously convert with rate control alone (see rate control agents in table 6). For patients with persistent AF and significant symptoms despite attempts to control ventricular response, pharmacologic or electrical cardioversion can be considered. When AF nears 48 hours in duration, such pharmacologic or electrical cardioversion may be reasonable, particularly in patients who are at high risk for bleeding, to avoid anticoagulation that would otherwise be indicated for AF persisting longer than 48 hrs (see Section 5.3.1.). Pretreatment with an antiarrhythmic drug (see in table 7) can be useful to enhance the success of electrical cardioversion and prevent recurrent AF. However, this requires some caution if the preoperative or current status of sinus node function is unknown. If sinus node dysfunction is present, since most antiarrhythmic drugs suppress sinus node function, successful cardioversion can be associated with initial prolonged asystole and/or prolonged hypotension. In such patients, readiness for external pacing should be anticipated. If the status of sinus node function is unknown, proceeding to electrical cardioversion without administration of a pre-cardioversion antiarrhythmic drug is reasonable.

For recurrent AF after initial conversion to sinus rhythm, cardioversion may be considered, often after initiation of an antiarrhythmic drug to prevent further recurrences. For recurrent or refractory AF, evaluation for potential triggering causes should be investigated. These include bleeding, pulmonary embolism, pneumothorax, pericardial processes, airway issues, myocardial ischemia, infection, sepsis, or use of catecholaminergic inotropes. Should AF manifest as frequent paroxysms with intervening episodes of sinus rhythm, electrical cardioversion is not recommended, unless AF becomes persistent, as AF is likely to recur after cardioversion. In these situations, an antiarrhythmic drug may be beneficial.

For AF >48 hrs in duration, anticoagulation with warfarin (INR 2.0 to 3.0), a direct thrombin inhibitor (e.g. dabigatran), factor Xa inhibitor (e.g. rivaroxaban, apixaban), or low molecular weight heparin is recommended for at least 3 weeks prior to and 4 weeks after cardioversion, as in other patients with AF. As an alternative to anticoagulation prior to cardioversion of AF, a TEE may be performed in search of thrombus in the LA or LAA. It is preferable to perform the TEE on full anticoagulation with heparin or therapeutic levels of oral anticoagulants, and then to perform electrical or pharmacologic cardioversion immediately afterwards on therapeutic anticoagulation. This is preferred over performing a TEE while off anticoagulation or on sub-therapeutic anticoagulation, as a thrombus may form between the time of TEE and full anticoagulation. In patients with no identifiable thrombus, cardioversion is reasonable immediately after TEE on therapeutic anticoagulation with anticoagulation continued for at least 4 weeks afterwards, as for patients undergoing elective cardioversion. For patients with an identified thrombus, cardioversion should be deferred until a longer period of anticoagulation is achieved and in accordance with established AF guidelines. The TEE-guided cardioversion approach is supported by results of the ACUTE trial, which enrolled 1222 patients with AF of greater than 2 days duration and randomized them to TEE-guided cardioversion vs warfarin anticoagulation for at least 3 weeks prior to cardioversion. There was no difference between groups in the rate of embolic events, but the rate of hemorrhagic events was lower in the TEE group. It should be noted that exclusion of left atrial thrombus by TEE does not preclude thromboembolism in the absence of therapeutic anticoagulation. Black *et al.* [150], reported 17 patients with nonvalvular AF who had embolic events 2 hours to 7 days after cardioversion despite a TEE showing no LA thrombus. None of the patients were on therapeutic anticoagulation at time of embolism. Thus, the TEE-guided cardioversion strategy should be coupled with therapeutic anticoagulation at the time of and after cardioversion for patients whose AF is greater than 48 hours in duration.

It is recognized that in the thoracic surgery population, some patients will not be candidates for TEE because of esophageal procedures, including esophagectomy (or those with esophageal pathology). In these patients, if AF duration is > 48 hrs, an initial rate control approach is reasonable with therapeutic anticoagulation, using warfarin (INR 2.0 to 3.0), a direct thrombin inhibitor (e.g. dabigatran), factor Xa inhibitor (e.g. rivaroxaban, apixaban), or LMWH, recommended for at least 3 weeks prior to and 4 weeks after cardioversion. Cardiac CT has been used to assess for LAA thrombus, predominantly prior to AF catheter ablation. A recent meta-analysis [151] reported accuracy comparable to TEE, especially when delayed images were acquired, with a sensitivity and specificity of 96% and 92%

compared to TEE, a positive predictive value of 41% and negative predictive value of 99%. As clinical outcomes studies are needed to assess its clinical utility for cardioversion, in the case of patients with esophageal surgical procedures precluding TEE, the rate control strategy with deferred cardioversion until at least 3 weeks of therapeutic anticoagulation is achieved seems reasonable. For selected patients, a cardiac CT may be of some value.

RECOMMENDATION

5.7. Recommendation for EP catheter ablation

Class III

5.7.1. Catheter or surgical ablation of AF is not recommended for management of patients with postoperative AF after thoracic surgery. (LOE C).

REASONING—Catheter ablation of AF is a well-established and commonly employed therapeutic option for managing patients with symptomatic AF [2], [3]. At the present time, catheter ablation of AF plays no role in the management of patients who develop AF in the early post-operative setting. This recommendation is based on a number of important considerations. First, all patients who undergo catheter ablation of AF must be anticoagulated for a minimum of two months following ablation. Patients who cannot be anticoagulated continuously for two months are not considered to be ablation candidates. Second, catheter ablation of AF is a complex and lengthy procedure (3 to 6 hours) that is most commonly performed under general anesthesia. Third, it is very common for AF to recur in the 2 – 3 month post ablation “healing phase.” This reflects the presence of considerable inflammation and lesion maturation that occurs post ablation. The presence of these “healing phase” arrhythmias means that AF ablation is an inappropriate strategy for control of acute, symptomatic AF, such as occurs in the postoperative setting. Fourth, the efficacy of catheter ablation is modest. In optimal candidates for the procedure with paroxysmal AF who are otherwise healthy the single procedure success rate at 12 months is 60% to 80%. Late recurrences following 12 months of follow-up are common. And finally, AF ablation is associated with a significant risk of complications. For more information regarding the technique, risks, indications, and outcomes of AF ablation, please refer to the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation [152].

RECOMMENDATIONS

5.8. Surgical and interventional treatment options

5.8.1. Recommendations for Pre-Existing AF

5.8.1.1. Pre-existing AF should be managed according to existing guidelines for non-postoperative AF (see section 6).

REASONING—Pre-existing AF should be treated according to the existing guidelines for non-surgical AF [2], [3]. In the rare situation where a patient cannot be treated with anticoagulation, consideration could be given to intra operative left atrial appendage resection or ligation. This could only be done if the patient is undergoing a left thoracotomy procedure. Regarding pulmonary vein isolation procedures, a complete bilateral procedure

can only be performed in the rare situation when bilateral thoracotomies are performed or if a clam-shell incision is employed.

New onset AF following thoracic surgery: An intraoperative procedure is not indicated based solely on a prediction model for patients likely to develop POAF. Procedures such as pulmonary vein isolation (PVI) and/or left atrial appendage resection or ligation are not routinely practiced for prevention of POAF in cardiac surgery, where the exposure allows such procedures to be performed easily.

New onset AF following thoracic surgery: long term strategies: It is well known that the overwhelming majority of POAF is self-limiting to 4–6 weeks. For persistent AF beyond that time or POAF requiring long term anticoagulation, patients should be referred to a cardiologist/cardiac electrophysiologist for future management according to general AF guidelines. If such patients are intolerant of antiarrhythmic medications, a catheter-based ablation procedure may be offered according to the existing guidelines for AF ablation. A surgical ablation procedure can be offered in the rare instance of a patient requiring a cardiac surgical procedure. A full PVI or LA maze and possible RA maze procedure may be performed. In addition, a left atrial appendage exclusion procedure could be also performed. If such patients are intolerant of long-term anticoagulation, left atrial appendage exclusion could be considered [127], [153].

6. Management of the patient with pre-existing AF (figure 7)

Patients with preexisting AF represent a high-risk population for stroke, heart failure and other POAF related complications. Some may have valvular heart disease. The management of their antiarrhythmic medications, and their perioperative anticoagulation may pose a challenge.

RECOMMENDATIONS

6.1. Criteria for obtaining cardiology consult for pre-operative AF

Class IIa

6.1.1. Pre-operative cardiology consult can be useful for patients with pre-operative AF that is either newly diagnosed or persistent and symptomatic. (LOE C)

6.2. Perioperative management of anticoagulation for patients on long-term (warfarin or NOAC) anticoagulation

Class I

6.2.1. Decisions regarding the duration of interruption of anticoagulation and/or the need for perioperative heparin bridging should be based on the patient's stroke risk profile (based on their CHA_2DS_2-VASc score). (LOE C)

Class IIa

6.2.2. For patients who have a high stroke risk (based on their CHA_2DS_2-VASc score (figure 9 and 10), history of prior stroke, or presence of a mechanical heart valve,

perioperative bridging with a short-acting anticoagulant (i.e. enoxaparin) is reasonable for patients with eGFR>50% when warfarin anticoagulation is withheld. (LOE C)

Class IIb

6.2.3. Short-term withdrawal of anticoagulation without bridging may be considered for those patients who are on anticoagulation preoperatively as part of their treatment for persistent AF but have a CHA_2DS_2-VASc score less than 2, have not had heart failure, have an EF above 35%, and/or for whom bridging anticoagulation would be burdensome or otherwise undesirable. (LOE C)

6.3. Post-operative resumption of anti-coagulation

Class IIa

6.3.1. If anticoagulation is interrupted, the duration should be minimized. It is reasonable to base decisions about the duration of interruption and the time of resumption of anticoagulation on the patient's stroke risk profile (CHA_2DS_2-VASc score) weighed against the risk of postoperative bleeding. (LOE C)

6.4. Post-operative follow-up

Class IIb

6.4.1. It is reasonable to consider postoperative follow-up with a cardiology specialist for patients with preoperatively identified AF who meet one or more of the following criteria:

6.4.1.1. Ejection fraction ≤ 45% or diagnosis of systolic heart failure or cardiomyopathy;

6.4.1.2. Discharged on a new rate control and/or rhythm control agent(s);

6.4.1.3. Dose of a home rhythm control agent(s) was adjusted while inpatient;

6.4.1.4. Discharged on a new anticoagulant (parenteral and/or oral). (LOE C)

REASONING—In the Rocket AF trial comparing warfarin and rivaroxaban for the prevention of thromboembolism in non-valvular AF, 33% of the 14,236 patients had a temporary interruption of anticoagulation of greater than or equal to 3 days (mean duration 5 days). 81% of these patients had persistent AF and greater than 99% had a $CHADS_2$ score greater than or equal to 2 (mean 3.4) [154]. 50% of the patients had a history of stroke or TIA and 62% had a history of CHF. 40% of the temporary interruptions were for procedures, though only 14% were for abdominal, thoracic, orthopedic, or cardiac procedures. The 30 day stroke or systemic embolism rate of 0.36%, though similar in both the rivaroxiban and warfarin groups, 0.30% vs. 0.41% (HR 0.74 C.I. 0.36–1.5 p=0.4) was higher than the overall 2.2%/year rate throughout the study.

In the Rocket AF study [154], bridging of anticoagulation for temporary interruptions was tracked, and only 6% of the temporary interruptions were bridged, 98.6% with low molecular weight heparin (LMWH) and 1.4% with fondaparinux. The bridge group was slightly older, 74 vs 73 years (p 0.019), had a fractionally higher $CHADS_2$ score, 3.52 vs

3.40 (p 0.0094), more often had diabetes, 48 vs 41% (p 0.0049), and had more temporary interruptions. The bridge group prior stroke and TIA as well as CHF rates were similar to the non-bridge group. The bridged patients had only 1 stroke/embolic event, a 30 day rate of 0.17%, whereas the non bridge group 30 day event rate was 0.37%. Major bleeding was similar in both groups, but the bridged group had a higher incidence of major/non major clinically relevant bleeding, 4.83% vs. 3.02%. Due to small numbers and variable reasons for bridging, statistical significance was not calculated. These data raise the concern that discontinuation of anticoagulation may expose the patients to a small but significant risk of stroke.

