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Management of Recent Onset Sustained Atrial Fibrillation: Pharmacological and Non-Pharmacological Strategies

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ABSTRACT

Purpose: Recent studies have highlighted significant variations in the management of recent onset sustained atrial fibrillation (AF). Here, we aim to provide a succinct and clear management algorithm for physicians managing patients with recent onset sustained AF.

Methods: We performed a comprehensive search of the literature on the management of recent onset sustained AF with focus on studies reporting cardioversion of AF, anti-arrhythmic agents and anticoagulation. We also reviewed recent practice guidelines on AF management.

Findings: This review provides a guide on a tailored management approach of patients with recent onset sustained AF. Following initial detailed clinical assessment, optimal rate and rhythm control options can be provided depending on hemodynamic stability, duration of AF episode and AF stroke risk. Issues surrounding electrical and pharmacological cardioversion were discussed in detail. We emphasized the importance of thromboembolic risk assessment and appropriate anticoagulation surrounding the point of cardioversion. Last, we highlighted the need for appropriate specialized follow-up care following acute AF management.

Implications: Despite the highly heterogeneous clinical presentations, management of recent onset sustained AF must include stroke risk assessment, appropriate anticoagulation and follow-up care in all patients beyond optimum rate and rhythm control strategies.

Keywords: Atrial fibrillation; anti-arrhythmic drugs; electrical cardioversion; anticoagulation.

INTRODUCTION

Despite the tremendous advances made in cardiovascular medicine over the last century, atrial fibrillation (AF) has emerged as a global epidemic in this new millennium with enormous public health and economic burden.(1) The estimated cost of AF is at least one percent of the healthcare budget in developed nations and this figure is set to climb further with recent evidence of increasing AF related hospitalizations.(1-3) Optimal management of AF is essential given its association with increased risk of stroke (3 to 5 fold) as well as mortality (1.5 to 2 fold).(1) However, significant variations in the management of acute sustained AF have been consistently identified among emergency physicians and cardiologists in different countries.(4-6) This is perhaps not surprising given the heterogeneity of the patient population presenting with AF and the diversity of available treatment options. This review is focused on the holistic management of AF with specific attention to the pharmacological and non-pharmacological strategies for treating recent onset sustained AF as recommended in recent practice guidelines. (7-9)

AF: Tailored Management Approach

The primary goals of AF management are to reduce symptoms, improve quality of life and lessen the associated morbidities such as heart failure and stroke. When a patient presents with symptomatic acute AF, the focus of management is often on effective rhythm and rate control. However, when managing the highly heterogeneous group of patients with AF, the complexity of the arrhythmia requires careful considerations beyond the paradigm of rate and rhythm control. A tailored management approach is essential after careful clinical evaluation of the different

aspects as outlined in Table 1. Management strategy for the acute AF episode is often undertaken with consideration of the patient's preferences.

Recommended management of acute sustained AF

Approximately 50% of acute AF episodes will terminate spontaneously within 24 hours in the absence of secondary causes of AF.(10) If there is an identifiable precipitant for the acute AF episode, treatment of the underlying condition will be helpful in the management of the arrhythmia. In patients with more persistent form of AF whereby previous cardioversion attempts have failed and rhythm control has been abandoned, the focus of acute management should be on adequate rate control and anticoagulation to prevent thromboembolic complications. Figure 1 outlines our recommendations for managing patients presenting with acute sustained AF. The key factors to consider are: hemodynamic stability, duration of AF episode, thromboembolic risk stratification and anticoagulation management. In general, they fall into four different groups as detailed below:

I. Hemodynamically stable AF with onset <48 hours

Initial rate control strategy can be implemented in those who are hemodynamically stable, aiming for a target resting heart rate of <100 bpm (Table 2). Commonly used rate control agents include beta-blockers (e.g. metoprolol) and non-dihydropyridine calcium channel blockers (e.g. diltiazem or verapamil). In general, digoxin is used only as a second line agent due to lower efficacy with slower onset of action and poor heart rate control during exertion. Intravenous magnesium is less effective than beta-blockers or calcium channel blockers for rate control in patients with acute

onset AF from meta-analysis of randomized controlled trials although overall patient numbers were low.(11) The use of intravenous magnesium is not a recommended strategy in current practice guidelines.(7-9) In patients with low stroke risk and improved symptoms following good rate control, one possible strategy is to discharge the patient on rate control medications with follow-up the next day (within 48 hours of AF onset) for cardioversion if AF persists. In those who are highly symptomatic or those with inadequate rate control, cardioversion with drugs or direct-current can be considered if the patient has a low thromboembolic risk and the onset of AF was within 48 hours. However, if the patient has increased thromboembolic risk (CHA_2DS_2-VASc score >1), effective peri-cardioversion anticoagulation is required followed by subsequent long-term anticoagulation.(9,12) This recommendation is in keeping with recent data from a large Finnish multicenter cohort study showing that age, female sex, heart failure and diabetes were independent predictors of thromboembolic complications following cardioversion of acute AF with <48 hours duration.(13) In that study, the highest thromboembolic risk was in those with both heart failure and diabetes (9.8%), as compared to those with age <60 years and without heart failure (0.2%).(13)

II. Hemodynamically stable AF with onset >48 hours or unknown duration

Patients with AF lasting more than 48 hours or of unknown duration have increased risk of left atrial thrombus formation rendering cardioversion (chemical or electrical) unsafe. Therefore, the mainstay of initial therapy is to aim for good ventricular rate control of <100bpm at rest (Table 2). Cardioversion can be attempted in these patients only with therapeutic anticoagulation for at least 3 weeks prior and

continued for at least 4 weeks after. However, transesophageal echocardiography guided cardioversion can be facilitated in the absence of left atrial and left atrial appendage thrombus.(14) In this instance, it is essential that effective peri-cardioversion anticoagulation is commenced and maintained for at least four weeks after to reduce new thrombus formation due to atrial stunning following restoration of sinus rhythm.(15,16) Importantly, the effect of atrial stunning is not limited to those who underwent electrical cardioversion with documented negative atrial inotropic effect seen in those treated with anti-arrhythmic drugs.(17) For patients with increased thromboembolic risk, oral anticoagulation would need to be maintained long-term.

III. Hemodynamically compromised AF

A small proportion of patients with acute AF may be hemodynamically compromised thereby necessitating urgent cardioversion. The practicality of administrating peri-cardioversion anticoagulation will depend on the urgency of the situation. In some cases, this may only be feasible following stabilization of the patient with restoration of sinus rhythm. The recommendation is to administer anticoagulation as soon as possible.(9) The duration of AF episode and thromboembolic risk of the individual patient will guide long-term anticoagulation strategy.

IV. Recurrent hemodynamically stable AF

In a select group of patients with structurally normal heart and frequent recurrent symptomatic AF without hemodynamic compromise, a “pill-in-the-pocket” strategy can be considered in the outpatient setting to reduce emergency room

presentations and hospitalizations.(18) However, it is important to first establish the safety of this approach with initial electrocardiographic monitoring to ensure tolerability without pro-arrhythmia effects or significant bradycardia following AF termination. This strategy involves a Class IC anti-arrhythmic drug (flecainide or propafenone) always administered in conjunction with a rate-slowing drug (beta-blocker or non-dihydropyridine calcium channel blocker) to prevent 1:1 rapid ventricular response during atrial flutter.(18-20) The safety of this approach can also be enhanced with careful selection of patients by avoiding usage in the very elderly group (>70 years old) as in-hospital intravenous administration may not predict future adverse events with oral pill-in-the-pocket strategy.(21)

Cardioversion of AF: Electrical vs. Pharmacological

When rhythm control is desired, several factors will need to be considered when choosing between electrical and pharmacological approaches. Recent data from the prospective international multi-center RHYTHM-AF observational study demonstrated a 90% success rate with electrical cardioversion as compared to 69% with pharmacological cardioversion.(22) Both modes of cardioversion are safe and effective with very low rate of complications as reported in the RHYTHM-AF study.(22) However, under-treatment and over-treatment with anticoagulation therapy has also been identified.(23) Appropriate assessment of stroke risk and AF duration must be undertaken in all patients regardless of the mode of cardioversion.

