NEW ONSET ATRIAL FIBRILLATION IN THE SURGICAL PATIENT

SUMMARY

Atrial fibrillation is a common postoperative arrhythmia and can represent a major source of morbidity and mortality. Treatment of atrial fibrillation is directed at three main objectives: controlling the ventricular response, preventing thromboembolism, and maintaining sinus rhythm. Therapeutic decisions also hinge on patients' hemodynamic stability. In patients who are hemodynamically unstable, direct current cardioversion is the first line therapy and pharmacotherapy should be used as adjunctive treatment. In patients who are hemodynamically stable, pharmacologic treatment including class II (beta-blockers), class III (amiodarone), or class IV (nondihydropyridine calcium channel blockers) agents are viable options.

RECOMMENDATIONS

- **Level 1**
  - Beta-blockade (esmolol or metoprolol), nondihydropyridine calcium channel blockers (diltiazem or verapamil), and amiodarone are pharmacologic options to manage new onset atrial fibrillation (see table for dosing).
    - Beta-blockers are the first line therapy for postoperative atrial fibrillation to achieve rapid ventricular rate control and conversion to sinus rhythm. Diltiazem is second line rate control agent when beta-blocker therapy has failed. Both therapies should be avoided in hypotensive patients.
    - Amiodarone can provide both rate and rhythm control and is an alternative therapy to beta-blockade for postoperative atrial fibrillation especially when the patient is hemodynamically unstable or has a known ejection fraction of < 40%.
  - Digoxin, due to its delayed onset of action and ineffectiveness, should not be used for acute rate control in atrial fibrillation, but may have a role for chronic rate control and in patients with heart failure in which negative inotropic effects are undesired.
  - All patients with atrial fibrillation for greater than 48 hours duration should be considered to receive therapeutic anticoagulation for 3 weeks before and 4 weeks after cardioversion – electric or pharmacologic – unless emergency cardioversion is indicated.
- **Level 2**
  - Duration of treatment of new onset atrial fibrillation may be from 1 to 3 weeks.
  - AV nodal blocking agents (beta-blockers, calcium-channel blockers, and digoxin) should be avoided in Wolf-Parkinson-White and other pre-excitation syndromes.
  - Immediate cardioversion with heparinization followed by 4 weeks of anticoagulation may be performed if no atrial thrombus is visualized using transesophagealechocardiography (TEE).
- **Level 3**
  - Emergent cardioversion is indicated in patients with life threatening hemodynamic instability.

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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INTRODUCTION

Of the supraventricular arrhythmias, atrial fibrillation (AF) is the most commonly encountered in the ICU and is associated with the potential for serious consequences including stroke, deterioration of underlying cardiac disease, prolonged hospital stay, and increased mortality. AF is an irregular, disorganized, electrical activity of the atria characterized by absent P waves and an irregular baseline on ECG. Supraventricular tachycardia (SVT) is common after surgery with a frequency of 4% in patients undergoing major noncardiac procedures, 3.2% in patients undergoing abdominal aortic aneurysm repair, and almost 13% in patients undergoing thoracotomy for lung cancer (1,2). AF is more common after cardiac surgery, with frequencies of 12-40% following coronary artery bypass grafting and up to 60% following valve replacement. While postoperative AF has been studied extensively following cardiac surgeries, data is scarce concerning the management of postoperative AF in the medical and surgical ICU population (1,3, 4). Some risk factors for postoperative AF have been identified including:

- increased age
- postoperative electrolyte shifts
- pericarditis
- history of preoperative AF
- atrial distention
- history of congestive heart failure
- chronic obstructive pulmonary disease (COPD)
- increased catecholamine levels
- hyperthyroidism
- diabetes mellitus
- alcohol ingestion

Recent studies have been aimed at identifying biomarkers of inflammation, oxidative stress and even miRNA that may help predict patients that are at risk of developing new onset AF. Increased inflammatory markers such as CRP and IL-6 have been identified in serum of AF patients. CRP in particular has been predictive of AF, as well as recurrence of AF after cardioversion. Oxidative stress, evident in atrial tissue of AF patients has been linked with up regulation of particular genes and atrial substrate differences that predispose patients to develop reactive oxygen species that may play a role in new onset AF (5,6,7).

