

*** Warning ***

FDA Drug Safety Communication: Changes to the Heparin Sodium USP Monograph

Safety Announcement

[04-07-2010] Laboratory studies performed at the request of the U.S. Food and Drug Administration (FDA) have shown that Heparin Sodium, USP (heparin) made under the new United States Pharmacopeia (USP) Monograph ("new heparin") has approximately 10% less blood-thinning (anticoagulant) activity compared to heparin prepared using the previous ("old") USP Monograph. The studies were performed in order to better understand the clinical impact of the change in potency for heparin.

The FDA first alerted the public to changes in the potency of heparin in a Public Health Alert in October 2009.

The results of these studies reinforce FDA's previous recommendation for healthcare professionals to exercise clinical judgment in determining the dose of heparin for a patient and consider the clinical circumstances where the potency decrease may require dosage adjustments and more frequent monitoring.

Healthcare professionals should be aware that heparin products, i.e., those made using both the old and the new USP standards may be available for some time. Healthcare professionals may wish to consider not using the products interchangeably. Pharmacies and hospitals may wish to consider separating the supplies of old and new heparin and exhausting the supplies of "old" heparin before transitioning to the "new" product (see Table below, "How to Identify Heparin Products made to the New USP Standard").

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals:

- Be aware that there is an approximate 10% decrease in the anticoagulant activity (potency) of the "new heparin" compared with the "old heparin."
- Continue to exercise clinical judgment in determining the dose of heparin.
- Continue to individualize heparin dosing to the specific patient/patient-specific clinical situation.
- Understand that the labeling for heparin, including the recommended doses for heparin has not changed.
- Consider those clinical circumstances where the potency decrease may require dosage adjustments and more frequent monitoring, such as where aggressive anticoagulation is essential to the treatment of the patient, including:

- pediatric patients undergoing extracorporeal membrane oxygenation
- adults and children undergoing cardiopulmonary bypass
- the treatment or prevention of life-threatening thromboses
- Report any adverse events associated with the use of heparin

Data Summary

Studies to assess differences in heparin activity were performed in animals (*in-vivo*) and in human plasma (*in-vitro*). The results of the human plasma and animal studies were consistent in demonstrating an approximate 10% decrease in heparin activity of the "new" heparin products compared to "old" heparin products. The average activated partial thromboplastin time (aPTT) response to a dose of heparin changed in a dose-proportional manner.

The same studies also demonstrated that there were large individual variations in aPTT responses to a given dose of heparin. Therefore, in a clinical setting, a 10% decrease in heparin dose might not be reflected in the results of an aPTT or ACT (Activated Clotting Time) for an individual patient.

Given the inherent individual variability in response to a dose of heparin, a 10% decrease in heparin activity (potency) is not likely to have clinical significance. However, special clinical situations such as cardiac surgery and/or use in pediatric patients may require more intensive monitoring to achieve optimal therapeutic response. Since heparin therapy is routinely titrated to each patient (there are many patient-specific factors that can influence heparin dosing) the usual method of individualizing dosing will continue to ensure patient safety.

Table to Distinguish Between "New" and "Old" Heparin

Since new heparin will be available, starting October 2009 there will likely be supplies of both the old and new heparin stocked for use in hospitals and pharmacies for a period of about three years. Facilities that have stocks of old and new heparin may wish to consider segregating stores of the old heparin from the new and using the "old" heparin products first. The table below provides information on how to distinguish between the old and new product and company website for additional information.

How to Identify Heparin Products made using the New USP Standard

Manufacturer	(Date) Availability of Lots Made to the New USP Standard	How to Identify the New Product	Additional Information/Company Contact
APP	October 2009	"N" will appear after the Expiration Date	http://www.appdrugs.com
B. Braun	October 2009	"N" will appear after the Lot Number	http://www.bbraunusa.com
Hospira	October 2009	Lot Numbers will begin with the number "82" or higher	http://www.hospira.com/Files/HeparinUSP.pdf
Baxter	October 2009	"N" will appear before the Lot Number	http://www.baxter.com/index.html



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Health Care Guideline: Atrial Fibrillation

The information contained in this ICSI Health Care Guideline is intended primarily for health professionals and the following expert audiences:

- physicians, nurses, and other health care professional and provider organizations;
- health plans, health systems, health care organizations, hospitals and integrated health care delivery systems;
- health care teaching institutions;
- health care information technology departments;
- medical specialty and professional societies;
- researchers;
- federal, state and local government health care policy makers and specialists; and
- employee benefit managers.

This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. If you are not one of the expert audiences listed above you are urged to consult a health care professional regarding your own situation and any specific medical questions you may have. In addition, you should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in your individual case.

This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. An ICSI Health Care Guideline rarely will establish the only approach to a problem.

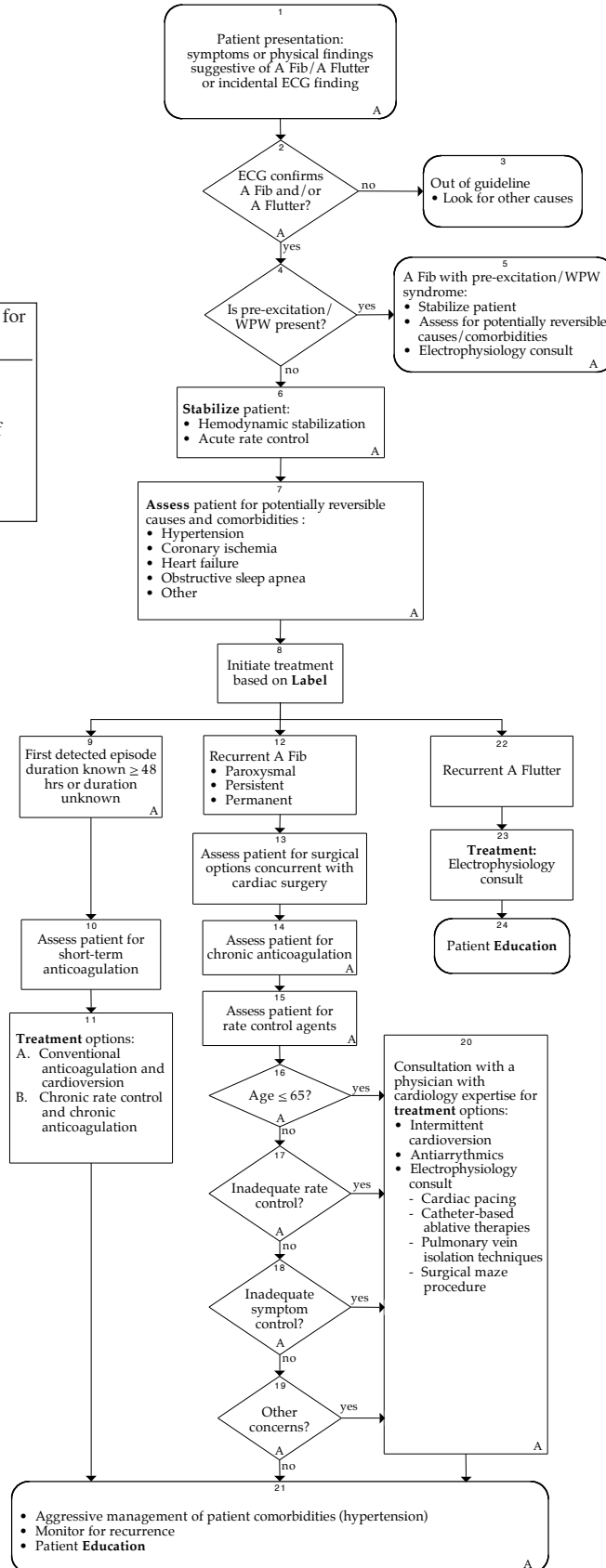
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Five key management steps for Atrial fibrillation: **SALT-E**

S – stabilize
A – assess
L – label for stratification of treatment options
T – treat
E – educate



RECOMMENDATIONS TABLE
Acute Episode of Atrial Fibrillation
Evaluation
2 D echocardiogram TSH Estimation of risk of bleeding for short-term anticoagulation
Treatment
Warfarin unless the short-term risk of bleeding exceeds the risk of thromboemboli (INR greater than or equal to 2.0 for 4 consecutive weeks) prior to cardioversion and anticoagulation (INR 2.0-3.0) for 8 weeks following cardioversion Note: there is insufficient evidence to recommend TEE-directed anticoagulation prior to cardioversion
Chronic Atrial Fibrillation
Evaluation
Estimation of risk of thromboembolism – CHADS2 Estimation of risk of bleeding for chronic anticoagulation
Treatment
Warfarin or aspirin based on CHADS2 score – unless the long-term risk of bleeding exceeds the risk of thromboemboli For patients receiving warfarin – INR monthly and as needed Note: there is insufficient evidence to recommend the addition of warfarin to patients who require aspirin + clopidogrel Resting pulse less than 80 and assessment of exercise heart rate in active patients Digoxin alone only if beta-blockers and calcium channel blockers are contraindicated Rhythm control (with anticoagulation based on CHADS2 score) only if symptoms caused by atrial fibrillation are not adequately controlled with rate control alone
Any History of Atrial Fibrillation
Treatment – Probably Beneficial
Aspirin (or warfarin when appropriate – see above) – unless contraindicated Beta blocker ACE inhibitor or ARB Statin

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Work Group Leader

Thomas Munger, MD
*Cardiology/
Electrophysiology, Mayo
Clinic*

Work Group Members

Cardiology/

Electrophysiology

David Dunbar, MD
St. Paul Heart Clinic
Humberto Vidaillet, MD
Marshfield Clinic

Internal Medicine

Mark Morrow, MD
Aspen Medical Group

Pharmacy

Tonja Larson, PharmD,
BCPS
Marshfield Clinic
Krissa Skoglund, PharmD,
BCPS
*HealthPartners Medical
Group*

Measurement/ Implementation Advisor

Penny Fredrickson
ICSI

Facilitator

Joann Foreman, RN
ICSI

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Foreword

Scope and Target Population

This guideline addresses first detected episode and recurrent (paroxysmal, persistent and permanent) atrial fibrillation and atrial flutter in the adult population that present in primary care, emergency room and the inpatient settings. The scope includes stabilization, assessment, labeling (classification), treatment and patient education.