Additional data that suggest the importance of considering the risk of stroke when contemplating the temporary interruption of anticoagulation was derived from data obtained after the closing of the Rocket AF trial. Following cessation of study medication, the rivaroxiban patients required an average of 13 days to achieve a therapeutic INR, while the patients receiving warfarin required only 3 days. The rivaroxiban group had 22 embolic events while the warfarin group had 7 events over 31 days of follow-up [155]. The full role of perioperative bridging will be further elucidated in two ongoing randomized trials, BRIDGE (Effectiveness of bridging anticoagulation for surgery [http://trials.gov]) and PERIOP-2 (a double blind randomized controlled trial of post operative low molecular weight heparin bridging therapy vs. placebo bridging therapy for patients who are at high risk for arterio-thromboembolism [http://trials.gov]).

7. Management of anticoagulation for new onset POAF

In order to minimize the risk of perioperative bleeding while providing sufficient protection from the POAF-related strokes a careful evaluation of the patients' stroke risk is essential. The recently approved novel oral anticoagulants (NOAC; direct thrombin inhibitors and anti-Factor Xa agents) offer alternatives to warfarin, and are gaining popularity in the community for the long-term management of AF-related anticoagulation.

RECOMMENDATIONS

Class I

7.1. For the prevention of strokes for patients who develop POAF lasting longer than 48 hours, it is recommended to administer antithrombotic medications similarly to non-surgical patients (figure 8). Decision to initiate therapy should be based upon the benefit of reducing stroke risk versus the risk of bleeding in the post-operative period [15], [17], [42], [45], [95], [97], [116], [118], [119], [156]–[158]. (LOE A)

7.1.1. For effective anticoagulation, an INR range of 2–3, with a target of 2.5, for warfarin is recommended unless otherwise contraindicated [120]–[122], [159], [160]. (LOE A)

7.1.2. The INR should be determined at least weekly during initiation of therapy and monthly when the doses of anticoagulant and the INR are stable [123], [161]–[163]. (LOE A)

REASONING—The overall risk of a perioperative stroke in all patients undergoing anesthesia has been estimated at 0.5–0.8% in large studies of patients who have had non-cardiac surgery [164], [165]. One of these studies use the Nationwide Inpatient Sample of 131,067 patients and determined that among 39,339 patients undergoing pulmonary lobectomy/segmentectomy the incidence of acute ischemic stroke was 0.6% which rose to 0.8% for patients over 65 yr., respectively [164]. Risk factors associated with perioperative stroke in that study were renal disease, atrial fibrillation, history of stroke and cardiac valvular disease [164]. Mortality in patients who developed a stroke after lung resection was 33% compared to 3.2% in those who did not [164]. The reported incidence of stroke or transient neurological injury of 1.6–3.3% after cardiac operations is consistently greater for patients who develop persistent postoperative AF compared to 0.2–1.4% for those without AF [166]. It has been established that oral anticoagulation with warfarin is associated with 60–70% reduction from the 4–5% overall risk of ischemic stroke per year in patients with persistent or chronic non-valvular AF not receiving warfarin [45], [157], [158], [167]. Depending of the type of surgery (total hip replacement, hemicolectomy or lung resection), 12–33% of arterial thromboembolic events are fatal and more than 40% result in serious permanent disability [156], [158]. On the other hand, 3% of episodes of major postoperative bleeding are fatal but most patients make a full recovery. As many as 50% of bleeding episodes require a re-operation [156]. A retrospective study of patients who developed new onset AF after general thoracic surgery compared patients that received some form of antithrombotic therapy for AF to those who did not receive anticoagulation and found that patients who were anticoagulated had stroke rate of 2.2% compared to 0.6%, respectively as well as had a greater incidence of bleeding episodes [167]. In that study patients who were anticoagulated had more comorbidities and greater risk score for stroke. Whether individuals require short-term anticoagulation must be individualized for each patient based on the intrinsic risk for thromboembolism and risk of bleeding [45], [157], [158]. For most types of surgery initiation or resumption of warfarin can be undertaken 12–24 hours after surgery unless the patient is at special risk for bleeding such as those with a low platelet count, prolonged excessive chest drainage or those who might require an invasive procedure within days or weeks of discharge such developing an anastomotic leak after esophagectomy, for example [45], [156]–[158], [167]. These latter patients may better be managed by LMWH and/or by a TEE-guided “fast-track” strategy to rule out a left atrial appendage thrombus and then receive DC cardioversion [157], [158], [166]. Since the potential for thromboembolism with new onset AF develops early, prompt attempts to restore sinus rhythm within this period should be made. If the arrhythmia persists beyond 24–48 hrs anticoagulant therapy should be considered after weighing the risk of postoperative bleeding. In a prospective study of 330 patients undergoing anatomic lung resection, 1 of 60 patients (1.7%) with postoperative AF developed a stroke within 24 h of AF onset and Holter monitoring later showed that the initial 12 h of AF were asymptomatic [27]. Others have questioned the 48 h window and suggest that it might be reasonable to start anticoagulation therapy in the first 48 h if multiple risk factors for stroke are present. They further suggest that a TEE-guided strategy may prove useful in situations where both the risk of stroke and risk of postoperative bleeding pose a dilemma regardless of the fact that AF was not present for 48 h [168].

The goal of anticoagulation should balance the risk of stroke and the risk of bleeding. The range should be optimal for adequate stroke prevention but at the same time should be at the minimal bleeding threshold. In AF, INR range of 2.0–3.0 with target of 2.5 should fulfill this requirement [169]. Randomized control studies have shown that warfarin therapy with an INR 2.0–3.0 was associated with improved outcome compared to aspirin [170]. Hylek *et al.* retrospectively studied 13559 patients with non-valvular AF and showed that INR<2 at admission was associated with an increased number of strokes [159]. Recently, in the RE-LY trial, a randomized controlled trial which compared the outcomes of warfarin vs dabigatran treatment in AF patients. Warfarin was managed with the target INR was 2.0 to 3.0 and the maximum interval between INR tests was 4 weeks. They used an algorithm to manage the INR, e.g. +15% dose/week increase for INR<1.5, +10% dose/week increase for INR 1.5–1.99, −10% dose/week decrease for INR 3.01–4.00. Instillation of this algorithm resulted an increase in TTR [160].

For in-hospital patients on warfarin, INR is measured every day until it is therapeutic. For outpatient follow-up, INR is followed every few days until it reaches the stable therapeutic target, then the interval can be prolonged as long as 4–6weeks. The frequency of follow up depends on patients' compliance, drug and food interactions, interruption for surgical procedures and existence of other comorbidities [161]. Its frequency should be increased when switching over to another type of anticoagulant, such as heparin-bridge. Pengo *et al.* randomized 124 patients to 4-week interval and 6-week interval follow-up of INR testing for patients with prosthetic mechanical valves and showed that there was no difference in their time in therapeutic range (TTR) [162]. Schulman *et al.* showed in their randomized study of 250 patients receiving warfarin, followed at 4-week intervals versus 12-week intervals with phone follow up every 4 weeks that the 12-week interval group had similar TTR and bleeding/embolic events [163]. The American College of Chest Physicians recommends follow up interval of up to 12 weeks if INR is stable [161].

RECOMMENDATIONS

Class I

7.2. Anticoagulation within the first 48-hrs of POAF (figure 9) should be considered based on the CHA_2DS_2-VASc risk score (figure 10) of the patient for stroke weighed against the risk of postoperative bleeding. (LOE C)

7.2.1. For risk assessment, the following may serve as a guide: CHA_2DS_2-VASc risk score (figure 10) for stroke [2]–[4], [147]. (LOE A):

S=0: no anticoagulation recommended

S=1: anticoagulation should be considered if its benefits outweigh the risk of bleeding

S=2 anticoagulation is highly recommended if its benefits outweigh the risk of bleeding

7.2.2. The presence of impaired renal function should weigh in favor of anticoagulation. Caution should be exercised when patients on dialysis are considered

for anticoagulation as the benefits for those patients are less certain [2], [3], [171]–[174]. (LOE A)

7.2.3. If not precluded by concerns for bleeding, anticoagulation is also recommended when conversion to sinus rhythm is attempted by (DC or chemical) cardioversion (as above) [2], [3], [45], [157], [158]. (LOE C)

REASONING—Since the analysis by the Atrial Fibrillation Investigators (AFI) of the first 5 prospective, randomized, clinical trials comparing oral anticoagulants with placebo and sometimes with aspirin, we have learned that not all patients with atrial fibrillation have the same risk of stroke [175], [176]. The AFI demonstrated that stroke risk may be stratified by several factors, including a prior thromboembolic event or transient ischemic attack, hypertension, diabetes, congestive heart failure, poor left ventricular function, and age 65 years of age or older. Stroke risk was further stratified to mild, moderate and severe categories. Other risks such as coronary artery disease, peripheral vascular disease, gender, thyrotoxicosis, rheumatic mitral valve disease, and hypertrophic cardiomyopathy were also important risk markers to consider.

To translate these risks derived from group data to the individual, there are now several stroke risk stratification schemes available. Initially, most guidelines adopted the $CHADS_2$ stroke risk stratification scheme, and it has been widely used for many years [2], [3]. Recently the CHA_2DS_2-VASc stroke risk stratification scheme (figure 10) has taken prominence, having being adopted by the European Society of Cardiology, and the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society guidelines [2], [3], [147]. A major reason for its use is that it is better at sorting out those patients with low stroke risks who really don't need anticoagulation for prophylaxis, and those who do. Thus, a $CHADS_2$ score of 0 or 1 is associated with an annual risk of 1.9% to 2.8%, respectively, not really small risks at all. However, when applying the CHA_2DS_2-VASc stroke risk scheme to those same patients, the CHA_2DS_2-VASc score is anywhere from 0 to 4. A CHA_2DS_2-VASc of 3 or 4 carries an indication for use of anticoagulation therapy, whereas a CHA_2DS_2-VASc score of 0 does not. A CHA_2DS_2-VASc score of 1 carries the recommendation to consider the use of anticoagulation therapy.

The recommendations using the CHA_2DS_2-VASc score are that if CHA_2DS_2-VASc score is 0, the patient does not require anticoagulation. For a CHA_2DS_2-VASc score of 1, oral anticoagulation could be considered, while for a CHA_2DS_2-VASc of 2 or more, oral anticoagulation is generally indicated [147]. Although the recently published ACCF/AHA/HRS AF guidelines suggested that for a CHADS-VASC score of 1, it is reasonable to consider to use no antithrombotic therapy or aspirin if the burden of cardiovascular disease is otherwise low [2], [3]. However, the vast majority of thoracic surgical patients who develop (or have) AF would likely have an indication for anticoagulation using the CHA_2DS_2-VASc risk scoring system. Because of its ease of use, and its wide acceptance, the use of the CHA_2DS_2-VASc score is recommended for the assessment of stroke risk.

Several scoring systems have been reported to identify the risk of bleeding following the initiation of anticoagulation [171]–[173]. These scoring systems are not recommended for routine use as standard practice. However, among the risk factors, end-stage renal disease on hemodialysis is considered to pose a significant risk for bleeding when these patients are anticoagulated. Recently published retrospective review of 1626 dialyzed patients and non-dialyzed patients, anticoagulation for dialyzed patients did not decrease the risk of stroke, but increased the incidence of bleeding episodes with 44% [174].