Most postoperative AF is self-limited, although it tends to recur. AF that persists for greater than 48 hours is associated with an increased risk of stroke and transient ischemic attack (TIA). Thus, after 48 hours of AF, anticoagulation should be considered, weighing the potential benefits against the risk of postoperative bleeding. The risk of stroke due to chronic AF varies greatly depending upon age and coexisting disease (8). Risk factors for stroke include previous stroke or TIA, history of hypertension, congestive heart failure, advanced age, diabetes mellitus, coronary artery disease and thyrotoxicosis.

A scoring system, ($CHADS_2$), has been devised to assess this risk and to direct anticoagulation therapy. Patients with total scores of 2 or higher should be anticoagulated with warfarin (9,10). The risk of stroke in patients with non-rheumatic, chronic AF is five-fold higher than in patients in sinus rhythm, corresponding to a 4% to 5% annual incidence of stroke. The proportion of stroke resulting from AF increases with age, rising from 6.5% for ages 50-59 years to approximately 31% for ages 80-89 years (3,8). In these high risk groups, long term anticoagulation has been shown to reduce stroke risk by 67% (11).

$CHADS_2$:

Risk Factor	Points
Congestive heart failure	1
Hypertension	1
Age $\geq$ 75 years	1
Diabetes mellitus	1
Prior stroke or TIA	2

The 2014 AHA/ACC/HRS guidelines for management of patients with AF advise that patients categorized as low risk by the $CHADS_2$ scoring system may benefit from risk assessment with the $CHADS_2DS_2VAS_C$ scoring system. This allows for the assessment of additional risk factors as well as a wider range of scores which have been shown to identify patients in the $CHADS_2$ low risk group into higher risk categories (#) Patients with a $CHADS_2DS_2VAS_C$ score of 2 or higher are recommended to receive anticoagulation.

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$CHADS_2DS_2VAS_C$

Risk Factor	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Prior stroke or TIA	2
Vascular disease	1
Age 65-74	1
Female sex	1

The choice to use systemic anticoagulation in these patients at high risk must be weighed against with the risk of bleeding, which may be assessed by the HAS-BLED risk scoring system, which quantifies risk based on presence of hypertension, liver or renal dysfunction, history of stroke or bleeding, elderly age as well as use of drugs that promote bleeding or alcohol (5). The choice of which antithrombotic therapy is appropriate for a particular patient is multifactorial and should be individualized to the particular patient.

Treatment of AF is directed at three primary objectives: 1) controlling the ventricular response, 2) preventing thromboembolism, and 3) maintaining sinus rhythm. Efforts to hasten conversion of AF with anti-arrhythmic agents have been largely unsuccessful due to poor efficacy and undesired side effects. Thus, ventricular rate control remains the principal goal of therapy for patients in the ICU (12). In patients with persistent AF greater than 15 minutes, initiation of therapy to control the ventricular rate is recommended. Intravenous beta-blockers are a logical choice in postoperative patients with high sympathetic tone. Use of beta-blockers during the perioperative period has been suggested to reduce mortality and cardiovascular complications up to two years after surgery (13). Amiodarone should be used in patients with decreased left-ventricular dysfunction (ejection fraction < 40%). Calcium-channel blockers may be used in COPD patients who should not receive beta-blockade. Digoxin is less effective in achieving acute rate control because of a delay in onset of action and a lack of efficacy in the hyperadrenergic postoperative state. However, digoxin may be useful in heart failure since it does not have negative inotropic effects. The use of beta-blockers, calcium-channel blockers, and digoxin should be avoided in patients with pre-excitation syndromes (e.g. Wolf-Parkinson-White) as it can lead to the development of heart block (14). Thus, there is no single agent that has emerged as the drug of choice for converting AF to sinus rhythm (1,15,5).