This document is not intended to replace the comprehensive ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation, which the interested provider is encouraged to review.

Clinical Highlights and Recommendations

There are five key steps in the management of patients with atrial fibrillation or atrial flutter (SALT-E): stabilize, assess, label, treat and educate.

After confirming the diagnosis of atrial fibrillation or atrial flutter with a 12-lead electrocardiogram (*Annotation #2*):

Stabilize

- Assess for hemodynamic instability (hypotension, myocardial ischemia, uncompensated congestive heart failure, altered mental status or end-organ dysfunction). (*Annotation #6*)
- Treat hemodynamic instability with emergent direct current cardioversion and obtain an emergent cardiology or internal medicine consult. (*Annotation #6*)
- Establish adequate rate control. (*Annotation #6*)

Assess

- Assess for potentially reversible causes and for comorbidities of atrial fibrillation/atrial flutter. (*Annotation #7*)
- Hypertension is one of the most common causes of atrial fibrillation. In addition, hypertension is one of the most common risk factors for thromboembolic complications associated with atrial fibrillation. Treatment for hypertension should be initiated early. (*Annotation #7*)

Label

- Label (classify) patients into one of three categories:
 - First Detected Episode, Duration Known $\geq 48^{\circ}$ or Duration Unknown
 - Recurrent atrial fibrillation
 - Paroxysmal
 - Persistent
 - Permanent
 - Recurrent atrial flutter

Treatment options are determined by these three categories. (*Annotations #9, 14, 15, 18, 19, 20*)

Treat

First Detected Episode, Duration Known \geq 48 hours or Duration Unknown

- Patients with stable atrial fibrillation or atrial flutter with duration greater than 48 hours or duration unknown require appropriate anticoagulation (international normalized ratio greater than or equal to 2.0) for three weeks prior to electrical cardioversion or use of antiarrhythmics/chemical cardioversion. (*Annotation #9*)

Recurrent atrial fibrillation

- Patients with paroxysmal, persistent or permanent atrial fibrillation require assessment for chronic anticoagulation (risk of thromboembolism compared with risk of bleeding) (*Annotation #14*) and adequate rate control. (*Annotation #15*)
- Patients with persistent symptoms despite adequate rate control may require intermittent cardioversion, antiarrhythmic agents and/or electrophysiology consultation. (*Annotation #20*)

Recurrent atrial flutter

- Patients with recurrent atrial flutter should be referred for an electrophysiology consultation. (*Annotation #20*)

Educate

Patient education is a critical component in the management of all patients with atrial fibrillation/atrial flutter. Patients who have experienced one or more episodes of atrial fibrillation should be taught to periodically monitor their pulse and have a plan for treatment if they detect an irregular pulse. (*Annotation #21*)

Priority Aims

1. Increase the percentage of adult patients (age 18 years and older) who are accurately diagnosed with atrial fibrillation/flutter. (*Annotation #2*)
2. Improve the consistency of anticoagulation therapy in adult patients (age 18 years and older) with non-valvular paroxysmal, persistent or permanent atrial fibrillation/flutter. (*Annotation #14*)
3. Improve rate control in adult patients (age 18 years and older) with permanent atrial fibrillation. (*Annotation #17*)
4. Increase the percentage of adult patients (age 18 years and older) with a confirmed diagnosis of atrial fibrillation/atrial flutter who, along with their family, have received education around atrial fibrillation/flutter and anticoagulation therapy. (*Annotation #21*)
5. Reduce the percentage of patient harm associated with the use of anticoagulation therapy. (*Annotation #14*)
6. Increase the percentage of adult patients (age 18 years and older) with a confirmed diagnosis of atrial fibrillation/flutter, receiving dietary monitoring. (*Annotation #21*)
7. Increase the percentage of adult patients (age 18 years and older) with a confirmed diagnosis of atrial fibrillation/flutter who have a medication communication/reconciliation plan throughout the continuum of care. (*Annotations #7, 15, 21*)

Key Implementation Recommendations

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Develop a process for accurate diagnosis of atrial fibrillation/flutter:
 - Documentation of an electrocardiogram along with results in the medical record.
 - Process for communicating to physicians that a diagnosis of atrial fibrillation/flutter was confirmed by electrocardiogram.
2. Develop a process for implementing the five key steps in the management of atrial fibrillation/flutter (SALT-E):
 - Stabilize (*Annotation #6*)
 - Assess (*Annotation #7*)
 - Label (*Annotations #9, 14, 15, 18, 19, 20*)
 - Treat (*Annotations #9, 14, 15, 20*)
 - Educate (*Annotation #21*)
3. Patient education is essential in the treatment of atrial fibrillation/flutter. Patients and caregivers should be informed of signs and symptoms that require contact with their health care provider.

(*Annotations #1, 21*)
4. Develop a process to assure that patients who are diagnosed with atrial fibrillation/flutter and are initiated on warfarin have a baseline international normalized ratio that is documented in the medical record.
5. Develop and implement a defined anticoagulation management program.
6. Develop a process for appropriate referral to specialty; this should include a process for communication across the continuum of care.
7. Develop a process that will assure the completion of a patient medication list for the purpose of communicating to the next provider of service, when the patient is referred, or transferred to another setting, service, practitioner or level of care within or outside the organization.

Related ICSI Scientific Documents

Guidelines

- Antithrombotic Therapy Guideline Supplement
- Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS)
- Hypertension Diagnosis and Treatment

Technology Assessment Reports

- Implantable Cardioverter-Defibrillators for the Primary Prevention of Sudden Cardiac Death Due to Ventricular Arrhythmias (#89, 2005)
- Rhythm Therapy versus Rate Control for Long-term Management of Recurrent Atrial Fibrillation (#77, 2003)

Disclosure of Potential Conflict of Interest

ICSI has adopted a policy of transparency, disclosing potential conflict and competing interests of all individuals who participate in the development, revision and approval of ICSI documents (guidelines, order sets and protocols). This applies to all work groups (guidelines, order sets and protocols) and committees (Committee on Evidence-Based Practice, Cardiovascular Steering Committee, Women's Health Steering Committee, Preventive & Health Maintenance Steering Committee and Respiratory Steering Committee).

Participants must disclose any potential conflict and competing interests they or their dependents (spouse, dependent children, or others claimed as dependents) may have with any organization with commercial, proprietary, or political interests relevant to the topics covered by ICSI documents. Such disclosures will be shared with all individuals who prepare, review and approve ICSI documents.

David Dunbar, MD receives research/grant funding from Medtronic and Boston Scientific for clinical research.

No other work group members have potential conflicts of interest to disclose.

Introduction

This document was developed and/or revised by a multidisciplinary work group utilizing a defined process for literature search and review, document development and revision, as well as obtaining input from and responding to ICSI members.

For a description of ICSI's development and revision process, please see the Development and Revision Process for Guidelines, Order Sets and Protocols at <http://www.icsi.org>.

Evidence Grading System

A. Primary Reports of New Data Collection:

- Class A: Randomized, controlled trial
- Class B: Cohort study
- Class C: Non-randomized trial with concurrent or historical controls
Case-control study
Study of sensitivity and specificity of a diagnostic test
Population-based descriptive study
- Class D: Cross-sectional study
Case series
Case report

B. Reports that Synthesize or Reflect Upon Collections of Primary Reports:

- Class M: Meta-analysis
Systematic review
Decision analysis
Cost-effectiveness analysis
- Class R: Consensus statement
Consensus report
Narrative review
- Class X: Medical opinion

Citations are listed in the guideline utilizing the format of (*Author, YYYY [report class]*). A full explanation of ICSI's Evidence Grading System can be found at <http://www.icsi.org>.

Algorithm Annotations

Introduction

This guideline follows closely the AHA/ACC/ESC 2006 and the American Academy of Family Physician guidelines. Areas of divergence from other clinical practice guidelines are transesophageal echocardiography and rhythm versus rate control. The purpose of this guideline is to provide primary care with a guideline that outlines areas for systems improvement for the diagnosis and treatment of atrial fibrillation in primary care.