RECOMMENDATIONS

Class IIa

7.3. New oral anticoagulants (Dabigatran, Rivaroxiban, Apixiban; [177]–[180]) are reasonable as an alternative to warfarin (table 8) for patients who do not have a prosthetic heart valve, hemodynamically significant valve disease, and/or severe renal impairment or risk of GI bleeding [2], [26], [106], [128]–[130], [155]. (LOE B)

7.4. It is reasonable to continue anticoagulation therapy for 4 weeks after the return of sinus rhythm because of the possibility of slowly resolving impairment of atrial contraction with an associated ongoing risk for thrombus formation and for delayed embolic events [45], [157], [158]. (LOE C)

REASONING—Newer oral anticoagulant drugs have recently become available, including dabigatran, rivaroxaban, and apixaban. Dabigatran is an oral direct thrombin inhibitor, while rivaroxaban and apixaban are factor Xa inhibitors. Compared with warfarin, these agents offer the advantage of not requiring monitoring of the International Normalized Ratio (INR). The efficacy of dabigatran for stroke prevention in nonsurgical, nonvalvular AF was compared with that of warfarin in the Randomized Evaluation of Long-Term Anticoagulation therapy (RE-LY) trial [181], which was a prospective noninferiority study that randomized 18,113 patients into three groups: dabigatran 110 mg twice daily or dabigatran 150 mg twice daily, administered in blinded fashion, or warfarin titrated to an INR of 2.0–3.0, administered in unblinded fashion for a median duration of 2 years. Dabigatran 150 mg twice daily significantly reduced the risk of stroke or systemic embolism by 34% compared to warfarin. There was no significant difference in the incidence of death in either dabigatran group compared with that in warfarin-treated patients. There was no difference between the warfarin and dabigatran 150 mg twice-daily groups in incidence of major bleeding. However, dabigatran 150 mg twice daily was associated with a significantly lower incidence of hemorrhagic stroke compared with that in the warfarin group. The efficacy of rivaroxaban for reducing risk of stroke in patients with nonsurgical, non-valvular AF was compared with that of warfarin in the Rivaroxaban Once Daily Oral direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism in Atrial Fibrillation (ROCKET-AF) trial [155]. In this non-inferiority study, 14,264 patients with AF were randomized in double-blind fashion to receive rivaroxaban 20 mg orally daily or warfarin, titrated to an INR of 2.0–3.0 for a median treatment period of 590 days (median follow-up 707 days). Compared with warfarin, rivaroxaban significantly reduced the risk of stroke or systemic embolism by 21%. Using an intention-to-treat analysis, there was no significant difference between rivaroxaban and warfarin in the

incidence of stroke or systemic embolism. There was no difference between the groups in the incidence of major and non-major clinically relevant bleeding. However, the incidence of intracranial hemorrhage and fatal bleeding was significantly lower in rivaroxaban-treated patients. The efficacy of apixaban compared to that of warfarin for stroke prevention in nonsurgical, non-valvular AF was investigated in the Apixaban for Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) non-inferiority trial [182]. Patients (n=18,201) with AF and at least one additional risk factor for stroke were randomized to receive apixaban 5 mg orally twice daily or warfarin, titrated to an INR of 2.0–3.0 for a median duration of follow-up of 1.8 years. The risk of ischemic or hemorrhagic stroke or systemic embolism in the apixaban group was significantly lower than in the warfarin group, as was the incidence of death from any cause. The incidences of major bleeding and hemorrhagic stroke were also significantly lower in apixaban-treated patients. There was no difference between the groups in the incidence of ischemic or uncertain type of stroke.

Patients who received standard anticoagulation upon discharge from the hospital can return for cardioversion between 3 – 12 weeks after initiation of anticoagulant therapy [45], [156], [166]. Patient who convert to sinus rhythm but are experiencing intermittent paroxysms of AF may be considered for anticoagulation for 1 month after the return of sinus rhythm since it has been shown that impaired atrial mechanical function can persist for several weeks after return of sinus rhythm [45], [157].

RECOMMENDATIONS

Class III

7.5. New oral anticoagulants should be avoided for patients at risk for serious bleeding (including gastrointestinal bleeding) as they cannot be readily reversed. However, their use may be recommended in situations where achievement of a therapeutic INR with warfarin has proved to be difficult [2], [128], [130], [183]. (LOE C)

REASONING—A large phase II randomized control study, namely RE-ALIGN trial which studied patients who underwent implantation of mechanical valve (aortic or mitral) or have undergone implantation of mitral bileaflet valve < 3 months before randomization [183]. The trial was terminated due to increase in strokes (5% vs 0%), myocardial infarction (MI) and major bleeding (4% vs 2%) in dabigatran group. Currently, dabigatran is contraindicated and should not be used in patients with mechanical valves.

8. Recommendations for long-term management and follow-up of patients with persistent new onset POAF (figure 11)

Those patients with POAF-related perioperative complications, and those requiring long-term management of antiarrhythmics and anticoagulants are likely to benefit from cardiology follow-up after their discharge.

RECOMMENDATIONS

8.1. Post-discharge follow-up and management recommendations for persistent new onset POAF

Class I

8.1.1. For patients who have a complicated in-hospital course related to their POAF, who have underlying structural heart disease, or who experience sequelae of AF, such as MI or decreased LVEF, follow-up with cardiology should be arranged at the time of discharge. (LOE C)

Class IIb

8.1.2. Patients with well-controlled new onset POAF (either converted to sinus rhythm or with good rate control) may be seen in routine follow up by the surgical team without cardiology follow up. (LOE C)

REASONING—The majority of cases of POAF are self-limited and even when present at discharge, will have resolved by the time of follow-up. There is little literature regarding post-discharge risks for general thoracic patients specifically. Recommendations regarding cardiology follow up for complicated patients seem self-evident. The appropriate timing for cardiology follow up should be individualized prior to discharge. For uncomplicated patients there is some evidence for guidance. Following lung resection, Rena *et al.* demonstrated that 98% of POAF resolved after discharge, although as an older study, 80% were given digitalis. The duration was between 1 and 12 days, with an average of 2 days [106]. It has been estimated that approximately 50% of episodes of POAF spontaneously convert to normal sinus rhythm within 12 hours [184]. Given the relatively short duration of POAF in most cases, it is unclear when the first postoperative visit to the surgeon in uncomplicated cases should be. The 2010 guidelines of the Canadian Cardiovascular Society recommend that medical management of AF and anti-coagulation should be reassessed at 6–12 weeks postoperatively, although this primarily was intended for cardiac surgical patients. This was considered a strong recommendation, with moderate evidence but no reference was given [185]. Kowey reported a retrospective analysis of 116 patients with POAF following coronary bypass surgery. There were 36 patients treated with antiarrhythmic and rate control drugs compared to 76 treated with rate control agents alone. Only 1 patient in each group was still in AF at 6-week follow-up [186]). In another study following coronary bypass surgery, Izhar *et al.* randomized 129 patients who had converted to sinus rhythm before discharge to 1, 3, or 6 weeks of antiarrhythmic therapy. There was no difference in the rate of recurrent AF with 0, 2, and 0 patients in the three groups. The majority of the patients were managed with amiodarone [187]. On this basis, it seems reasonable that the timing of routine surgical follow up should be dictated by surgical considerations, and the presence or absence of AF assessed at that time.

Despite the relatively self-limited nature of the vast majority of cases of POAF, the long-term significance of a single episode of POAF is unknown [188]. Ahlsson has studied the late outcome of patients who developed POAF after coronary bypass surgery and found that the development of AF was a risk factor for late mortality. Whether this applies to patients

after non-cardiac thoracic surgery is unknown. However, it seems prudent to ensure communication with the primary care physician for vigilant follow up of cardiovascular and AF risk factors.

RECOMMENDATIONS

8.2. Management of anti-arrhythmic medications

Class IIa

8.2.1. For patients who have converted to sinus rhythm prior to hospital discharge, it is reasonable to consider discontinuation of anti-arrhythmic medications 4 weeks after the ECG documented return of normal sinus rhythm or at the first post-operative visit (usually 2–6 weeks after discharge). (LOE C)

Class IIb

8.2.2. For patients with new onset POAF who were discharged in AF but who are in normal sinus rhythm (ECG confirmed) at the first post-operative visit, it may be reasonable to instruct the patients to self discontinue the anti-arrhythmic medications 4 weeks following the visit if no signs of AF recur. (LOE C)

REASONING—There is no clear evidence to guide duration of anti-arrhythmic therapy following non-cardiac thoracic surgery. Landymore *et al.* followed 58 patients following coronary artery bypass grafting with ambulatory Holter monitoring, including 3 patients who developed spontaneous symptomatic AF and received digitalis for rate control. Sixteen patients (group 2) continued taking digoxin for 8 weeks following operation, 13 patients (group 3) discontinued digoxin treatment 5 weeks following operation, and 14 patients (group 4) discontinued digoxin treatment 3 weeks following operation. Twenty-four hour Holter monitoring indicated that asymptomatic AF was common in the treatment groups after digitalization just before discharge from hospital. Recurrence of AF was rare following discharge [189]. Yilmaz performed a similar smaller study, with 120 patients who had converted to sinus rhythm (pharmacologically or with DCC) enrolled to a prospective randomized trial of placebo or 1 of three drugs (amiodarone, verapamil, or quinidine) post discharge. Patients underwent 24-hour Holter monitoring 6 times over 9 months postoperatively. Recurrent AF usually developed within 15 days of discharge. AF occurred in only one patient (3.33%) in group 1, and two each (6.66%) in each of the drug groups [190].

RECOMMENDATIONS

8.3. Management of anticoagulation

Class I

8.3.1. For patients who are started on anticoagulants, the anticoagulation should continue for a minimum of 4 weeks after return to NSR is documented. (LOE C)

Class IIa

8.3.2. More prolonged anticoagulation (longer than 4 weeks after return to NSR) can be beneficial in the presence of stroke risk factors (CHA_2DS_2-VASc score) or if the patient had a prior stroke. The concomitant presence of mild or moderately impaired kidney function weighs in favor of a longer period of anticoagulation. (LOE B)

8.4. Recommendations for long-term management of new onset, persistent POAF

Class IIa

8.4.1. Patients with new onset POAF persisting for or recurring after 4–6 weeks (or at the time of the first post-operative visit) can benefit from referral to a cardiologist for long-term management of stroke risk as well as anti-arrhythmic or anticoagulant medications.. (LOE C)

REASONING—The ideal duration of anti-coagulation following POAF is unknown. European guidelines have concluded that there is insufficient evidence to make any recommendation [191]. Others have concluded that it is reasonable to continue anti-coagulation for 4 weeks, on the basis that atrial contraction is impaired long after the AF has ceased [4]. All the current evidence in this area is Level C.

Recommendations for future AATS efforts: The taskforce recommends the establishment of a *high fidelity thoracic surgery database*, that uses the uniform definitions and monitoring strategies recommended here, stratifies by surgery type, and systematically documents the occurrence, duration, and complications of POAF and its treatment. The aim would be to develop risk prediction models, and eventually randomized interventional trials, for the prevention and treatment of POAF, specific to thoracic surgery. This could be most readily accomplished by enriching the STS data collections system.

Recommendations for the use of the guidelines: *These guidelines are best used* as a guide for practice and teaching. The applicability of these recommendations to the individual patient should be evaluated on a case-by-case basis, and only applied when clinically appropriate. Additionally, these guidelines can serve as a tool for uniform practices, to guide preoperative evaluations, and form the basis of large, multicenter cohort studies for the thoracic surgical community.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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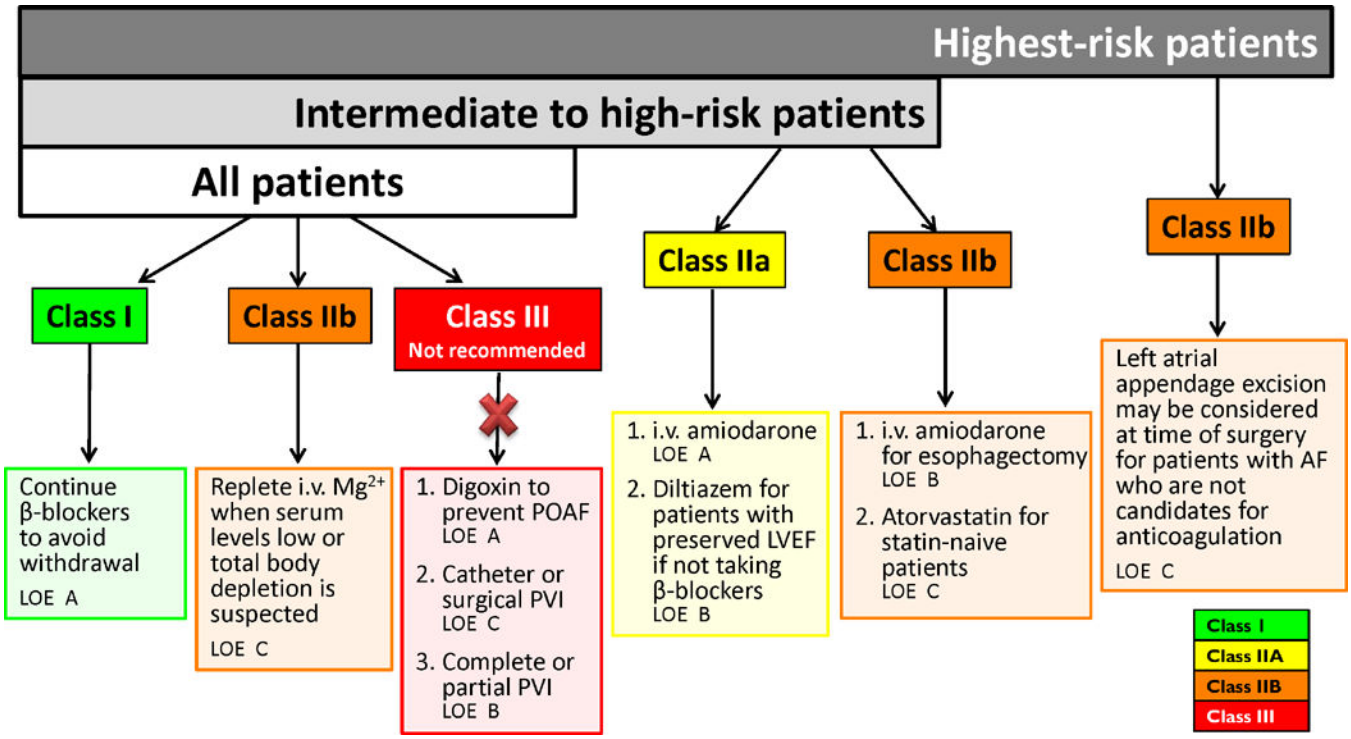


Figure 1.