The American College of Chest Physicians as well as the American Heart Association recommend that all patients with AF of more than 48 hours duration receive therapeutic anticoagulation for 3 weeks before and 4 weeks after cardioversion - electric or pharmacologic - unless emergency cardioversion is indicated . An alternative is to screen patients for intra-atrial thrombus using transesophagealechocardiography (TEE). If no clot is seen, the patient may be cardioverted immediately with heparinization, but should still receive at least 4 weeks of therapeutic anticoagulation after conversion. No anticoagulation is required when patients have AF for less than 48 hours (3,16, 5).

LITERATURE REVIEW

Rate vs. Rhythm Control

Brathwaite et.al. prospectively observed 462 consecutive noncardiac, nonthoracic surgery patients in the ICU for atrial arrhythmias. New arrhythmias occurred in 10.2% of patients. Most began within the first two postoperative days. These patients had a significantly higher mortality rate (23.4% vs. 4.3%), longer ICU stay (8.5 ± 17.4 vs. 2.0 ± 4.5 days), and longer hospital stay (23.3 ± 23.6 vs. 13.3 ± 17.7 days) than patients without atrial arrhythmias ($p<0.02$). Although not the cause of death, atrial arrhythmias appear to be markers of increased morbidity and mortality (2).

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A growing body of literature has compared rhythm versus rate control strategies for treatment of AF. Wyse et.al. has published the largest study to date following 4060 patients for a mean of 3.5 years. At 5 years, 60% of the rhythm control group and 35% of the rate control group were in sinus rhythm. There was no difference in mortality between the groups; however, the rhythm control group had significantly more hospitalizations and adverse drug effects. Furthermore, the rhythm control group was much more likely to be either subtherapeutic or off of anticoagulation, placing them at greater risk for cerebral vascular disease (21).

Van Gelder et.al. randomized 522 patients to rhythm and rate control arms and followed them for a mean of 2.3 years. The rhythm control cohort showed sinus rhythm in 39% of the group while the rate control cohort had a sinus rhythm in 10% of the group. These two groups also showed no significant difference in outcomes (22). In general, the rhythm control groups in these studies showed better exercise tolerance. This is balanced against increased hospitalizations, risk of adverse drug affects, and a trend towards increased thromboembolic events (11,23).

Rate vs. rhythrm control remains one of the highly debated areas in the management of acute AF. The clinical decision should ultimately be based on the hemodynamic stability of the individual patient. In patients with life threatening hemodynamic instability, direct electric cardioversion with or without anticoagulation is recommended in conjunction with pharmacologic treatment.

Pharmacologic Management

Mooss et.al. randomized 30 patients with AF after coronary bypass and/or valve replacement surgery to receive either esmolol or diltiazem. During the first 6 hours of treatment, 67% of the esmolol-treated patients converted to sinus rhythm compared to 13% of the diltiazem-treated patients ($p< 0.05$). At 24 hours, 80% of esmolol-treated patients had converted to sinus rhythm compared to 67% of the diltiazem group (not significant) (17).

Vardas et. al. investigated the efficacy and safety of amiodarone administration as the drug of choice in the conversion of AF in a prospective, randomized, controlled clinical trial. One-hundred eight patients with a history of cardiac disease received amiodarone (300mg IV for 1 hour, then 20 mg/kg IV for 24 hours, then 200 mg TID orally for 1 week, then 400 mg/day for 3 weeks) and 100 patients received placebo treatment. All patients were loaded with 1 mg of digoxin initially followed by a daily dose. Conversion to sinus rhythm was achieved in 81% of patients in the amiodarone group, and in 40% of patients in the placebo group ($p<0.0001$) (18).

Joseph et.al. conducted a prospective, randomized, controlled, multi-center trial comparing the efficacy and safety of sotalol and amiodarone in conversion of new-onset AF to sinus rhythm at 48 hours compared with rate control with digoxin alone. One hundred and twenty patients who presented to the emergency room with AF for less than 24 hours were randomized to receive sotalol, amiodarone, or digoxin using a single intravenous dose followed by 48 hours of oral treatment. There was a significant reduction in the time to conversion with both sotalol (13.0 ± 2.5hours, $p<0.01$) and amiodarone (18.1 ± 2.9 hours, $p<0.05$) groups compared with digoxin (26.9 ± 3.4 hours). At 48 hours, the sotalol and amiodarone groups were significantly more likely to convert AF to sinus rhythm compared to the digoxin group. There were also more adverse events associated with digoxin use, including left ventricular failure (19).