Atrial fibrillation is a common arrhythmia and an important independent risk factor for stroke. The prevalence of atrial fibrillation increases from 0.5% for the 50- to 59-year-old age group to 8.8% in the 80- to 89-year-old age group. Symptoms vary from none to severe disabling palpitations, dyspnea and syncope. Patients with atrial fibrillation have a mortality rate double that of control subjects. Atrial fibrillation is one of a number of factors that increase the risk of systemic thromboembolic events including cerebrovascular events and peripheral arterial emboli. An individual patient's risk can be reliably estimated based on history of congestive heart failure, hypertension, age > 75, diabetes and secondary prevention. (See Annotation #14 CHADS2 score.)

1. Patient Presentation: Symptoms or Physical Findings Suggestive of Atrial Fibrillation/Atrial Flutter or Incidental Electrocardiogram Finding

Key Points:

- Atrial fibrillation or atrial flutter can be symptomatic or asymptomatic – even in the same patient.

Atrial fibrillation or atrial flutter can be symptomatic or asymptomatic – even in the same patient. Symptoms may include:

- palpitations
- chest pain
- dyspnea
- fatigue
- lightheadedness
- confusion
- syncope – Syncope is a rare but serious complication that usually indicates a sinus node dysfunction, an accessory atrioventricular pathway, valvular aortic stenosis, hypertrophic cardiomyopathy or cerebrovascular disease.

Physical findings may include:

- irregular pulse
- heart failure
- hypoxia
- thromboembolism

(Fuster, 2006 [R])

2. Electrocardiogram Confirms Atrial Fibrillation and/or Atrial Flutter?

An electrocardiogram is essential to establish the diagnosis and treatment of atrial fibrillation or atrial flutter.

Electrocardiogram Characteristics of Atrial Fibrillation

Atrial fibrillation is characterized by disorganized rapid atrial activity (greater than 350 beats per minute) and may be either coarse or fine. Ventricular complexes are irregular.

Electrocardiogram Characteristics of Atrial Flutter

Atrial flutter is an organized reentrant rhythm, which is characterized by quite regular atrial activity (flutter or F waves) that form a sawtooth pattern that is most prominent in electrocardiogram leads II, III and AVF. Atrial rates are typically between 240-320 beats per minute in the untreated state, but can slow significantly with antiarrhythmic drug therapy. Ventricular rates can be either regular or irregular. Regular rates are commonly about 150 beats per minute with a 2:1 atrioventricular block. Atypical atrial flutter is also quite regular, but may differ in flutter wave morphology and rates. It is usually seen in patients who have had prior surgical atriotomies, particularly for correction of congenital heart disease.

Atrial flutter can degenerate into atrial fibrillation, atrial fibrillation can initiate atrial flutter, or the electrocardiogram patterns can alternate between atrial flutter and atrial fibrillation.

The distinction between atrial fibrillation and atrial flutter is particularly important in that typical atrial flutter can be easily ablated. See Annotation #20, "Consultation with a Physician with Cardiology Expertise for Treatment Options."

Atrioventricular Node Conduction (Atrial Fibrillation/Atrial Flutter)

Ventricular response to atrial fibrillation and atrial flutter depends on the ability of the atrioventricular node to conduct electrical impulses to the ventricle. Atrioventricular nodal conduction is affected by intrinsic properties of the atrioventricular node, parasympathetic (vagal) inputs, sympathetic (adrenergic) inputs, drugs that depress atrioventricular nodal conduction such as beta-blockers, calcium blockers and digoxin and drugs that may enhance conduction.

Associated Cardiac Conditions That May Influence Therapy

The electrocardiogram should also be examined for other underlying cardiac conditions, which may influence choice of therapy:

- Pre-excitation/Wolff-Parkinson-White syndrome
- Bundle branch block
- Left ventricle hypertrophy
- Acute myocardial infarction
- Prior acute myocardial infarction
- QT prolongation
- P-wave duration and morphology or fibrillatory waves
- Other atrial arrhythmias

(Fuster, 2006 [R])

5. Atrial Fibrillation with Pre-Excitation/Wolff-Parkinson-White Syndrome

Atrial fibrillation in patients with Wolff-Parkinson-White syndrome is characterized on the electrocardiogram by an irregular wide complex tachycardia (pre-excited QRS complexes conducted over the accessory atrioventricular pathway). Often there may be interspersed narrow QRS complexes from beats conducted

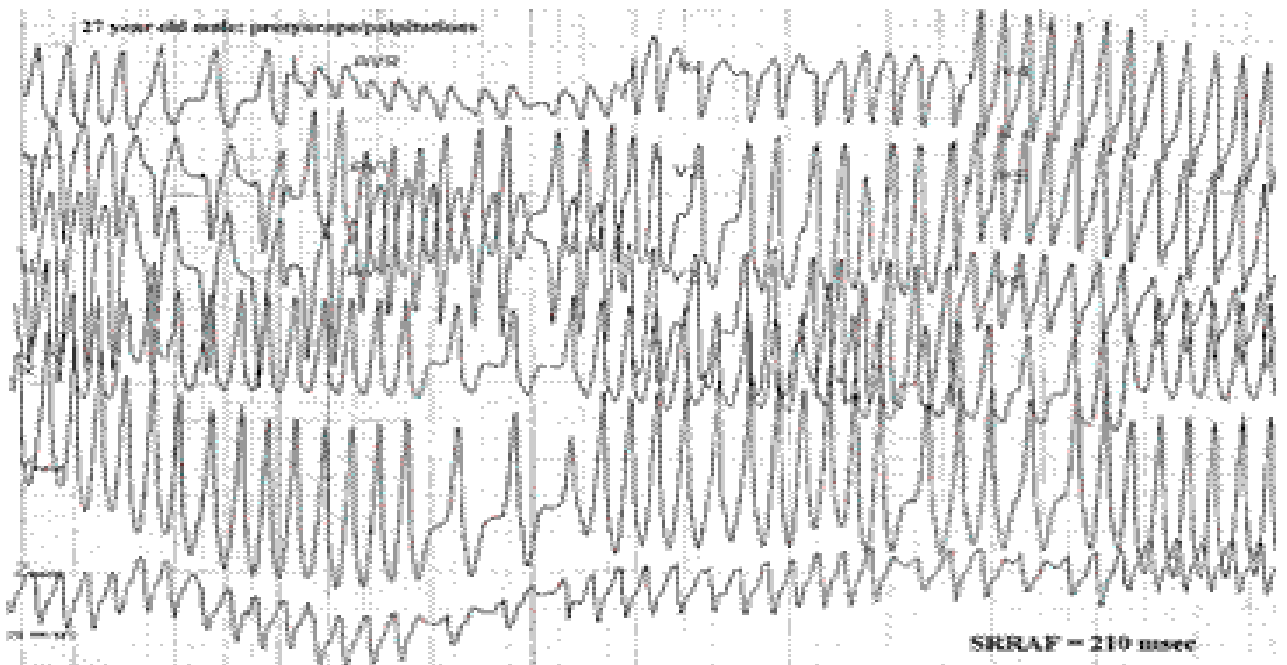
Algorithm Annotations

over the atrioventricular node. The ventricular response can be dangerously rapid (R-R intervals greater than 250 millisecond) with the potential for degeneration to ventricular fibrillation. Differential diagnosis includes ventricular tachycardia, which is usually regular when monomorphic, or polymorphic when irregular. Atrial fibrillation with bundle branch block aberrancy is also in the differential. Comparison with old electrocardiograms should show a short PR interval with a delta wave for Wolff-Parkinson-White.

Recognition of atrial fibrillation with pre-excitation is critical. The drugs commonly used to control ventricular response – such as diltiazem, verapamil and digoxin – are ineffective and can facilitate conduction through the accessory pathway, increasing the risk for ventricular fibrillation. Direct current cardioversion is commonly the treatment of choice due to hemodynamic compromise related to rapid rates and risk of ventricular fibrillation. In less severely affected patients, rate can be controlled with intravenous amiodarone, intravenous ibutilide or intravenous procainamide by depressing accessory pathway conduction. Patients should be referred to an electrophysiologist for consideration of accessory pathway ablation. Ablation removes the potential for life-threatening rapid ventricular response and may decrease the likelihood of recurrent atrial fibrillation.

(Fuster, 2006 [R])

Example of electrocardiogram showing pre-excitation syndrome



This is a 27-year-old man with Wolff-Parkinson-White in atrial fibrillation. Because of the Wolff-Parkinson-White, his QRS complex is widened and irregular; this can simulate polymorphic VT as such.

6. Stabilize Patient

Key Points:

- Hemodynamically unstable patients represent a unique group that often has underlying structural or electrical cardiopulmonary disease.

Algorithm Annotations

- Hemodynamically unstable patients require hospitalization and emergent consultation from a physician with cardiology expertise, and if indicated, emergent direct current cardioversion.

Hemodynamic Stabilization

Hemodynamically unstable patients may exhibit the following symptoms:

- Hypotension
- Myocardial ischemia
- Uncompensated heart failure
- Altered mental status
- End-organ dysfunction
- Clinical deterioration

These patients represent a unique group that often has underlying structural or electrical cardiopulmonary disease, including Wolff-Parkinson-White syndrome, severe stenosis of the mitral or aortic valves, hypertrophic obstructive cardiomyopathy, cardiac tamponade/pericarditis, severe coronary artery disease (*Crenshaw, 1991 [C]*) or pulmonary embolism.