Prevention Strategies and Their Efficacy for Postoperative Atrial Fibrillation (POAF)

Abbreviations: PVI: pulmonary vein isolation; LVEF: left ventricular ejection fraction; AF: atrial fibrillation

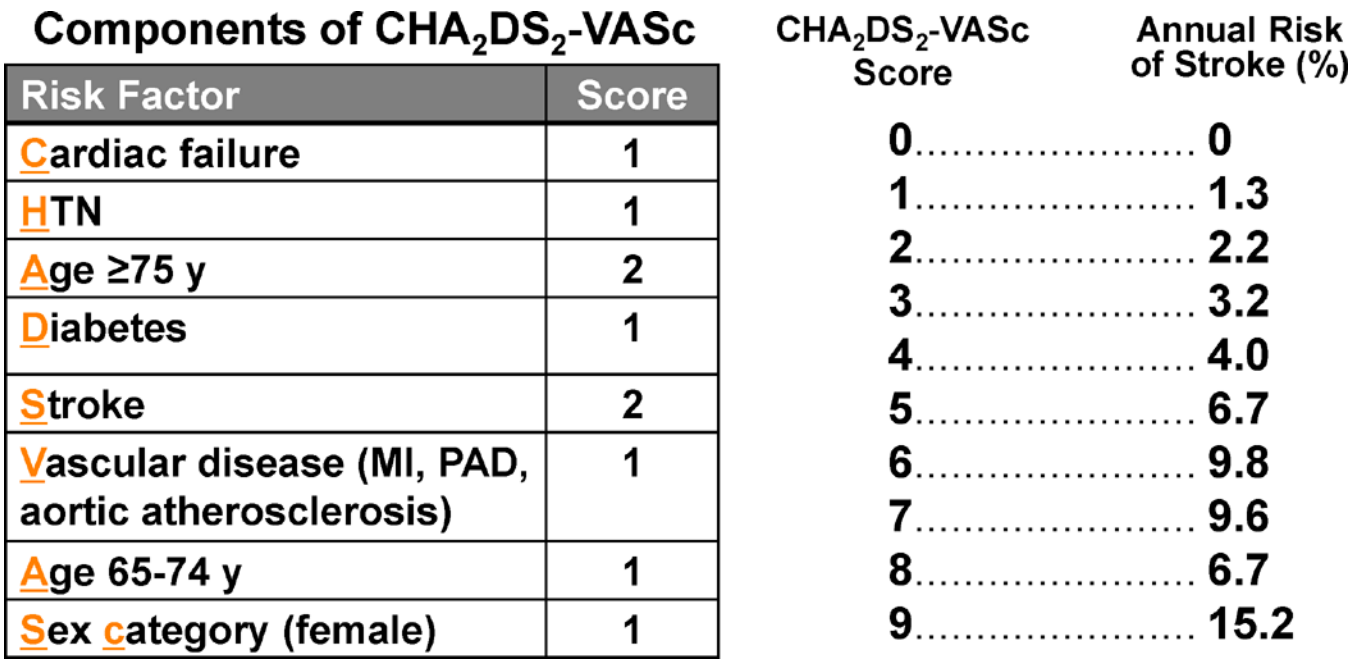


Figure 2.

Management Algorithm for Postoperative Atrial Fibrillation (POAF)

Abbreviations: AF: atrial fibrillation; MI: myocardial infarction; HF: heart failure; WPW: Wolf-Parkinson-White syndrome

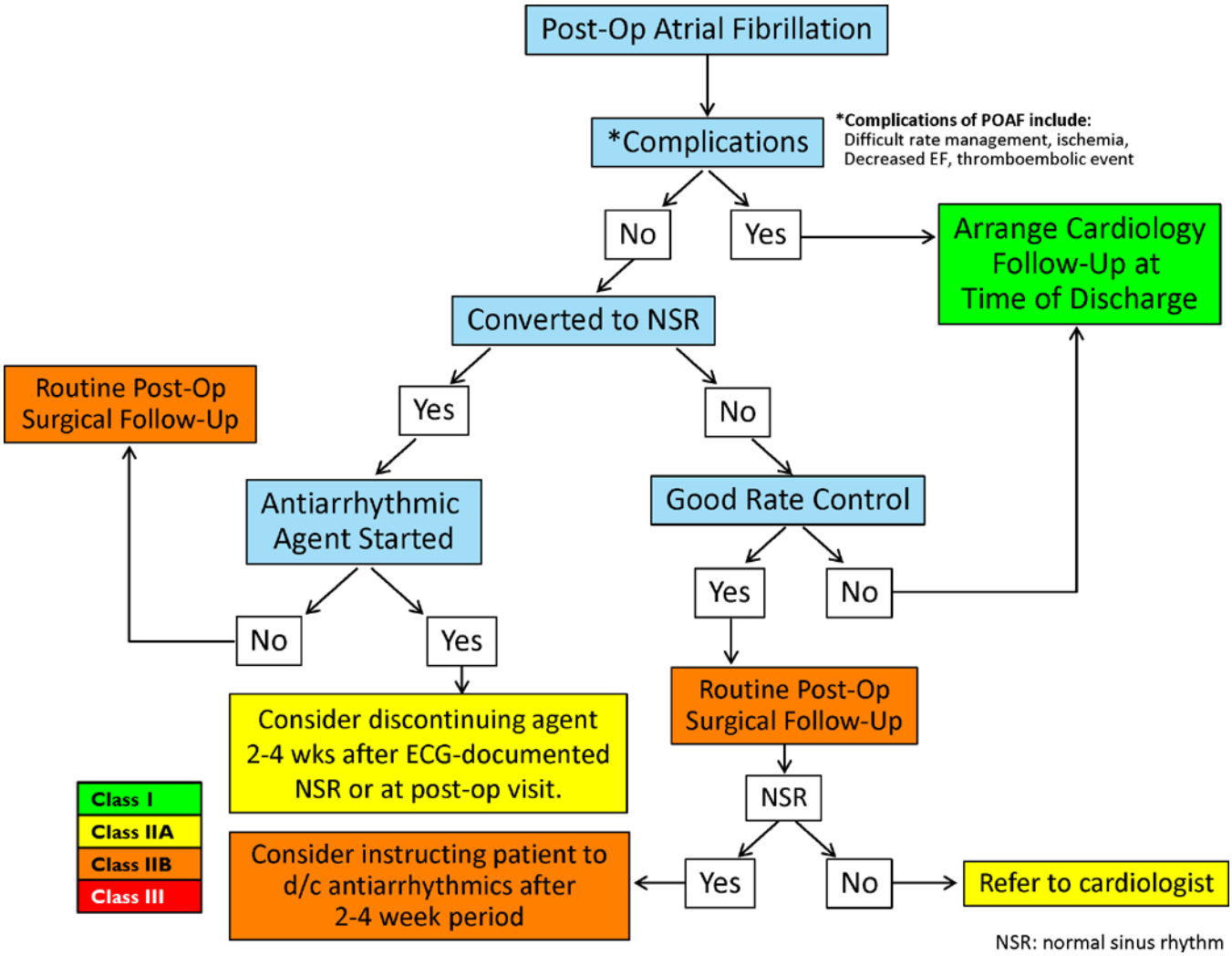


Figure 3.

Management of the Hemodynamically Unstable Patient with New Onset Postoperative Atrial Fibrillation (POAF)

Abbreviations: AF: atrial fibrillation; HF: heart failure; DC cardioversion: direct current cardioversion; i.v.: intravenous

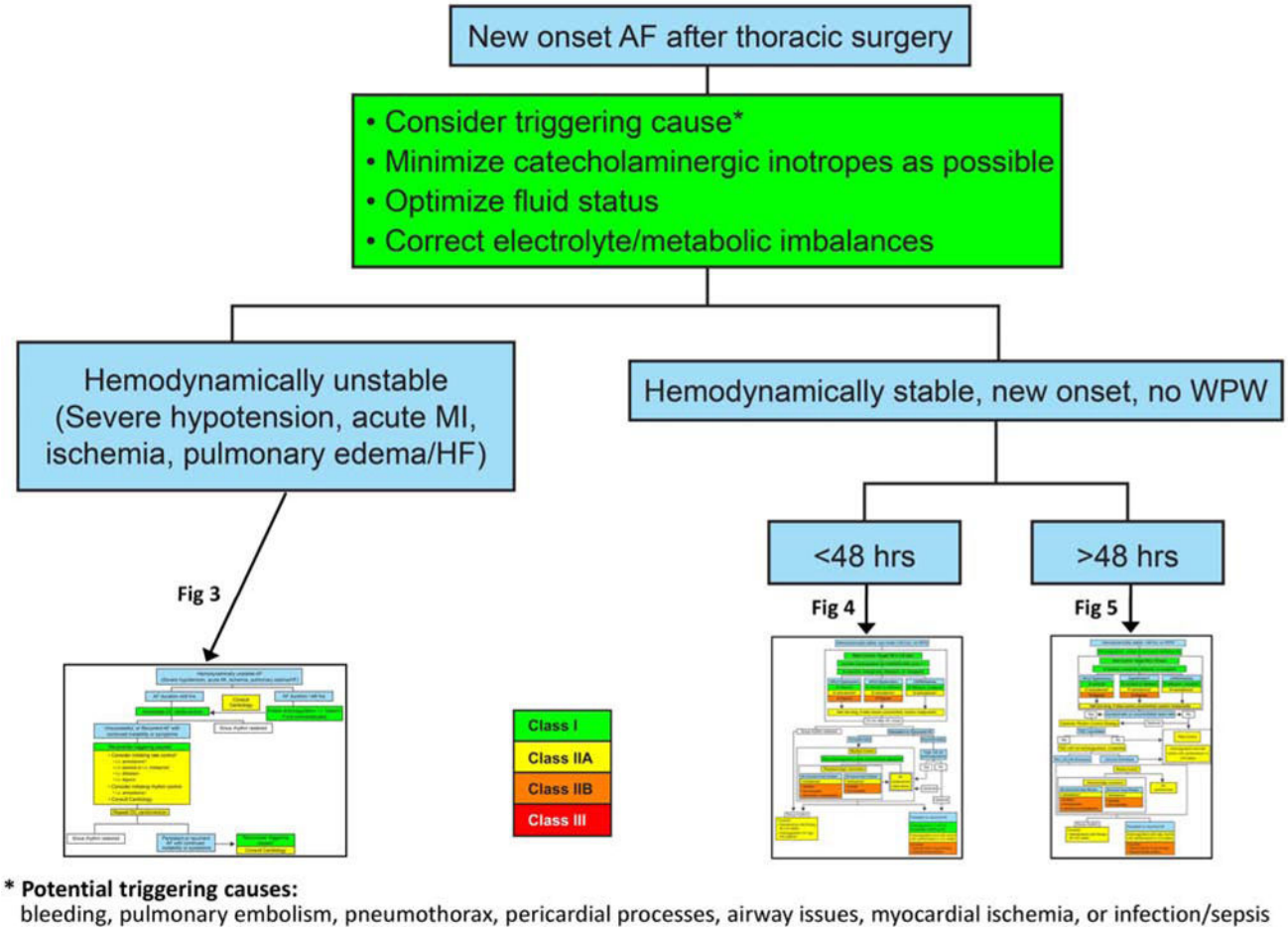


Figure 4.