Karth et.al. conducted a prospective, randomized, controlled study to compare the rate-lowering effect of diltiazem and two amiodarone regimens in critically ill patients (primary diagnosis included CHF and CAD) with recent-onset atrial tachyarrhythmias. In patients achieving tachycardia control, diltiazem showed a significantly better rate reduction over time ($p=0.001$) when compared to the amiodarone groups. However, the primary study end point (>30% rate reduction within 4 hours), was met by all groups without any significant differences. Premature drug discontinuation due to hypotension was occurred more often in the diltiazem group ($p<0.05$). The study concluded that rate control can by achieved in critically ill patients with atrial tachyarrhythmias using either diltiazem or amiodarone. Although diltiazem allowed for significantly better 24 hour heart rate control, this effect was offset by a significantly higher incidence of hypotension requiring discontinuation of the drug. Amiodarone may be an alternative in patients with severe hemodynamic compromise (20).

Balser et. al. randomized 64 noncardiac surgical ICU patients with recent-onset SVT to receive intravenous diltiazem or intravenous esmolol. Patients who received esmolol experienced a 59% rate of conversion to sinus rhythm within 2 hours of treatment compared with only 33% of the patients randomized to receive diltiazem (intention to treat, p=0.049). After 12 hours of therapy, the number of patients converting to sinus rhythm increased in both groups (esmolol 85%; diltiazem, 62%), and the rates of conversion were no longer significantly different. The in-hospital mortality rate and ICU length of stay were not statistically different between the two treatment groups (12).

Kanji et. al. conducted a systematic review of prospective randomized controlled trials on pharmacologic management of new onset AF in noncardiac ICU patients. Of the 44 trials evaluated, only 4 trials, including 143 patients, were included for the analysis and various medications were used including amiodarone, procainamide, flecainide, esmolol, diltiazem, and magnesium infusion. The conversion rate to sinus rhythm was comparable among all agents ranging between 50-80% at 12 hours from initiation of therapy. This review affirmed that there is currently no single agent that is superior to another. Beta-blockers (esmolol and metoprolol) may be a good initial choice in hemodynamically stable AF patients due to the associated heightened adrenergic response during the immediate postoperative period. Amiodarone can provide both rate and rhythm control and should be considered either as first line or in patients who failed beta-blocker or calcium channel blocker therapy (4).

One prospective randomized study addressed the treatment duration for new onset postoperative atrial fibrillation in coronary artery bypass patients (25). Various medication including beta blockers, amiodarone, and calcium channel blockers were used to treat patients with atrial fibrillation for 1 week, 3 weeks, or 6 weeks. Overall, there was no difference in the rate of recurrent atrial fibrillation during the follow up period in each group. The findings suggest that short term treatment (1-3 weeks) for new onset post operative atrial fibrillation is likely sufficient.

Common Medication Dosages

Beta-blockers	
Metolprolol	5-10 mg IVP Q5 minutes x 3 doses
Esmolol	50-300 mcg/kg/min IV infusion ± bolus 500 mcg/kg x1
Propanolol	1mg IVP Q2 minutes x 3 doses
Calcium Channel blockers	
Diltiazem	Bolus 0.25 mg/kg, 5-15 mg/hr IV infusion
Verapamil	Bolus 0.075-0.15 mg/kg, may give additional 10mg after 30 min if no response, then 0.005 mg/kg/min infusion
Digoxin	0.25 mg IV with repeat dosing to max of 1.5mg over 24 hours*
Amiodarone	Bolus 150 mg IV over 10 min, may repeat bolus if rhythm control not obtained within 1st hour; then 0.5-1 mg/min IV infusion over 24 hours