Additional evaluation of patients with atrial fibrillation/atrial flutter presenting with hemodynamic instability may include:

- emergent echocardiography
- computed tomography scan of the chest
- coronary/pulmonary angiography

Hemodynamically unstable patients require hospitalization and emergent consultation from a physician with cardiology expertise, and if indicated, emergent cardioversion.

Additional urgent treatments may include:

- radiofrequency catheter ablation
- internal cardioversion
- balloon valvuloplasty
- percutaneous transluminal coronary angioplasty
- pericardiocentesis
- septal ablation (alcohol or surgical)
- pulmonary embolectomy, and/or
- coronary bypass or valve replacement/repair

Antithrombotic is favored prior to and following emergent cardioversion if there are not specific contraindications, although little evidence exists (*Albers, 2001 [R]*). Initiation of intravenous unfractionated heparin in addition to warfarin should be considered for the following:

- Patients who have been in atrial fibrillation for a few days and then develop hemodynamic instability
- Patients in whom recurrent atrial fibrillation is likely because of past experience
- Patients with mitral valve disease or left ventricular dysfunction
- Patients who, following cardioversion, demonstrate spontaneous echocardiogram contrast in the left atrium or left atrial appendage

Heparin should be continued until the international normalized ratio is greater than 2.0. There is little experience reported on the use of low-molecular-weight heparins following cardioversion.

For more information on anticoagulation, please refer to the ICSI Antithrombotic Therapy Guideline Supplement.

(Li, 1998 [R]; Pratt, 1998 [R])

Acute Rate Control

Adequate rate control may help relieve symptoms including palpitations, chest pain, dyspnea, fatigue or light-headedness. Patients with acute myocardial infarction or acute coronary symptoms require lower ventricular rates to decrease myocardial oxygen demand and limit the infarction size (Schumacher, 1998 [R]).

Amiodarone has become a popular antiarrhythmic choice, but its use should be reserved for patients with coronary artery disease with heart failure or with substantial left ventricular hypertrophy. Refer to Annotation #15, Table 11, "Medications Used for Rate Control."

Acute rate control agents

Beta-blockers are generally favored for pharmacologic rate control. Beta-blockers control heart rate at rest and with exercise, and also provide cardioprotective benefits. They may be used with caution with asthma or chronic obstructive pulmonary disease. Beta-blockers are preferred for patients with atrial fibrillation and heart failure.

Calcium channel blockers are alternative rate control agents when beta-blockers are contraindicated. Calcium channel blockers control heart rate at rest and with exercise but may exacerbate systolic heart failure. Calcium channel blockers should not be administered in the presence of wide QRS/Wolff-Parkinson-White/pre-excitation.

Concomitant use of a beta-blocker with a calcium channel blocker can, in rare circumstances, cause profound negative dromotropic, chronotropic and inotropic effects. These effects may be further exacerbated by type I or type III antiarrhythmic agents or underlying structural heart disease.

Digoxin is a third-line agent for rate control. Digoxin does not lower blood pressure and has a positive inotropic effect, but works more slowly than beta-blockers and calcium channel blockers, has no effect on the sympathetically mediated enhancement of atrioventricular node conduction during exercise (Matsuda, 1991 [A]), and is no better than placebo for conversion to normal sinus rhythm. Digoxin should not be administered with wide QRS/Wolff-Parkinson-White/pre-excitation, hypokalemia, hypomagnesemia and renal impairment.

Amiodarone is a first-line agent for patients with decompensated heart failure. Amiodarone has side effects including thyroid disease, hepatic dysfunction, lung disease, neurologic dysfunction and bradycardia and should be reserved for patients with coronary artery disease with heart failure, moderate to severe systolic dysfunction, or hypertension with significant left ventricle hypertrophy.

If ventricular response remains rapid despite attempts to control rate with beta-blockers, calcium channel blockers and/or digoxin, consultation from a physician with cardiology expertise is recommended. Treatment options include immediate cardioversion if the risk of thromboembolism is acceptable.

7. Assess Patient for Potentially Reversible Causes and Comorbidities

Cardiovascular

- Hypertension
- Heart failure
- Primary pulmonary hypertension
- Acute myocardial infarction or unstable coronary syndrome

Algorithm Annotations

- Atrioventricular node reentry/paroxysmal supraventricular tachycardia
- Accessory pathway/Wolff-Parkinson-White
- Pericarditis/myocarditis
- Mitral valve disease/tricuspid disease
- Amyloidosis
- Congenital heart disease
- Hypertrophic cardiomyopathy

Pulmonary

- Pulmonary embolus
- Chronic obstruction pulmonary disease
- Carbon monoxide poisoning
- Obstructive sleep apnea

Metabolic

- Postoperative state/high catecholamine state
- Hyperthyroidism

Drugs

- Alcohol
- Caffeine
- Medications including antiarrhythmic and anticholinergic
- Illicit drugs including PCP, cocaine and other stimulants
- Absence of any of the risk factors listed above

(Fuster, 2006 [R])

Other

- Perioperative period
- Pregnancy

Patients presenting with a first detected episode of atrial fibrillation/atrial flutter should be assessed with:

- chest x-ray
- echocardiogram

Patients presenting with a first detected episode of atrial fibrillation/atrial flutter or with difficult rate control or with unexpected recurrence after cardioversion should also have:

- thyroid function tests

9. First Detected Episode Duration Known \geq 48 Hours or Duration Unknown

Key Points:

- Antithrombotic with warfarin (international normalized ratio greater than or equal to 2.0 for three weeks) is recommended before electrical or pharmacologic cardioversion back to sinus rhythm.
- Transesophageal echocardiography-guided cardioversion without traditional pre-cardioversion anticoagulation cannot be routinely recommended.

Algorithm Annotations

- Amiodarone is the most effective antiarrhythmic drug for maintenance of normal sinus rhythm. However, it also is associated with the highest potential for non-cardiac toxicity, and requires regular scheduled medical follow-up.
- ACE inhibitors and angiotensin receptor blockers have a role as adjunctive medical therapies to antiarrhythmic drugs for maintenance of normal sinus rhythm.

General Recommendations

When the duration of atrial fibrillation or atrial flutter is unknown, the risk of thromboembolic complications is as high as 7% following cardioversion without anticoagulation. Thus, in this setting, anticoagulation with warfarin is required (international normalized ratio greater than or equal to 2.0 for three consecutive weeks). Though not a consistent clinical practice, the American College of Chest Physicians also recommends anticoagulation with warfarin (international normalized ratio greater than or equal to 2.0 for three consecutive weeks) prior to the initiation of antiarrhythmics.

Alternatively, the patient and/or physician may opt for chronic anticoagulation (see Annotation #14, "Assess Patient for Chronic Anticoagulation") and chronic rate control (see Annotation #15, "Assess Patient for Rate Control Agents"). However, if this represents the first episode of persistent atrial fibrillation for the patient, there is general consensus that most patients deserve one trial of conversion back to normal sinus rhythm, given the high likelihood of initial success.

Short-Term Antithrombotic Issues Prior to and Following Cardioversion

There are no placebo-controlled, randomized trials of anticoagulation prior to direct current or chemical cardioversion. In 1967, Lown reported an incidence of embolization of 1.2% of 450 patients treated with direct current cardioversion without cardioversion. In 1969, Bjerkelund and Orning reported a prospective cohort study. The rate of embolic complications after cardioversion was 5.3% in the low-risk patients who received no anticoagulation and 0.8% in the high-risk patients who received anticoagulation. Three other case studies reported in the 1960s also favor the use of anticoagulation prior to direct current cardioversion. In 1959, Goldman reported a rate of embolization of 1.5% of 400 patients who received quinidine for chemical cardioversion of atrial fibrillation – similar to the rate Lown reported following direct current cardioversion. Therefore, Laupacis, et al. concluded, "It seems prudent to administer anticoagulants to individuals undergoing pharmacologic cardioversion in a similar manner to those undergoing electrical cardioversion." The ACC/AHA/ESC guidelines concur (*Albers, 2001 [R]; Bjerkelund, 1969 [C]; Fuster, 2006 [R]; Goldman, 1959 [R]; Lown, 1967 [R]; McCarthy, 1969 [D]; Morris, 1966 [D]; Resnekov, 1967 [D]*).

Though most reports of cardioversion pooled together patients with atrial fibrillation, atrial flutter and supraventricular tachycardia, there are several case reports of embolization following cardioversion of patients with pure atrial flutter. Delayed restoration of atrial function after cardioversion of patients with pure atrial flutter have been described. Albers, et al. recommended that "consideration should be given to treating patients with atrial flutter in the same manner as patients with atrial fibrillation at the time of cardioversion" (*Albers, 2001 [R]; Jordaens, 1993 [A]*).