Management of the Hemodynamically Stable Patient with New Onset POAF of Less than 48Hrs of Duration

Abbreviations: AF: atrial fibrillation; WPW: Wolf-Parkinson-White syndrome; ; i.v.: intravenous; HF: heart failure; DC cardioversion: direct current cardioversion

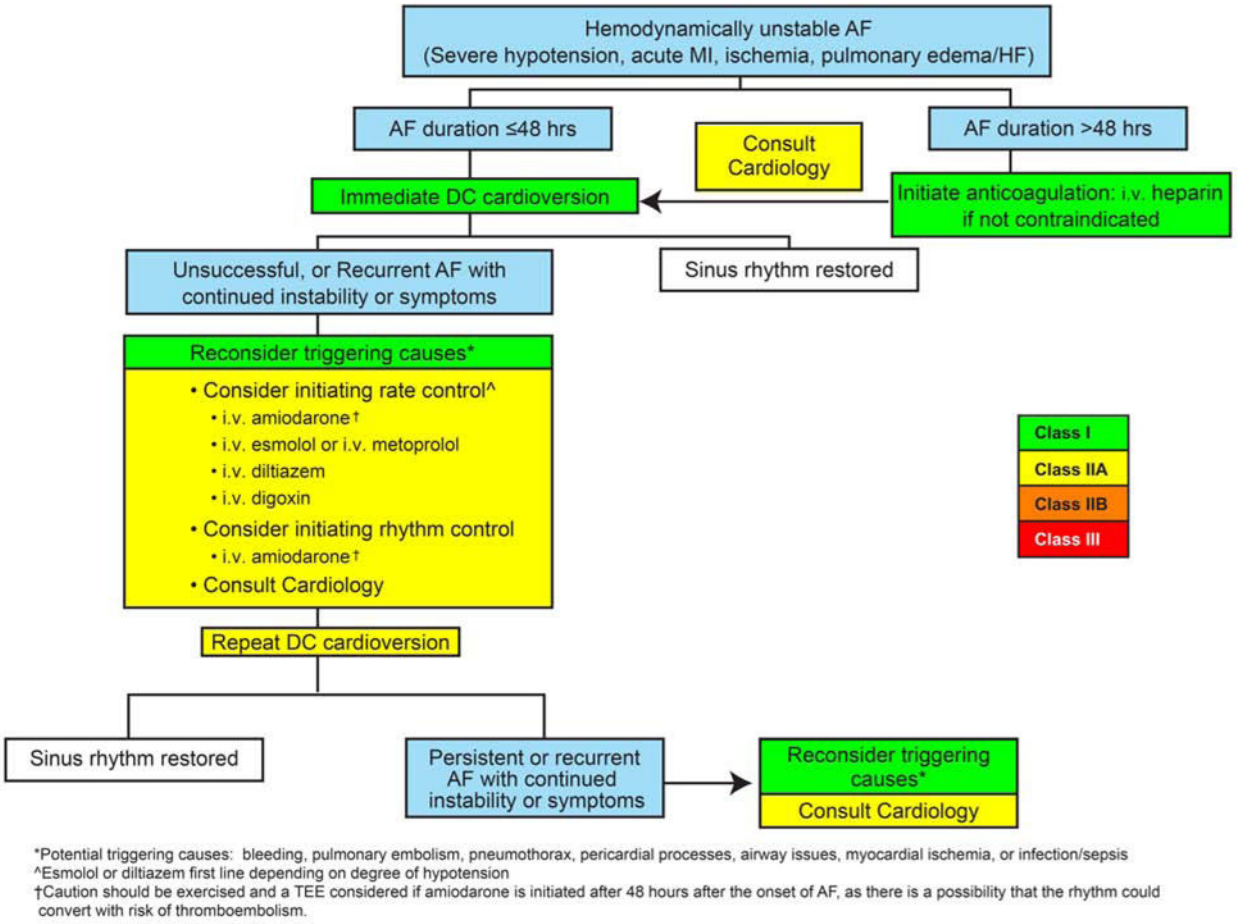
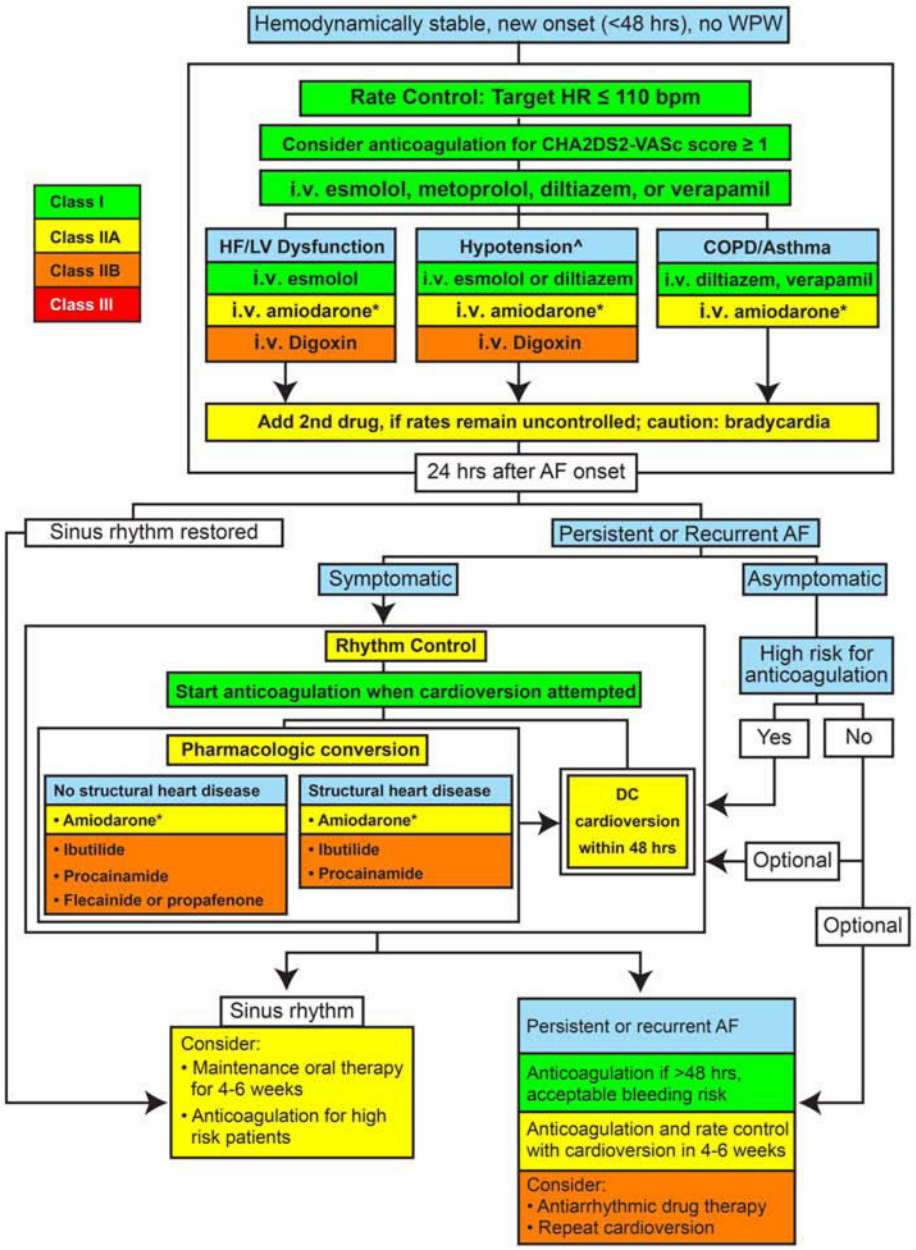


Figure 5.

Management of the Hemodynamically Stable Patient with New Onset Postoperative Atrial Fibrillation (POAF) of More than 48Hrs of Duration

Abbreviations: AF: atrial fibrillation; WPW: Wolf-Parkinson-White syndrome; ; i.v.: intravenous; HF: heart failure; DC cardioversion: direct current cardioversion; TEE: transesophageal echocardiogram; LA/LAA: left atrial / left atrial appendage



*Caution should be exercised and a TEE considered if amiodarone is used after 48 hours after the onset of AF, as there is a possibility that the rhythm could convert with risk of thromboembolism.
^Esmolol or diltiazem first line depending on degree of hypotension

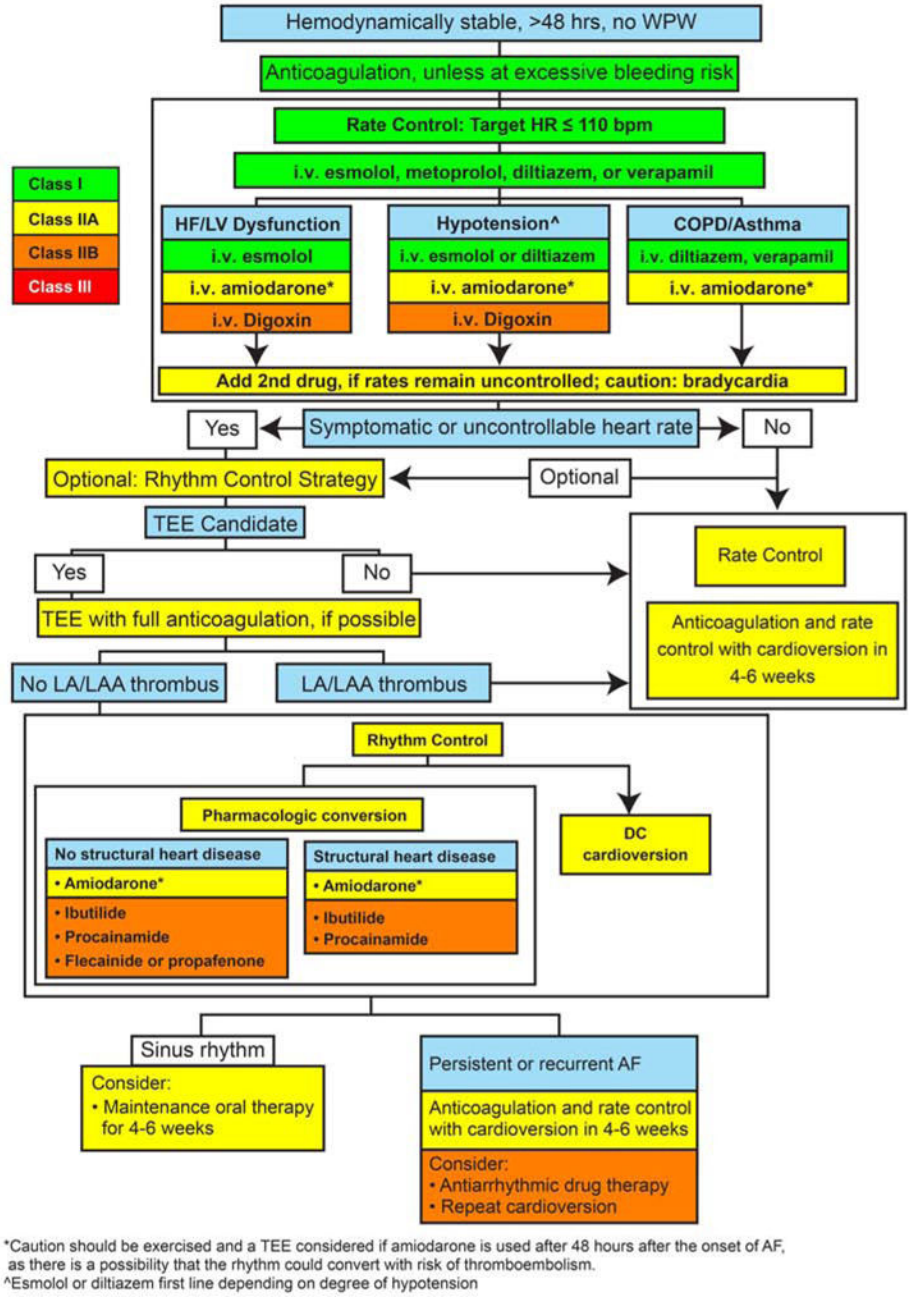


Figure 6.

a: Antiarrhythmic Drugs Recommended for Pharmacologic Cardioversion of Postoperative Atrial Fibrillation (POAF)

Abbreviations: MI: myocardial infarction; CAD: coronary artery disease, LV: left vertricular; CHF: congestive heart failure; AV: atrio-ventricular

b: Antiarrhythmic Drugs Recommended for Maintenance of Sinus Rhythm after Cardioversion of Postoperative Atrial Fibrillation (POAF)