*In normal renal function

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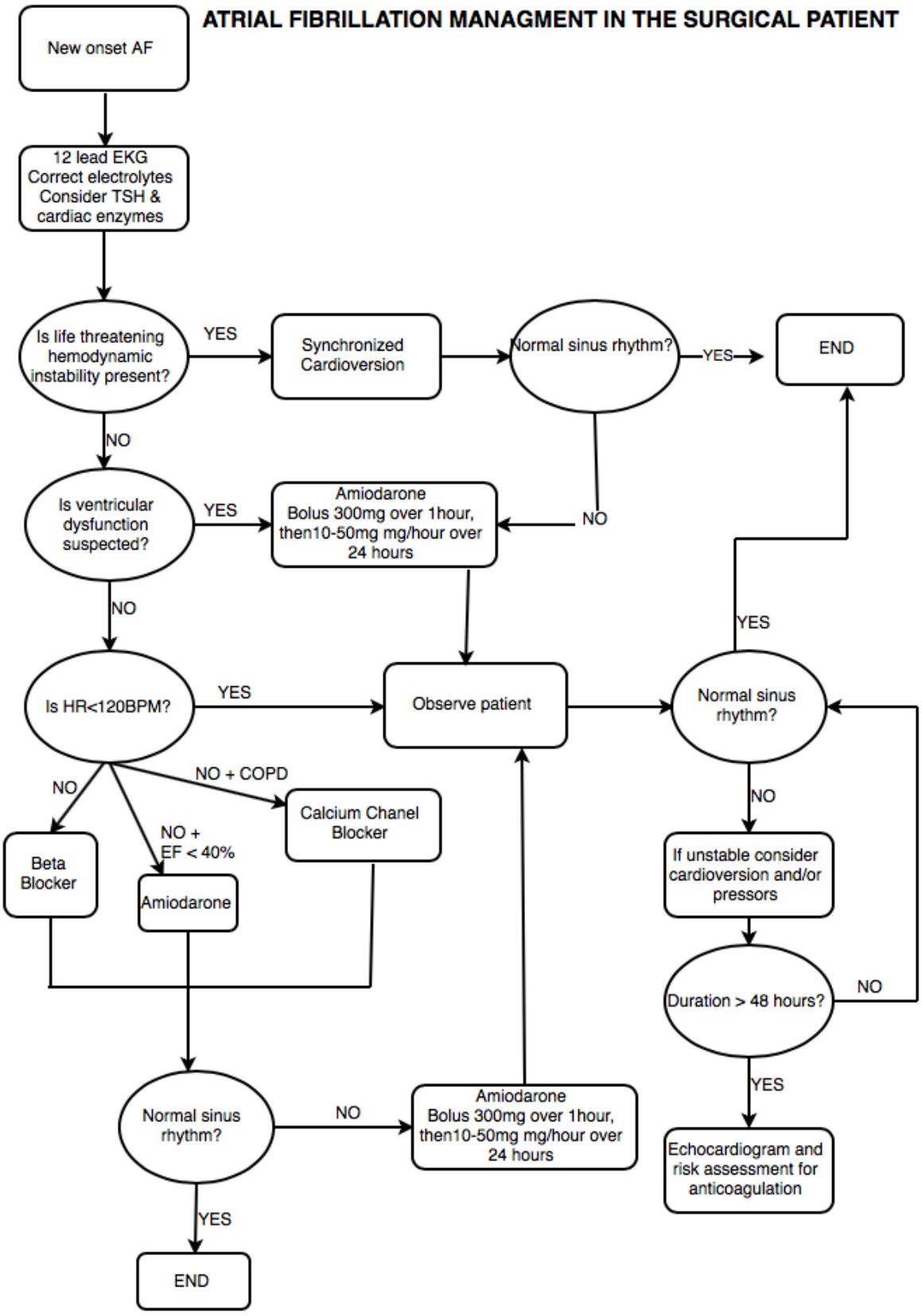
ATRIAL FIBRILLATION MANAGMENT IN THE SURGICAL PATIENT



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