In the postcardioversion phase, forceful atrial appendage contractions may not resume for up to four weeks. O'Neill, et al. reported that immediately after cardioversion, the degree of atrial contractility was variable and delayed (*O'Neill, 1990 [D]*). Manning, et al. reported that atrial contractility did not maximize until three weeks after cardioversion (*Manning, 1989 [D]*). Therefore, Albers, et al. recommended that anticoagulation be continued for four weeks after cardioversion to decrease the likelihood of fresh thrombus formation in the hypocontractile atrial appendage and to decrease the likelihood of thrombus formation if atrial fibrillation recurs (*Albers, 2001 [R]*).

Whenever possible, cardioversion should be undertaken with conventional anticoagulation prior to and following cardioversion.

When anticoagulation is temporarily contraindicated (refer to Table 1, below), cardioversion should be delayed if possible until appropriate anticoagulation can be given prior to and following cardioversion.

Table 1. Risk Factors for Bleeding for Short-Term Use of Warfarin

Risk Factors for Bleeding for Short-Term Use of Warfarin
Active significant bleeding
Craniotomy within two weeks
History of intracerebral hemorrhage within two weeks
Active intracranial lesions/neoplasms/monitoring devices
Vascular access/biopsy sites inaccessible to hemostatic control within 24 hours
Bacterial endocarditis, proliferative retinopathy

When anticoagulation is contraindicated and cardioversion cannot be delayed, transesophageal echocardiography may identify high-risk patients but may not change therapeutic decisions.

However, if transesophageal echocardiography is used to guide anticoagulant therapy, the patient must be anticoagulated with therapeutic (not prophylactic) levels of heparin and warfarin. Heparin should be continued until the international normalized ratio is greater than or equal to 2.0 for two consecutive days. Warfarin should be continued a minimum of four weeks following successful cardioversion.

At this time, there is insufficient evidence to recommend routine transesophageal echocardiography to guide anticoagulant therapy prior to or following cardioversion [*Conclusion Grade III: See Conclusion Grading Worksheet A – Annotation #9 (Transesophageal Echocardiography and Anticoagulation Therapy)*] (Black, 1994 [D]; Klein, 2001 [A]; Manning, 1995 [D]; Moreyra, 1995 [M]; Weigner, 2001 [D]).

The ACUTE trial (2001) compared transesophageal echocardiography-directed anticoagulation plus early cardioversion versus three weeks of warfarin prior to cardioversion. Both groups received warfarin for four weeks after cardioversion. Transesophageal echocardiography enabled patients to receive earlier cardioversion (3 days versus 31 days). Despite earlier cardioversion, the transesophageal echocardiography group had a similar frequency of successful cardioversion (80% versus 80%) and similar frequency of sinus rhythm at eight weeks (transesophageal echocardiography 53% versus conventional 50%). Transesophageal echocardiography did not reduce embolic complications (transesophageal echocardiography 0.8% versus conventional 0.5% – p value 0.50). Despite reduction of hemorrhagic complications (transesophageal echocardiography 2.9% versus conventional 5.5% – p value 0.03), there was a trend toward an increased risk of death in transesophageal echocardiography patients (2.4% versus 1.0% – p value 0.06). Therefore, at this time there is insufficient evidence to recommend the routine use of transesophageal echocardiography to guide anticoagulant therapy prior to cardioversion.

In case series of transesophageal echocardiography-guided anticoagulation, most patients were treated with heparin and warfarin, though a few patients received no or inadequate anticoagulation. Patients who received no or inadequate anticoagulation appeared to have a high risk of thromboembolic complications despite a negative transesophageal echocardiography. There are no trials of transesophageal echocardiography without anticoagulation completed or in progress. Therefore, all patients require four weeks of anticoagulation with warfarin (international normalized ratio greater than or equal to 2.0) following cardioversion.

There is little experience reported on the use of low-molecular-weight heparins prior to or following cardioversion (with or without transesophageal echocardiography). A pilot study of transesophageal echocardiography-guided enoxaparin plus warfarin versus transesophageal echocardiography-guided unfractionated heparin plus warfarin (ACUTE II) is in progress. Unfortunately, this trial does not include a conventional therapy group, which is a significant omission in light of the ACUTE trial results.

For additional information on anticoagulation with warfarin, please refer to the ICSI Antithrombotic Therapy Guideline Supplement.

Algorithm Annotations

As atrial fibrillation persists for longer periods of time, the efficacy of pharmacologic cardioversion decreases. Though direct current cardioversion requires conscious sedation, pharmacologic cardioversion is less effective and may cause serious arrhythmias, including torsades de pointes. Antiarrhythmics like ibutilide or propafenone may be administered prior to direct current cardioversion to increase the likelihood of its success (*Oral, 1999 [A]; Bianconi, 1989 [D]*).

Table 2. Comparison of Electrical and Chemical Cardioversion

	DC Cardioversion*	Chemical Cardioversion*
Success Rate	Greater than 90%	40% or more
Sedation, Anesthesia, Backup	Yes	No
Nothing by Mouth	Yes (except when hemodynamically unstable)	No
Contraindications		<ul style="list-style-type: none"> - Hemodynamic instability - Acute coronary ischemia - Marked bradycardia, digoxin toxicity - QTc 460 millisecon or more - Marked LV hypertrophy - Marked LV failure - Hypokalemia - Hypomagnesemia - Currently on an antiarrhythmic
Relative Contraindications	<ul style="list-style-type: none"> - Fresh chest wound - Fear of DC cardioversion 	<ul style="list-style-type: none"> - Duration greater than one month
Complications	<ul style="list-style-type: none"> - Rare respiratory suppression - Pulmonary edema 	<ul style="list-style-type: none"> - Torsades de pointes (TDP) 3%-5% - Hypotension
Comments	Consider adding an antiarrhythmic if: <ul style="list-style-type: none"> - initial DC cardioversion is unsuccessful - high likelihood of recurrence of atrial fibrillation after cardioversion 	

* Some institutions administer a single bolus of 5,000 units of unfractionated heparin prior to chemical and/or direct current cardioversion to patients who have no risk factors for bleeding.

See Annotation #20, Tables 12 and 13 comparing and contrasting antiarrhythmic medications.

Direct Current Cardioversion

Direct current cardioversion has been used to treat a variety of rhythm disturbances including atrial fibrillation and atrial flutter since the early 1960s (*Castellanos, 1965 [R]; Resnekov, 1967 [D]*). The success of external direct current cardioversion depends on patient selection and cardioversion technique. Success rates range from 65% to 95%. Success of cardioversion is increased if the left atrium is less than 60 mm (3 cm² body surface area) and if the arrhythmia is of short duration.

Transthoracic cardioversion of atrial fibrillation may now be performed with biphasic waveform defibrillation. It typically requires less energy and may have greater efficacy than monophasic wave forms (*Mittal, 2000 [A]*).

A recent study has shown that an anterior-posterior paddle position is superior to an anterior-lateral position in success of cardioversion. The anterior-posterior position also required lower energy levels for success (*Botto, 1999 [A]; Kirchhof, 2002 [A]*). If the first position is unsuccessful, paddle relocation should be considered.

Complications of direct current cardioversion are uncommon but include embolization, pulmonary edema, and arrhythmias including ventricular fibrillation and asystole (*Morris, 1966 [D]; Weigner, 1997 [D]; Yigitbasi, 1967 [D]*). Direct current cardioversion should be avoided in patients with known or suspected digoxin toxicity. It is unnecessary to interrupt digoxin therapy for cardioversion in patients without manifestations of toxicity.

Table 3. DC Cardioversion Technique

DC Cardioversion Technique:

- The patient should refrain from eating or drinking for six to eight hours prior to the procedure to avoid aspiration during conscious sedation/general anesthesia.
- Unless hemodynamically unstable, patients should be given conscious sedation or anesthesia.
- Some institutions administer a single bolus of 5,000 units of unfractionated heparin prior to chemical and/or direct current cardioversion to patients who have no risk factors for bleeding.
- The defibrillator is set to synchronous mode. Biphasic defibrillators are equally effective at lower levels of energy than monophasic defibrillators.
- Electrodes should be separated widely.
- Use a gel, cream or other coupling agent. Care should be taken to avoid smearing the couplant on the skin between electrodes, which may result in a low impedance pathway along the chest wall, causing useless shunting of current away from the heart with possible failure to achieve cardioversion. Handheld or self-adhesive electrode pads may be used.
- Use firm paddle-to-chest contact pressure.
- An anterior-posterior paddle position is superior to an anterior-lateral position in success of cardioversion. If the first position is unsuccessful, paddle relocation should be considered.
- Avoid on-breast electrode placement in women.

Antiarrhythmic/Chemical Cardioversion (*Fuster, 2006 [R]*)

All antiarrhythmics used to treat atrial fibrillation/atrial flutter can cause serious complications including the life-threatening arrhythmia torsades de pointes in up to 8% of patients (*Falk, 1992 [R]*). Therefore, antiarrhythmics should be initiated in the presence of a physician or nurse with expertise in the administration of antiarrhythmics with telemetry monitoring for at least four hours, or longer if QT remains prolonged.

Risk factors for proarrhythmia include:

- preexisting bradycardia or atrioventricular block,
- underlying structural heart disease,
- active heart failure or ischemia – hypokalemia or hypomagnesemia, and
- drug dosages (e.g., lower doses for quinidine and higher doses for sotalol).