Abbreviations: CAD: coronary artery disease; HF: heart failure; MI: myocardial infarction; CAD: coronary artery disease, LV: left vertricular; AV: atrio-ventricular

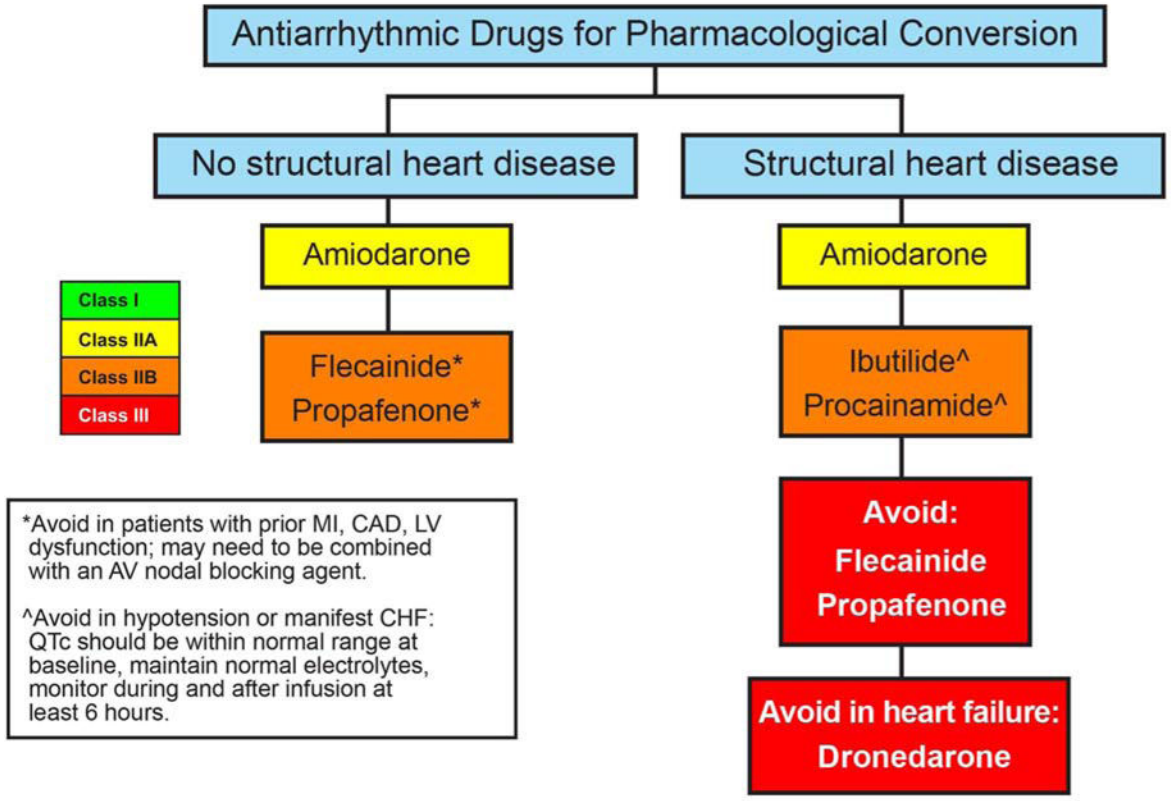


Figure 7.

Algorithm for the Management of Patients with Preoperative Atrial Fibrillation (AF)

Abbreviations: CHF: congestive heart failure; SOB: shortness of breath; CoR: Class of Recommendation; LOE: Level of Evidence; CHA2DS2-VASc: CHA2DS2-VASc score

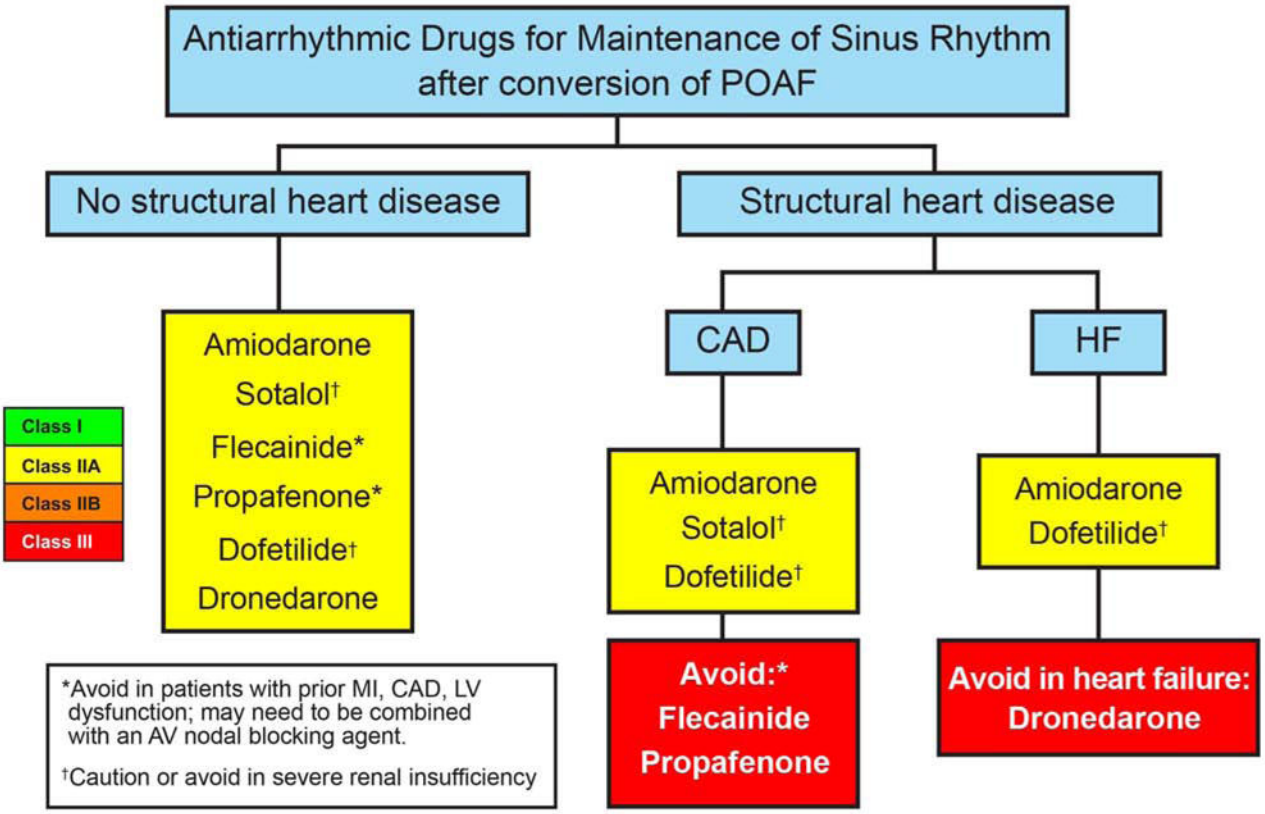


Figure 8.

Management of Anticoagulation for Postoperative Atrial Fibrillation (POAF) Lasting Longer than 48Hrs

Abbreviations: INR: international normalized ratio, NOAC: new oral anticoagulants

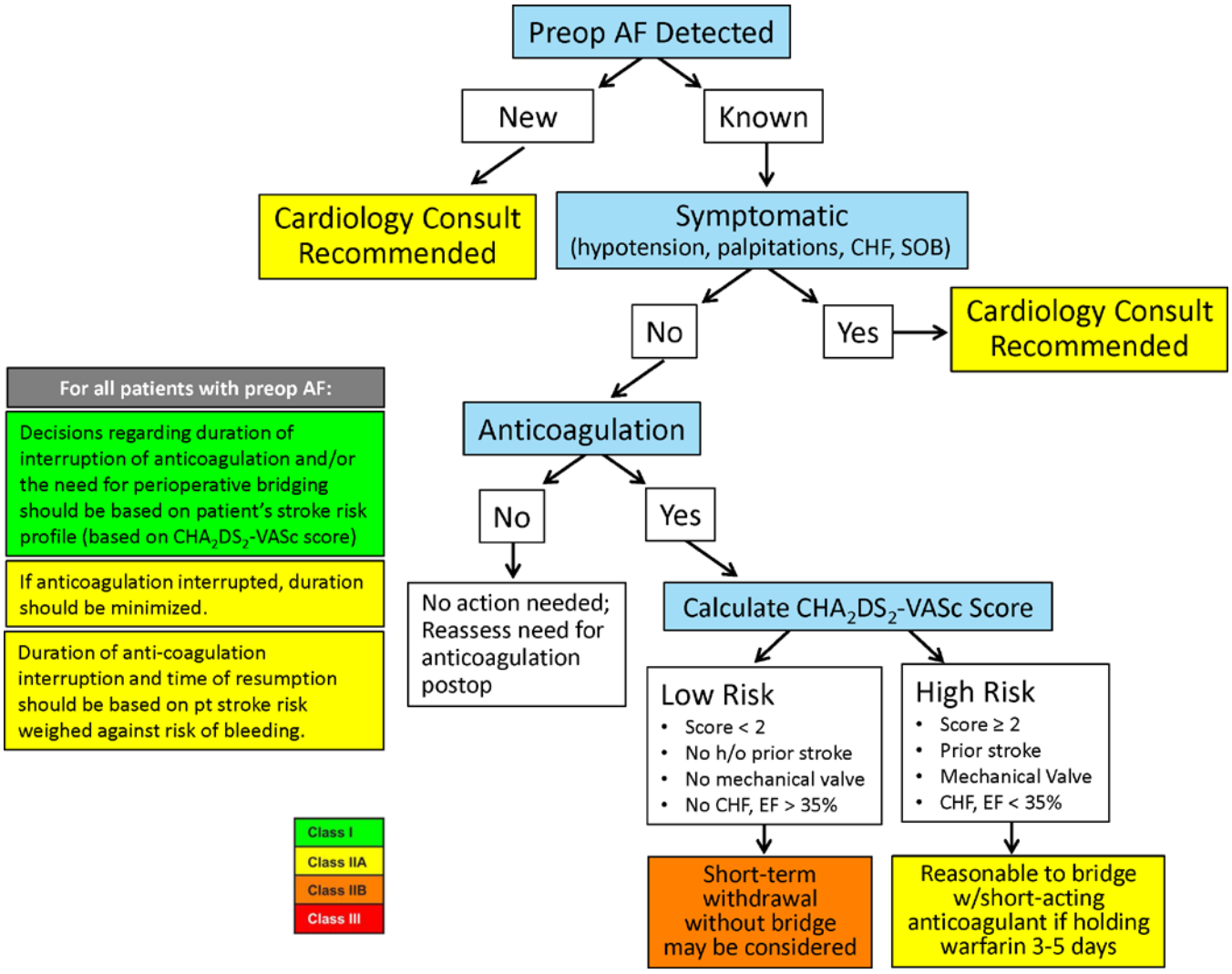


Figure 9.