Electrical Cardioversion

Although electrical cardioversion has a higher success rate in restoring sinus rhythm, it requires sedation or a light anesthesia and hence best performed in the post-absorptive state in patients who are hemodynamically stable. A biphasic external defibrillator is preferred over older monophasic devices for greater efficacy of cardioversion while requiring fewer shocks and at lower delivered energy with less risk of dermal injury.(24) Further, synchronized higher shock energy level (biphasic: 150-200J; monophasic: 360J) is recommended to ensure higher initial success and reduce the need for repeated shocks.(25,26) Placement of the defibrillation electrode pads in the antero-posterior position has been shown to be more effective than in the antero-lateral position.(27) Other strategies that may enhance success of electrical cardioversion include application of pressure on the defibrillation electrode pads to improve energy transfer and pre-treatment with anti-arrhythmic drugs.

Apart from the inherent risk of thromboembolism with cardioversion, complications specific to electrical cardioversion also include risk of sedation or light anesthesia; bradyarrhythmias especially in those with co-existing sinus node disease; ventricular arrhythmias especially in those with hypokalemia, digitalis toxicity; delivery of non-synchronized shock; and skin burns or irritation especially in those needing multiple shocks. On the whole, electrical cardioversion has been shown to be effective and safe in prospective registry data showing acute fatal complication rate of 0.1% (death, thromboembolic event, heart failure, major bleeding, bradycardia and hypotension) within first 5 days of cardioversion.(22)

Pharmacological Cardioversion

Availability of anti-arrhythmic drugs commonly used for pharmacological cardioversion of AF may vary by country or region. These agents can be administered orally or intravenously under medical supervision with continuous ECG monitoring and temporary pacing capability due to the likelihood of proarrhythmic events. Recent prospective observational data suggests intravenous administration of antiarrhythmic agents has slightly superior efficacy with shorter time to conversion as compared to oral route.(22) However, several others have shown little difference in overall conversion rate between routes of administration for amiodarone, flecainide and propafenone.(20,22,28-30) Table 3 presents a summary of the commonly used agents for conversion of AF. The clinical comorbidities of the individual patient must be considered with the potential adverse drug effects to guide selection of appropriate anti-arrhythmic agent. Patients with structural heart abnormalities including significant left ventricular hypertrophy, heart failure and coronary artery disease have more limited options as Class IC agents are contraindicated. Other factors to consider include baseline QT interval and patient's renal function.

Limited studies with small sample sizes have directly compared the efficacy of anti-arrhythmic agents to placebo or other drugs in converting acute AF.(31) Contemporary real life data suggests superior efficacy of Class IC agents to amiodarone which did not seem to be better than rate control agents in accelerating conversion of AF.(22) Intravenous magnesium is not recommended for conversion of acute onset AF due to limited efficacy.(11) More recent studies have shown that

vernakalant, a novel atrial selective anti-arrhythmic agent, demonstrates more rapid AF conversion as compared to amiodarone and Class IC agents.(32-34) Nevertheless, the choice of agents for conversion of AF must be based on patient safety, contraindications, adverse effects and availability.