Pharmacologic therapy aimed at restoring sinus rhythm is often helpful in patients with atrial fibrillation. As a general rule, regardless of the agent or route used, the conversion rate of atrial fibrillation of less than 48 hours duration is 60%-90%. Conversion rates drop to 15%-30% if present 48 hours or longer (*Jung, 1998 [R]*). Successful conversion of atrial flutter is generally higher than for atrial fibrillation. Published literature addressing the issue is limited. Many studies report small numbers of patients and the results, although often statistically significant, may be of little clinical relevance. Many investigations involve comparisons between antiarrhythmic agents and do not include a control group. Trials in conversion of acute atrial fibrillation involving a control group typically show rates of spontaneous cardioversion of up to 50%. Thus, the absence of a control group in any study on this subject is a considerable drawback. Head-to-head comparisons of antiarrhythmic agents for atrial fibrillation conversion are difficult to interpret due to the reasons given above, as well as difference in dosing algorithms, patient population studied, and varying duration of atrial fibrillation (the single most important determinant for successful conversion).

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A summary of the agents with proven efficacy for pharmacologic cardioversion of atrial fibrillation of up to seven days duration or atrial fibrillation present for more than seven days is described in Tables 4 and 5, below.

Table 4. Pharmacological Cardioversion Up to Seven Days

Recommendations for Pharmacological Cardioversion of Atrial Fibrillation of Up to Seven Days	
Agents with proven efficacy	Dofetilide, flecainide, ibutilide, propafenone and amiodarone
Less effective or incompletely studied patients	Disopyramide, flecainide, procainamide, propafenone and quinidine
Agents should not be administered	Digoxin and sotalol

Adapted from the ACC/AHA Atrial Fibrillation 2006 guideline (pages e299 and e300)

Table 5. Pharmacological Cardioversion for More Than Seven Days

Recommendations for Pharmacological Cardioversion of Atrial Fibrillation Present for More Than Seven Days	
Agents with proven efficacy	Dofetilide, amiodarone, ibutilide
Less effective or incompletely studied patients	Disopyramide, flecainide, procainamide, propafenone and quinidine
Agents should not be administered	Digoxin and sotalol

Adapted from the ACC/AHA Atrial Fibrillation 2006 guideline (pages e299 and e300)

Reported success rates vary in part because of the heterogeneity of patient populations – particularly with respect to the duration of atrial fibrillation in the published trials. Of the intravenous agents, only ibutilide is approved by the Food and Drug Administration for this indication.

*Torsades de pointes is a potentially life-threatening arrhythmia and requires prompt evaluation and treatment. See Table 7 for treatment of torsades de points.

Please refer to Annotation #20, Table 13, "Antiarrhythmic Agents," for more information on antiarrhythmic agents.

Ibutilide has been studied extensively for the conversion of recent onset atrial fibrillation and atrial flutter. Efficacy rates between 30% and 40% have been quoted in acute reversal of recent onset atrial fibrillation. Generally patients convert within 30 minutes. Significant adverse effect of torsades de points was noted in 4.3% of patients, 1.7% requiring electrical termination. There were no deaths or severe morbidities (*Ellenbogen, 1996 [A]; Howard, 1999 [R]; Stambler, 1996 [A]*).

Table 6. Use of Ibutilide

<p>Guidelines</p> <ul style="list-style-type: none"> • Patient requires close monitoring by Advanced Cardiac Life Support trained staff with equipment capabilities to treat life-threatening ventricular tachyarrhythmias or bradyarrhythmias • Avoid use if baseline QTc greater than 450 millisecon. • Use with caution with drugs that cause QTc prolongation (refer to Table 12 in Annotation #20 for more information on QTc prolongation drugs) • Correct K⁺ to greater than 4.0 meq/L • Correct Mg⁺⁺ to greater than 1.8 meq/L <p>Ibutilide Dosing</p> <p>If patient weighs less than 60 kg, administer 0.01 mg/kg over 10 minutes</p> <p>If patient weighs 60 kg or more, administer 1 mg over 10 minutes</p> <ul style="list-style-type: none"> • Observe for 10 minutes • If still in atrial fibrillation/atrial flutter, repeat same weight- appropriate dose • Risk of torsades de pointes increases with second dose • If still in atrial fibrillation/atrial flutter, DO NOT give third dose

Proarrhythmia associated with initiation of membrane antiarrhythmic agents relates to the presence of underlying structural heart disease, as well as the type of drug initiated. The drugs sotalol, dofetilide and quinidine should be initiated in all patients under telemetry guidance. These drugs should not be allowed to prolong QTc (similar to sotalol and dofetilide) to longer than 500 millisecon. The QTc prolongation maybe associated with torsades de pointes. Refer to Table 7, below, for treatment of torsades de pointes.

Amiodarone, the other Class III drug, is the subject of several articles regarding its efficacy in conversion of recent onset and permanent atrial fibrillation. Amiodarone is effective in converting atrial fibrillation both acutely and chronically. It has been studied by both the oral and intravenous routes. Amiodarone can be started at maintenance doses in the outpatient setting; when high-dose loading is required, or the drug is initiated in patients with structural heart disease, hospitalization should be advised. The Class I-C drugs propafenone and flecainide can also be initiated in the outpatient setting with appropriate follow-up of QRS duration that should not lengthen more than 25%. For patients with structural heart disease, these agents should also be initiated in the inpatient setting (*Kerin, 1996 [A]; Kochiadakis, 1999 [A]*).

In a study from the European Heart Journal comparing high-dose intravenous amiodarone and placebo, amiodarone was effective in converting 92% of patients and 85% of those who did not convert with placebo. Placebo was effective in 64% of patients within 24 hours (*Cotter, 1999 [A]*). In comparing amiodarone and propafenone, both were effective in converting recent onset atrial fibrillation of less than two weeks duration. Both groups achieved approximately 60% conversion rates, though propafenone had an earlier onset of action.

More recently, the Canadian Trial of Atrial Fibrillation Investigators group reported the superiority of amiodarone for prevention of atrial fibrillation as compared to either sotalol or propafenone in a study cohort of 403 patients. Sinus rhythm maintenance at one-year follow-up was noted in 69% of amiodarone patients as compared to 39% of the sotalol/propafenone groups (p < 0.001) (*Roy, 2000 [A]*).

Oral flecainide (300 mg single dose) has similar conversion rates compared to oral propafenone (600 mg single dose) when used in patients with atrial fibrillation of acute onset (approximately 72%-78% conversion rate at eight hours) (*Capucci, 1994a [A]*).

Table 7: Treatment of Torsades de Points

Treatment of torsades de pointes includes:

- Discontinue drugs that cause QTc prolongation (refer to Annotation #20, Table 13, for QTc prolongation drugs)
- Correct electrolytes (e.g., magnesium, potassium)
- Magnesium 1-2 grams (diluted in 10 mL D5W) intravenous push
- Overdrive pacing or isoproterenol 2-10 mcg per minute infusion
- Lidocaine 1-1.5 mg/kg intravenous push

Failed Cardioversion Treatment Options

If initial attempts to restore normal sinus rhythm for atrial fibrillation fail, cardioversion can be repeated following a parenteral or oral loading dose of an appropriate antiarrhythmic agent (*Capucci, 2000 [A]*; *Fuster, 2006 [R]*). However, this approach should be avoided in patients with ejection fractions less than 30% because of the increased risk of torsades de pointes.

Furthermore, it should be noted that this is not a strategy to maintain normal sinus rhythm but only a means to enhance conversion back to sinus rhythm. Appropriate anticoagulation practices are required prior to and following cardioversion if the duration of atrial fibrillation exceeds 48 hours. If atrial fibrillation continues despite these attempts, cardiology consultation is advised.

The patient and/or physician may also opt for chronic anticoagulation and chronic rate control at this point – though the general consensus is that most patients with a first episode of atrial fibrillation or atrial flutter have a high likelihood of successful conversion back to normal sinus rhythm.

Transthoracic cardioversion of atrial fibrillation may be achieved by applying biphasic waveform for defibrillation. It has been shown to be equally effective and uses less energy than monophasic waveforms.

In a randomized study, Oral, et al. (1999) found that cardioversion without ibutilide pretreatment resulted in sinus rhythm in 36 out of 50 patients (72%) and in all 50 patients who received ibutilide pretreatment. Pretreatment with ibutilide reduced the mean energy required for defibrillation from 228 ± 93 J to 166 ± 80 J (*Oral, 1999 [A]*).

A randomized trial published in 2000 compared cardioversion using a sine wave monophasic waveform with rectilinear biphasic waveform. In the 77 patients treated with sine wave monophasic waveform, the success rate was 79%, whereas of 88 patients cardioverted with biphasic waveform, 94% achieved sinus rhythm (p=0.005). Less energy was required using biphasic waveform (*Mittal, 2000 [A]*).

Maintenance of Sinus Rhythm Following Conversion

Several antiarrhythmic drugs have been demonstrated to improve sinus rhythm maintenance following cardioversion, including amiodarone, propafenone, disopyramide, sotalol, flecainide, dofetilide and quinidine (*McNamara, 2003 [M]*).