Considerations for the Management of Anticoagulation within the First 48hrs of Postoperative Atrial Fibrillation (POAF)

Abbreviations: CHA2DS2-VASc: CHA2DS2-VASc score

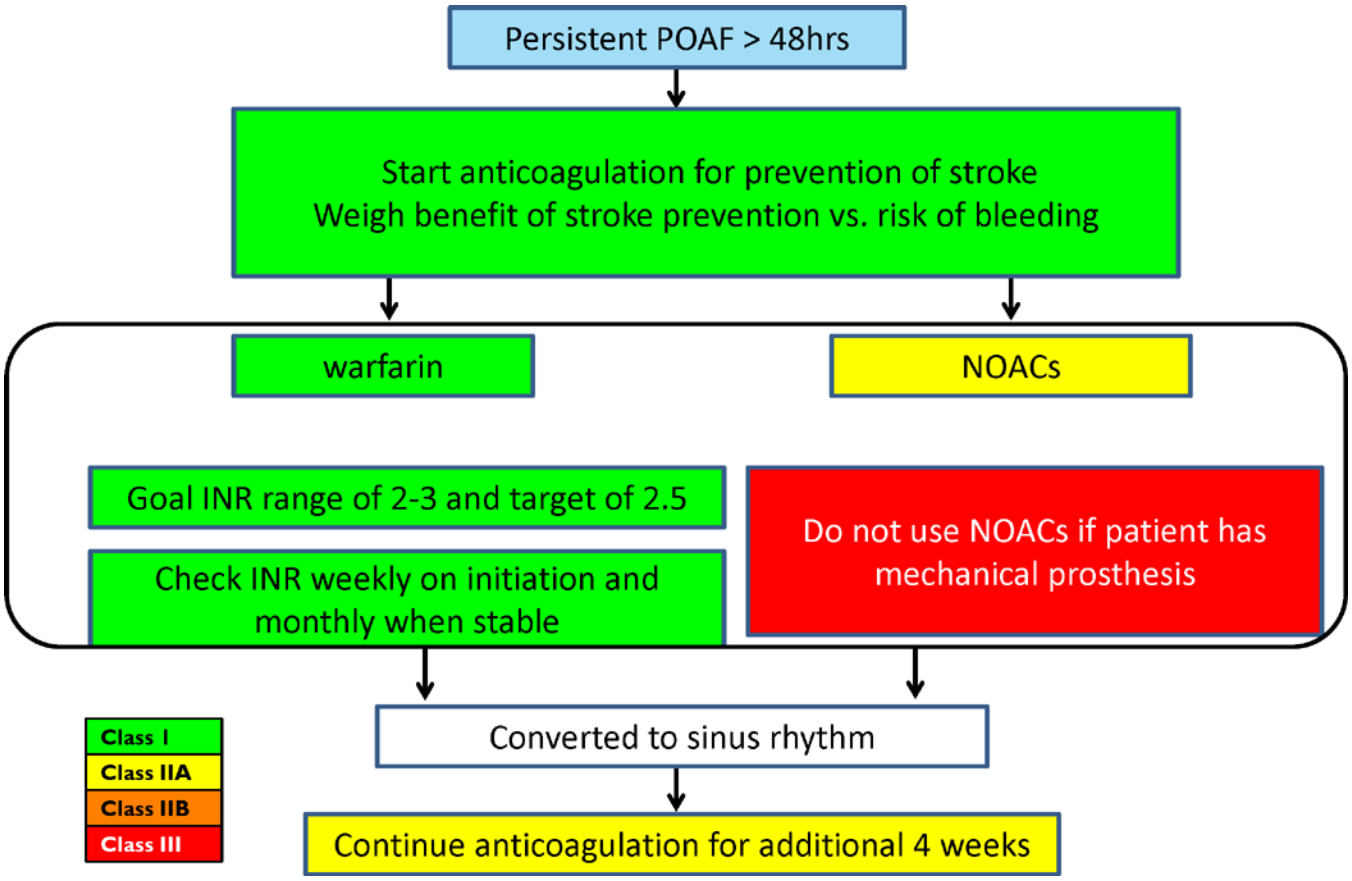


Figure 10.
Stroke Risk Stratification in Atrial Fibrillation

Abbreviations: CHA2DS2-VASc: CHA2DS2-VASc score, HTN: hypertension; MI: myocardial infarction; PAD: peripheral arterial disease

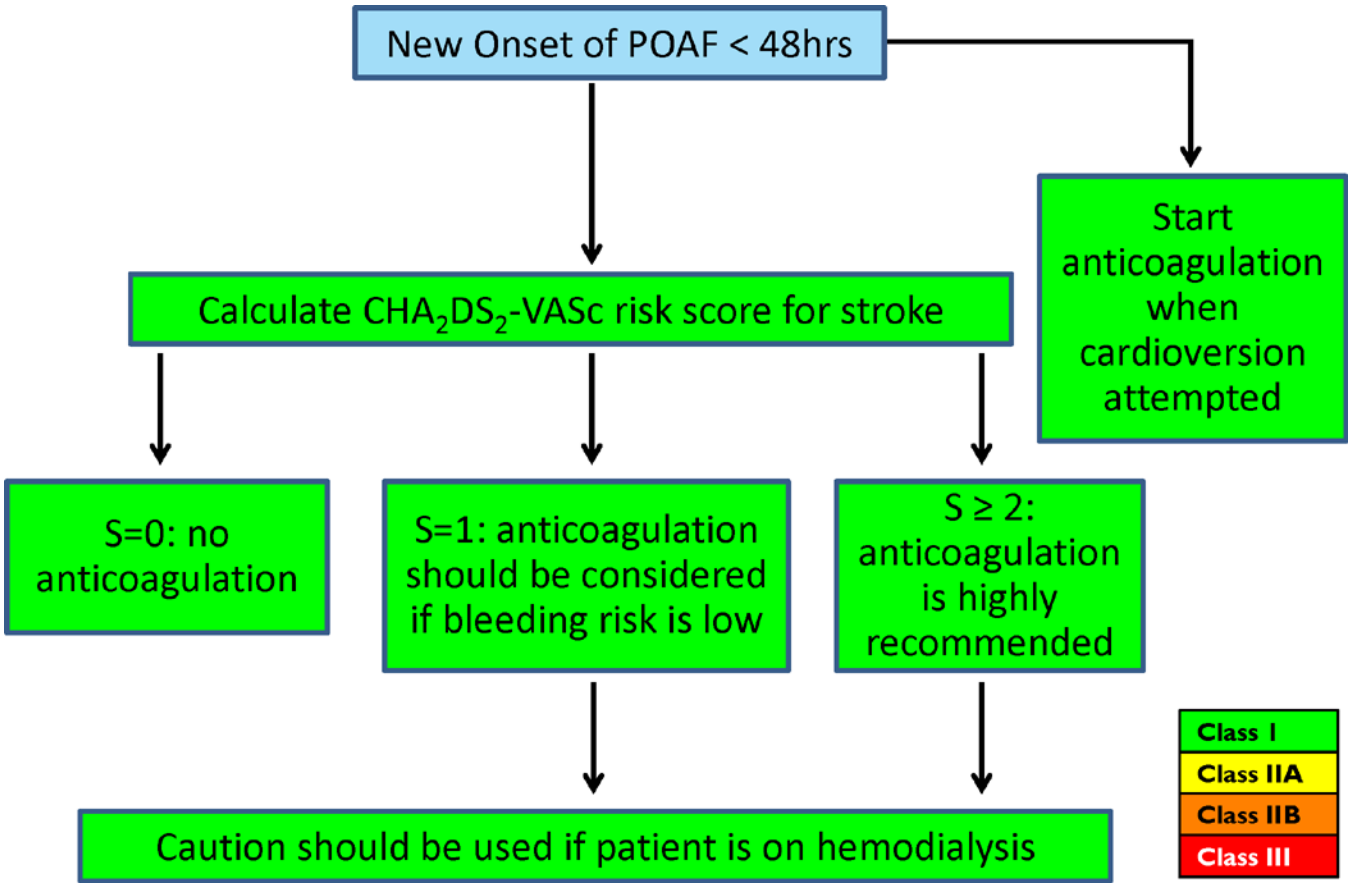


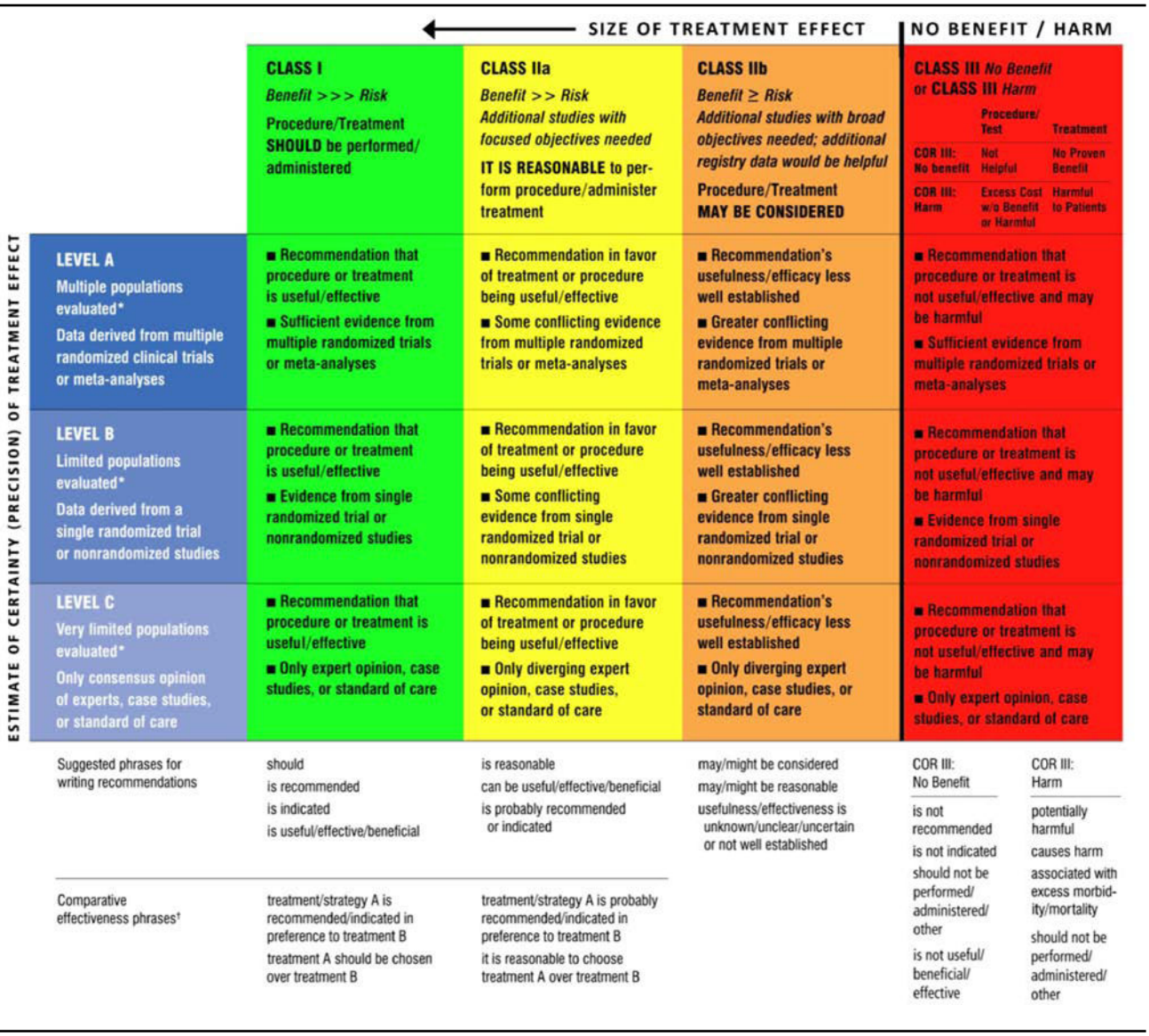
Figure 11.

Recommendation for the Post-Discharge Follow-Up for Patient with New Onset Postoperative Atrial Fibrillation (POAF)

Abbreviations: NSR: normal sinus rhythm; EF: ejection fraction

Table 1

Size of Treatment Effect and Level of Evidence for Its Impact



ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →			NO BENEFIT / HARM
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* — Procedure/Test: COR III: No benefit — Not Helpful; COR III: Harm — Excess Cost w/o Benefit or Harmful — Treatment: No Proven Benefit; Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

Schema used to guide the grading of available published evidence and the expected effect of the interventions for their impact on patient outcomes (the arrow indicates the direction of increased effects size).

Table 2

a: Risk Stratification of Thoracic Surgical Procedures for Their Risk of Postoperative Atrial Fibrillation (POAF)

Thoracic surgical procedures were divided into low (<5%), moderate (5–15%) and high (>15%) risk groups based on their expected incidence of POAF (references in parenthesis) in order to facilitate the preoperative risk stratification of patients.

b: Known Patient Risk Factors for and Comorbidities which Increase the Risk of Postoperative Atrial Fibrillation (POAF)

Patient risk factors and comorbidities which were shown to increase the risk of atrial fibrillation (AF) are listed. Much of this information was extracted from the general population, thoracic surgery specific references are listed when available. These risk factors/comorbidities should be assessed in conjunction with the procedure-related risks of AF in order to determine the true risk of POAF.