Thromboembolic Risk Assessment and Anticoagulation Therapy

Assessing thromboembolic risk and the need for anticoagulation therapy is crucial in the management of patients with AF. The clinical encounter when patients present with acute sustained AF is no exception. Recent real world data has highlighted the gap in current management with both under- and over-treatment with anticoagulation.(23) Assessment of stroke risk must be carried out using established risk score such as the CHA_2DS_2-VASc score [congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female)].(35)

Recently, several novel oral anticoagulants have become available as alternatives to vitamin K antagonist, warfarin. These agents either inhibit thrombin (dabigatran) or Factor Xa (rivaroxaban or apixaban) directly. They have been shown to be non-inferior to warfarin and in some instances, superior results for preventing stroke and systemic embolism as well as less hemorrhagic strokes without increased risk of major bleeding.(36) However, the safety and efficacy data on the usage of these novel agents at the time of cardioversion are derived from patients who are already on long-term therapy (more than 3 weeks).(37-39) However, it is likely that these

agents will provide at least the same protection for thromboembolic complications as warfarin surrounding cardioversion of AF.

Follow-up After Acute AF Management

The complexity of AF management and heterogeneity in the patients presenting with acute sustained AF demands specialized care following acute AF care. This is particularly so for patients with newly diagnosed AF whereby comprehensive AF risk factor assessment, ongoing patient education and anticoagulation management are warranted. Referral to heart rhythm specialists or cardiologists with interests in AF management is highly recommended for ongoing care. A proportion of AF patients may subsequently require and benefit from catheter ablation therapy that has been shown to be an effective and durable long-term option with decreasing peri-procedural complications.(40-42) Further, specialized nurse-led guidelines based chronic care of AF patients has been shown to reduce hospitalizations and improve outcomes.(43)

Clinicians must recognize that AF is a consequence of 'atrial myopathy' with increasing number of novel risk factors being identified in recent years including: pericardial fat, prehypertension, widened pulse pressure, aortic stiffness and sleep apnea.(44-48) Indeed, there has been a recent proposal for avoiding the use of the term 'lone AF'.(49) Therefore, the underlying modifiable risk factors must be actively targeted to reduce the arrhythmogenic substrate and AF burden in patients with this debilitating arrhythmia.(50)

CONCLUSIONS

This review details the options for tailored treatment approach in patients with recent onset sustained AF. In addition to the rate and rhythm control aspects of management, it highlights the need to assess stroke risk in all AF patients and arrange appropriate follow-up care following the acute episode to optimize long-term outcomes.

Conflicts of Interest:

Dr. Kalman report having served on the advisory board of and having received lecture fees from Medtronic and St Jude Medical. Dr Sanders reports having served on the advisory board of and having received lecture fees and research funding from Bard Electrophysiology, Biosense-Webster, Medtronic, Merck Sharp & Dohme, Sanofi-Aventis and St. Jude Medical.

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Table 1: Initial Assessments of Patients with Acute AF

Initial Assessments of Patients with Acute AF		
AF History	*Current episode:* known onset? within 48 hours? symptomatic? *Previous AF:* AF Type: Paroxysmal vs. Persistent vs. Chronic AF therapy: electrical cardioversion? anti-arrhythmic drugs, ablation Anticoagulation strategy	
Co-morbidities	*AF risk Factors:* Aging Hypertension Heart failure Coronary artery disease Valvular heart disease Congenital heart disease Diabetes mellitus Obesity Sleep apnea Infiltrative heart disease Familial AF	*Triggers for AF:* Systemic Infection or sepsis (e.g. pneumonia) Inflammation (e.g. pericarditis, myocarditis) Atrial ischemia (e.g. coronary syndrome) Endocrine (e.g. thyrotoxicosis) Drugs (e.g. caffeine, alcohol) Electrolyte disturbances Neurogenic (e.g. stroke, intra-cranial bleed) Left atrial strain (e.g. pulmonary embolism, acute hypertension, acute heart failure) Post-operative state Increased parasympathetic/sympathetic tone
Thromboembolic Risk Assessment	Use CHA_2DS_2-VASc score to determine need for long-term oral anticoagulation	
Clinical Evaluation	Hemodynamic stability Ventricular rate during AF Temperature Oxygen saturation Pulmonary edema Cardiac murmurs	
Investigations	12-lead ECG: ischemia, pre-excitation Biochemistry Full blood count Inflammatory markers Thyroid function test Cardiac enzymes Chest x-ray	