It is essential to establish adequate rate control before administering antiarrhythmics. Class 1A drugs can accelerate ventricular rates via anticholinergic effects on the atrioventricular node. Class 1C drugs can also accelerate ventricular rates by organizing and slowing atrial activity allowing 1:1 conduction. Additional drugs to slow atrioventricular nodal conduction are recommended when using Class 1C drugs. Amiodarone has been shown to be the single most effective agent of the lot, although it also contributes the most to non-cardiac drug-related toxicity (*Roy, 2000 [A]*). When administered at 800 mg per day for two weeks prior to elective cardioversion, amiodarone chemically converts one-fifth of patients with persistent atrial fibril-

lation, and when continued for eight weeks at 200 mg per day, doubled the number of patients in normal sinus rhythm at that time (*Channer, 2004 [A]*).

Non-Antiarrhythmic Medical Therapies for Maintenance of Sinus Rhythm

Both the ACE inhibitor, enalapril, and angiotensin receptor blocker, irbesartan, have been demonstrated to enhance the maintenance of normal sinus rhythm after cardioversion when added to amiodarone (*Ueng, 2003 [A]*; *Madrid, 2002 [A]*). A meta-analysis of studies using this class of compounds has added further credence to these initial observations (*Healey, 2005 [M]*).

There has been a demonstrated correlation between stroke risk and inflammatory marker (CRP) elevation in patients with non-valvular atrial fibrillation (*Lip, 2007 [B]*). Retrospective and prospective studies of lipid lowering with statin therapies (*Hanna, 2006 [D]*; *Ozaydin, 2006 [A]*; *Patti, 2006 [A]*) have demonstrated beneficial effects for the prevention of atrial fibrillation, both postcoronary artery bypass graft and de novo. Fish oil also has been demonstrated in small randomized control trials to have a significant beneficial effect (*Savelieva, 2008 [R]*).

Intravenous hydrocortisone has been revealed to have an antiarrhythmic effect for post-cardiac surgery (*Halonen, 2007 [A]*), while dexamethasone demonstrated no such effect (*Yared, 2007 [A]*).

Further study of all these adjunctive medications will be required to assess their appropriate roles, post-coronary artery bypass graft, postdirect current cardioversion, postablation, and as primary prevention tools.

14. Assess Patient for Chronic Anticoagulation

Key Points:

- All patients with paroxysmal, persistent or permanent atrial fibrillation should be assessed for chronic anticoagulation – balancing the long-term risk of thromboembolism against the long-term risk of bleeding.

Indications for Chronic Use of Anticoagulants in Atrial Fibrillation Patients

Patients with either paroxysmal or persistent atrial fibrillation may benefit from anticoagulation. The long-term risk of thromboembolic complications must be balanced against the long-term risk of bleeding.

Two decades ago, the natural history of lone atrial fibrillation (3% of atrial fibrillation patients in the Olmsted County study of 1987) was assessed in a geographically defined population of patients, and the risk of stroke was found to be exceedingly low (but not zero); an entire cohort of patients presenting with atrial fibrillation in such a population does not exist. These patients should be considered for aspirin therapy.

Beginning in the late 1980s, through the recent past, multiple randomized clinical trials of warfarin therapy versus aspirin versus placebo in patients with non-rheumatic atrial fibrillation have been completed. A recent meta-analysis of 29 of these trials was reported (*Hart, 2007 [M]*). The studies were conducted from 1989 to 2007, mostly in Europe (16), North America (7) and Asia (3). The trials included 28,044 patients with 42,450 patient-years of follow-up. The mean age of patients was 71 years, with a 2:1 ratio of men to women. The relative risk reduction favoring warfarin over control was 64% (CI = 49-74%). The relative risk reduction favoring warfarin over antiplatelet agents was 39% (CI = 22-52%). Antiplatelet therapy alone had a modest, yet significant, effect as well, compared to control – RRR = 22% (CI = 6-35%). The risk of intracranial bleeding utilizing warfarin compared to aspirin was twofold.

Risk factors from many of these trials were identified that maximized the benefits of vitamin K antagonist therapy. These have been summarized in a scoring system that accurately reflects the relative risks of thromboembolic stroke when following atrial fibrillation patients. This has been termed the CHADS2 score and is calculated as in Table 8.

Table 8. Chads2 Score

CHADS2 SCORE			
			Points
Congestive heart failure (any history)			1
Hypertension (any history)			1
Age ≥ 75			1
Diabetes mellitus			1
Secondary prevention (history of CVA, TIA, systemic emboli)			2
CHADS2 Score	Strokes / Year		Thromboembolic Prophylaxis
	No Warfarin	Warfarin	
0	0.49	0.25	Aspirin
1	1.52	0.72	Aspirin or warfarin
2	2.50	1.27	Aspirin or warfarin
3	5.27	2.20	Warfarin
4	6.02	2.35	Warfarin
5, 6	6.88	4.60	Warfarin

Patients with chronic atrial fibrillation (and perhaps most or all patients with paroxysmal atrial fibrillation) should be given warfarin or aspirin based on their CHADS2 score – unless the long-term risk of bleeding from warfarin or aspirin exceeds the long-term risk of thromboemboli. Trials evaluating the efficacy of warfarin in patients with non-valvular atrial fibrillation excluded 80% of patients on the basis of factors presumed to increase their risk of bleeding (*Sebastian, 2000 [R]*).

Recommendation from the 2006 consensus paper for warfarin versus aspirin therapy in patients with atrial fibrillation are shown in Table 8. These recommendations translate to warfarin therapy for patients with CHADS2 scores of two or more, while aspirin is a reasonable alternative in CHADS 2 = 0 patients. For those with a score of one, either approach is reasonable.

In patients who are at moderate risk for bleeding, current trends favor use of anticoagulation in light of the defined benefits for anticoagulation and poorly defined criteria for bleeding risk (*Man-Son-Hing, 2003*).

For detailed discussion of assessing risk factors for bleeding, please refer to the ICSI Antithrombotic Therapy Guideline Supplement.

Table 9. Exclusion Criteria Used in Trials Evaluating the Efficacy and Safety of Warfarin in Patients with Non-Valvular Atrial Fibrillation

Exclusion Criteria Used in Trials Evaluating the Efficacy and Safety of Warfarin in Patients with Non-Valvular Atrial Fibrillation
Active bleeding Active peptic ulcer disease Known coagulation defects Thrombocytopenia (platelet less than 50,000) or platelet dysfunction Recent hemorrhagic stroke Non-compliant or unreliable patient Psychologically or socially unsuitable patient Dementia or severe cognitive impairment History of falls (three within the previous year or recurrent, injurious falls) Excessive alcohol intake Uncontrolled hypertension (greater than 180/100) Daily use of NSAID Planned invasive procedure or major surgery

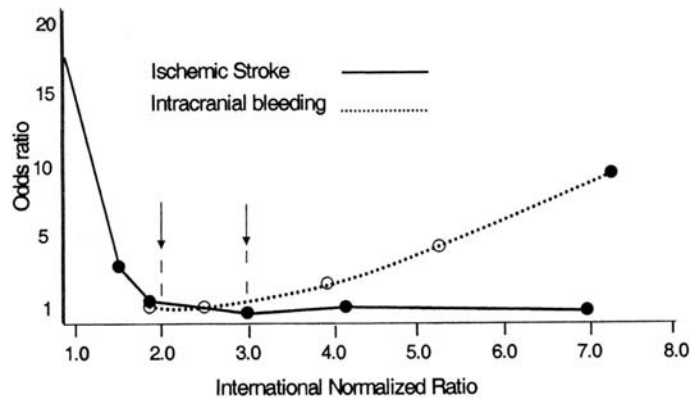
The following factors should be taken into consideration for all patients receiving warfarin long term.

Table 10. Risk Factors for Bleeding for Long-Term Use of Warfarin

Risk Factors for Bleeding for Long-Term Use of Warfarin
History of significant bleeding Known coagulation defects Thrombocytopenia (platelet less than 50,000) or platelet dysfunction Recent hemorrhagic stroke Uncontrolled hypertension (greater than 180/100) Daily use of any platelet inhibitor, including: aspirin clopidogrel NSAIDs herbal supplements Excessive alcohol intake Recurrent falls Inconsistent compliance Erratic INRs

It is critical that the international normalized ratio be regularly determined to enhance effectiveness of anti-coagulation and avoid bleeding given the narrow therapeutic index of warfarin. See Figure 1.

Figure 1.



Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation in randomized trials of antithrombotic therapy for patients with atrial fibrillation.

(Stöllerger, 1998 [C]; Stroke Prevention and Atrial Fibrillation Investigators Committee on Echocardiography, The, 1998 [C])

Please refer to the ICSI Antithrombotic Therapy Guideline Supplement for a more complete discussion of the use of aspirin and warfarin.

Antiplatelet/Anticoagulant Management for Patients with Paroxysmal or Persistent Atrial Fibrillation Who Require Percutaneous Coronary Intervention

A rapidly emerging area of uncertainty is the optimal management of patients with paroxysmal or persistent atrial fibrillation who require percutaneous coronary intervention. For patients undergoing percutaneous coronary intervention, research has shown less restenosis with drug-eluting stents compared with uncoated stents. Unfortunately, recent experience has identified a prolonged risk of coronary thrombosis following implantation of drug-eluting stents. Warfarin alone does not reduce the risk of coronary thrombosis associated with stents. Aspirin and/or clopidogrel reduce the risk of thromboembolic complications associated with atrial fibrillation but are inferior to warfarin. The combination of aspirin and clopidogrel and warfarin causes more hemorrhagic complications than any one of these drugs alone (Healey, 2008 [A]; Hermosillo, 2008 [M]).