Type of Procedures	**Risk of POAF by Surgical Procedures (References)**		
	Low Risk Procedures (<5 % Incidence)	**Intermediate Risk Procedures (5–15 % Incidence)**	**High Risk Procedures (>15% Incidence)**
Intra-Thoracic / Airway Procedures			
Minor Procedures	• Flexible Bronchoscopy with and without Biopsy • Photodynamic Therapy (PDT) • Tracheal Stenting • Placement of thoracostomy tube or Pleurex catheter • Pleuroscopy, pleurodesis, decortication		
Procedures with Moderate Stress	• Tracheostomy • Rigid Bronchoscopy • Mediastinoscopy • Thoracoscopic Wedge Resection (5, 6) • Bronchoscopic LASER Surgery	• Thoracoscopic Sympathectomy	
Major Procedures		• Segmentectomy (5, 6)	• Resection of Anterior Mediastinal Mass • Thoracoscopic Lobectomy • Open Thoracotomy for Lobectomy (5–11)

Type of Procedures	Risk of POAF by Surgical Procedures (References)		
	Low Risk Procedures (<5 % Incidence)	**Intermediate Risk Procedures (5–15 % Incidence)**	**High Risk Procedures (>15% Incidence)**
			• Tracheal Resection and Reconstruction/ Carinal Resection • Pneumonectomy (5–8, 11–13) • Pleurectomy (8) • Volume Reduction/ Bullectomy • Bronchopleural Fistula Repair • Clagett Window • Lung Transplantation (14–16)
Esophageal Procedures	• Esophagoscopy/PEG/Esophageal Dilation and/or Stenting	• Laparoscopic Nissen Fundoplication/Myotomy • Zenker's Diverticulectomy	• Esophagectomy (5, 8, 17)
Other Procedures			• Pericardial Window

Risk Factors and Co-Morbidities	Thoracic Surgery References
Modifiable Risk Factors	
Hypertension	*8, 10, 18*
MI	*19*
VHD	
Heart Failure	*5–6, 20*
Obesity	*10*
Obstructive sleep apnea	
Smoking	
Exercise	
Alcohol use	
Hyperthyroidism	
Increased pulse pressure	
Mitral Regurgitation	
LVH	
Increased LV wall thickness	
Non-Modifiable Risk Factors	
Increasing age	*5–6, 8, 10, 19–20*
African-American (protective factor)	*10*
Family history	
Genetic variants	
Male Sex	*5, 8, 10, 20*

Risk Factors and Co-Morbidities	Thoracic Surgery References
h/o Arrythmias	*5–6*

References in parentheses

Derived from 2014 AHA AF Guidelines and relevant literature for thoracic surgery.

Abbreviations: MI: myocardial infarction; VHD: ; LV: left ventricle; LVH: left ventricular hypertrophy; h/o: history.

Table 3

Probable Mechanisms Contributing to Postoperative Atrial Fibrillation (POAF)

- ■ Clinically meaningful **AF requires** the presence of both a **trigger** and a **vulnerable atrial substrate**
- ■ **Atrial substrate changes that facilitate AF**
  - ➢ Sympathetic or parasympathetic stimulation
  - ➢ Atrial dilation or acute atrial stretch
  - ➢ Pericarditis
  - ➢ Fibrosis
  - ➢ Inhomogeneous dispersion of conduction abnormalities
  - ➢ Short wavelength (conduction velocity × ERP)
  - ➢ Other (like Inflammation and oxidative stress)
- ■ **In addition, a driver(s) is thought to be needed to sustain AF in the vulnerable substrate**
  - ➢ Rapidly firing ectopic focus (atrial or other)
  - ➢ Reentrant circuit(s) of short cycle length (ordered reentry)
  - ➢ Potential role, if any, of multiple reentrant wavelets (random reentry)

Abbreviations: AF: atrial fibrillation; ERP:.

Table 4

Recommended Definitions for the Diagnosis of Postoperative Atrial Fibrillation (POAF)

Definitions		**COR**
Electro-physiologic definition/diagnosis	ECG recordings (one or more ECG leads) with ECG features of AF lasting at least for 30 seconds or for the duration of the ECG recording (if < 30 seconds). (LOE C)	**Class I**
Clinical definition/diagnosis	Clinically significant POAF: Intra- and post-operative AF requiring treatment, or anticoagulation, and/or extending the duration of hospitalization. (LOE C)	**Class I**

These measures should be included in the clinical documentation and reported in the clinical trials/studies.

Abbreviations: CoR: Class of recommendation; LOE: Level of evidence

Table 5

Recommendations for Physiologic (ECG) Monitoring

Recommendations for Monitoring		COR
Patients should be monitored with continuous ECG telemetry postoperatively for 48–72 hours (or less if their hospitalization is shorter) if:		**Class I**
	• they are undergoing procedures that pose high (> 15% expected incidence of AF) or intermediate (5–15%) risk for POAF or • they have significant additional risk factors (CHA_2DS_2-VASc >2) for stroke (LOE C).	
	• they have a history of preexisting or periodic recurrent AF before their surgery. These patients should also receive ECG monitoring in the immediate preoperative period if procedures (epidural catheter, regional anesthesia blocks, etc.) are performed. (LOE C).	
Not using routine ECG telemetry is reasonable for patients who ○ undergo low risk surgery (<5% expected incidence of AF) and ○ had no prior history of AF, or ○ have no significant risk for stroke and ○ have no relevant co-morbidities (like heart failure or prior stroke). (LOE C)		**Class IIa**
	If patients exhibit clinical signs of possible AF while not monitored with ECG telemetry, ECG recordings to diagnose POAF and continuous telemetry to monitor the period of AF should be immediately implemented. (LOE C)	**Class I**

Abbreviations: COR: Class of Recommendation; LOE: Level of Evidence; CHA_2DS_2-VASc: CHA_2DS_2-VASc score

Table 6

Commonly Used Rate Control Agents

Drug	Recommended doses	Significant limitations and known side effects
Diltiazem	0.25 mg/kg i.v loading dose over 2 minutes, then 5–15 mg/hr i.v. continuous infusion	Hypotension Bradycardia Heart failure exacerbation
Digoxin	0.25 mg i.v., repeated every 2–4 hours to a maximum dose of 1.5 mg over 24 hrs	Nausea, vomiting, anorexia Confusion AV block Ventricular arrhythmias Accumulates in acute kidney injury/chronic kidney disease
Esmolol	500 mcg/kg i.v. bolus over 1 minute, then 50–300 mcg/kg/min i.v. continuous infusion	Bradycardia Hypotension Bronchospasm Heart failure exacerbation
Metoprolol	2.5 – 5.0 mg i.v. bolus over 2 minutes; maximum 3 doses	Bradycardia Hypotension Bronchospasm Heart failure exacerbation
Amiodarone	150–300 mg i.v. over 1 hour, followed by 10–50 mg/hour i.v. continuous infusion over 24 hours	Bradycardia QT interval prolongation Pulmonary toxicity has not been demonstrated at this dose

* Detailed information in Section 3 of the online version of the guidelines and in Refs 1 and 2

Abbreviations: AV: atrio-ventricular; i.v.: intravenous;

Table 7

Commonly Used Anti-Arrhythmic Agents

Drug	Recommended doses	Significant limitations and known side effects	Ref.
Procainamide	Conversion to sinus rhythm: 20–50 mg/min i.v. continuous infusion until AF terminated, hypotension occurs, or QRS duration prolonged by 50%, or cumulative total dose of 17 mg/kg reached Alternative dose: 100 mg i.v. every 5 minutes until AF terminated or other conditions as listed above are met Not indicated for maintenance of sinus rhythm	Hypotension QT interval prolongation Torsades de pointes Contraindicated in patients with heart failure with reduced left ventricular ejection fraction Contraindicated in patients with pretreatment QTc interval > 470 ms (males) or 480 ms (females)	41
Flecainide	Conversion to sinus rhythm: 200–300 mg single oral dose Maintenance of sinus rhythm: 50–200 orally once every 12 hours	Dizziness Blurred vision Sinus bradycardia AV block Contraindicated in patients with heart failure with reduced left ventricular ejection fraction Contraindicated in patients with coronary artery disease/structural heart disease	2, 3
Propafenone	Conversion to sinus rhythm: 450–600 mg single oral dose Maintenance of sinus rhythm: 150–300 mg orally every 8 hours (immediate release); 225–425 mg orally every 12 hours (extended release)	Dizziness Blurred vision Sinus bradycardia AV Block Contraindicated in patients with heart failure with reduced left ventricular ejection fraction Contraindicated in patients with coronary artery disease/structural heart disease	2, 3
Amiodarone	Prophylaxis: 300 mg i.v. bolus, then 600 mg orally twice daily for 5 days Treatment: 150 mg i.v. over 10 minutes; then 1 mg/min i.v. continuous infusion for 6 hours; the 0.5 mg/min i.v. continuous infusion for 18 hours or change to oral administration	Bradycardia QT interval prolongation Pulmonary toxicity has not been demonstrated at this dose Bradycardia Hypotension QT interval prolongation Pulmonary toxicity has occurred at cumulative i.v. doses > 2,150 mg in patients undergoing pneumonectomy	2, 3, 97
Dofetilide	Not indicated for conversion to sinus rhythm Maintenance of sinus rhythm: Calculated creatinine clearance (CrCl) 20–40 mL/min: 125 mcg orally once every 12 hours Calculated CrCl 40–60 mL/min: 250 mcg orally once every 12 hours; Calculated CrCl > 60 mL/min: 500 mcg orally every 12 hours	QT interval prolongation Torsades de pointes Risk of torsades de pointes is greater in patients with heart failure Dose adjustment is very important in patients with acute kidney injury or chronic kidney disease Contraindicated in patients with calculated CrCl < 20 mL/min Contraindicated in patients with pretreatment QTc interval > 470 ms (males) or 480 ms (females) Monitor ECGs 2 hrs post doses, telemetry × at least 3 days	2, 3
Ibutilide	Conversion to sinus rhythm: Weight ≥ 60 Kg: 1 mg i.v. administered over 10 minutes Weight < 60 Kg: 0.01 mg/Kg i.v. administered over 10 minutes If the AF does not terminate within 10 minutes of completion of the 1st infusion, a 2nd dose of equal strength may be administered i.v. over 10 minutes Not indicated for maintenance of sinus rhythm	QT interval prolongation Torsades de pointes Risk of torsades de pointes greater in patients with heart failure Nonsustained ventricular tachycardia Sinus pauses following AF conversion Contraindicated in patients with pretreatment QTc interval > 470 ms (males) or 480 ms (females)	Corvert® Prescribing information 2006; Pfizer, Inc.
Sotalol	Not indicated for conversion to sinus rhythm Maintenance of sinus rhythm: 40–160 mg orally every 12 hours Dosing interval should be adjusted in patients with acute kidney injury or chronic kidney disease: Calculated CrCl 30–59 mL/min – every 24 hours	Sinus bradycardia AV block QT interval prolongation Torsades de pointes Heart failure exacerbation	2, 3

Drug	Recommended doses	Significant limitations and known side effects	Ref.
	Calculated creatinine clearance 10–29 mL/min – every 36–48 hours	Risk of torsades de pointes greater in patients with heart failure Bronchospasm Dose adjustment is very important in patients with acute kidney injury or chronic kidney disease Use with extreme caution in patients with calculated CrCl < 10 mL/min and in patients undergoing hemodialysis Contraindicated in patients with pretreatment QTc interval > 470 ms (males) or 480 ms (females)	

Abbreviations: AV: atrio-ventricular; i.v.: intravenous; CrCl: creatinine clearance;

Table 8

Commonly Used Anticoagulants

Drug	Mechanism	Half time (hr)	Mode of Clearance	Recommended Doses	Significant Limitations	References
Warfarin	Vitamin K antagonist	Up to 40	Renal (hepatically metabolized)	Variable (monitor INR)	Multiple food and drug interactions, need for frequent INR monitor and dose adjustments	2–3, 147
Dabigatran	Thrombin inhibitor	13	Renal	150mg bid 75mg bid for CrCl 30–50ml/min	Interaction with inhibitors of P-gp, no established antidote, not recommended in severe renal failure	2–3, 171
Rivaroxaban	Factor Xa inhibitor	7–11	Renal/Hepatobiliary	20mg daily 15mg daily for CrCl 15–50ml/min	Interaction with inhibitors of P-gp and CYP3A4, no established antidote, not recommended in severe renal failure	2–3, 172
Apixaban	Factor Xa inhibitor	12.7	Renal/fecal	5mg bid 2.5mg bid (AF) for at least two of the following: age>80, body weight<60kg, Cr>1.5mg/dL	Interaction with inhibitors of P-gp and CYP3A4, no established antidote, not recommended in severe renal failure	2–3, 172

Abbreviations: INR: international normalized ratio; AF: atrial fibrillation; Cr: serum creatinine; CrCl: creatinine clearance

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