Areas requiring further research

Research is urgently needed to identify the optimum choice of stents, the optimum combination of antiplatelet/anticoagulant therapy, and the optimum duration of combination therapy. Until data is available, the choice of stent, choice of antiplatelet/anticoagulation drugs, and duration of combination therapy should be determined by a cardiologist.

15. Assess Patient for Rate Control Agents

Key Point:

- Drugs that can be used for rate control of chronic atrial fibrillation include beta-blockers, non-dihydropyridine calcium channel blockers and digitalis.

The goals of therapy in the management of atrial fibrillation include relief of symptoms, prevention of stroke, and prevention of tachycardia-mediated cardiomyopathy. Recently published studies (AFFIRM/RACE) examined outcomes in patients randomized to a rate control strategy versus a strategy of restoration and

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attempted maintenance of sinus rhythm using antiarrhythmic drugs and cardioversion. Strategies aimed at maintaining sinus rhythm offered no significant advantages over rate control strategies, but were associated with a higher incidence of hospitalization and adverse drug effects. The important role of warfarin anticoagulation for prevention of stroke are well established and again demonstrated in these trials. Early discontinuation of anticoagulation and subtherapeutic anticoagulation were factors associated with thromboembolic events. These trials indicate that a rate control strategy is acceptable, particularly in older patients who are asymptomatic or minimally symptomatic.

Beta-blockers are generally favored for pharmacologic rate control. Beta-blockers control heart rate at rest and with exercise and also provide cardioprotective benefits. They may be used with caution with asthma or chronic obstructive pulmonary disease. Beta-blockers are preferred for patients with atrial fibrillation and heart failure.

Calcium channel blockers are alternative rate control agents when beta-blockers are contraindicated. Calcium channel blockers control heart rate at rest and with exercise but may exacerbate systolic heart failure. Calcium channel blockers should not be administered in the presence of wide QRS/Wolff-Parkinson-White/pre-excitation.

Concomitant use of a beta-blocker with a calcium channel blocker can, in rare circumstances, cause profound negative dromotropic, chronotropic and inotropic effects. These effects may be further exacerbated by type I or type III antiarrhythmic agents or underlying structural heart disease.

Digoxin is a third-line agent for rate control. Digoxin can be utilized for patients with significant systolic congestive heart failure, but is inferior for exercise rate control compared to the other agents (*Farshi, 1999 [A]*). Digoxin does not lower blood pressure and has a positive inotropic effect, but works more slowly than beta-blockers and calcium channel blockers, has no effect on the sympathetically mediated enhancement of atrioventricular node conduction during exercise, and is no better than placebo for conversion to normal sinus rhythm. Digoxin should not be administered with wide QRS/Wolff-Parkinson-White/pre-excitation, hypokalemia, hypomagnesemia and renal impairment.

Table 11: Medications Used for Rate Control

All antiarrhythmics used to convert atrial fibrillation/atrial flutter to sinus rhythm can cause serious complications, including torsades de points, and require the presence of a physician or nurse with expertise in the administration of rate control agents and treatment of their complications for at least four hours and until the QTc interval returns to normal.

Medication	Considerations
<p>Beta-Blockers</p> <ul style="list-style-type: none"> • esmolol • metoprolol • propranolol 	<p>Place in Therapy: Often the initial choice for rate control. Preferred in patients with atrial fibrillation and systolic heart failure.</p> <p>Precautions: Bradycardia, diabetes, lung disease, heart failure, hypotension, severe peripheral vascular disease.</p> <p>Beta-blockers should not be discontinued abruptly.</p> <p>Adverse Reactions: Bradycardia, bronchospasm, cold extremities, depression, fatigue, heart block, hypotension, precipitation of heart failure.</p> <p>Drug Interactions: Calcium channel blockers and digoxin may have additive effects.</p> <p><i>CYP450 Interactions</i> Metoprolol is a 2D6 substrate. Propranolol is a 2D6 & 2C19 substrate.</p>
<p>Non-dihydropyridine Calcium Channel Blockers</p> <ul style="list-style-type: none"> • diltiazem • verapamil 	<p>Place in Therapy: Second-line therapy when beta-blockers are contraindicated. May be preferred for long-term use in patients with reactive airway disease.</p> <p>Precautions: Bradycardia, heart failure, hypotension, patients with Wolff-Parkinson-White syndrome (WPW).</p> <p>Use cautiously or avoid use in patients with heart failure due to systolic dysfunction due to negative inotropic effects.</p> <p>Calcium channel blockers should not be discontinued abruptly.</p> <p>Adverse Reactions: Bradycardia, constipation (verapamil), heart block, hypotension, precipitation of heart failure.</p> <p>Drug Interactions: Beta-blockers and digoxin may have additive effects.</p> <p><i>CYP450 Interactions</i> Diltiazem is a 3A4 substrate and inhibitor. Verapamil is a 3A4 substrate and inhibitor.</p> <p><i>P-glycoprotein Interactions</i> Diltiazem and verapamil are inhibitors of P-glycoprotein and can affect drugs that are metabolized by P-glycoprotein.</p>

Medication	Considerations
Digoxin	<p>Place in Therapy: Third-line agent. Often used in patients with concomitant atrial fibrillation and systolic heart failure. Digoxin does not slow heart rate during activity.</p> <p>Precautions: Bradycardia, hypokalemia, hypomagnesemia, patients with WPW, renal impairment.</p> <p>Adverse Reactions: Anorexia, AV junctional tachycardia, bradycardia, diarrhea, dizziness, headache, heart block, nausea, visual disturbances (blurred vision yellow/green halos), ventricular arrhythmias, vomiting, weakness.</p> <p>Drug Interactions: Beta-blockers and calcium channel blockers may have additive effects.</p> <p><i>P-glycoprotein Interactions</i> Digoxin is metabolized by P-glycoprotein. Drugs that inhibit (e.g., diltiazem, erythromycin, verapamil) or induce (e.g., rifampin) P-glycoprotein can affect digoxin levels.</p> <p>Therapeutic Levels: Heart failure: 0.5-0.8 ng/mL Arrhythmias: 0.8-2 ng/mL</p>

Compiled using the following references:

Lexi-Comp's Drug Information Handbook, 17th edition 2008-2009, pages 143-157. Charles Lacy RPh, MS, PharmD, FCSHP.

The Top 100 Drug Interactions: A Guide to Patient Management 2008 Edition, pages 460-461. Philip Hansten PharmD and John Horn PharmD.

Antiarrhythmic Agents

See Annotation #20, "Consultation with a Physician with Cardiology Expertise for Treatment Options," under Antiarrhythmics and Table 13 concerning antiarrhythmic drug choices.

16. Age ≤ 65?

See Annotation #18, "Inadequate Symptom Control?"

17. Inadequate Rate Control?

Key Point:

- Adequate atrial fibrillation rate control should be assessed both at rest and exercise to eliminate symptoms and prevent the development of heart failure from tachycardia-induced cardiomyopathy.

Adequate rate control may help relieve symptoms including palpitations, chest pain, dyspnea, fatigue or lightheadedness. Also, tachycardia-induced cardiomyopathy is an important reversible complication of inadequate rate control. Tachycardia-induced cardiomyopathy can produce symptomatic congestive heart failure, thromboembolic complications, and potentially fatal ventricular arrhythmias. Thus, it is essential to maintain adequate rate control both at rest and during exercise. Patients with an acute myocardial infarction or acute coronary symptoms may require lower ventricular rates to decrease myocardial oxygen demand and limit infarction size.

At rest, the heart rate should be similar to individuals in sinus rhythm (less than 80-90 beats per minute). During exercise, the maximum rate should be no greater than the maximum set for individuals in sinus rhythm [$0.7 \times (220 - \text{age})$] and should not be reached during light exercise. A six-minute office walk, exercise stress test or Holter monitor (24-hour average less than 100 beats per minute) can assess this (*Fuster, 2006 [R]*).

If ventricular response remains rapid despite attempts to control rate with beta-blockers, calcium channel blockers and/or digoxin, consultation from a physician with cardiology expertise is recommended. When pharmacologic therapies fail, radiofrequency ablation of the atrioventricular node/His bundle followed by placement of a permanent pacemaker may be considered in medically refractory patients. It should be emphasized that the latter approach is irreversible and the patients may become pacemaker dependent. Right ventricular pacing may also induce dyssynchrony leading to future risk for developing heart failure although this problem occurs infrequently. For further information, refer to Annotation #20, "Consultation with a Physician with Cardiology Expertise for Treatment Options."

18. Inadequate Symptom Control?

Key Point:

- For the older patient over 65 years of age, rate control is an equal strategy to rhythm control for long-term management of atrial fibrillation.

Patients presenting with paroxysmal or persistent atrial fibrillation should be assessed for symptoms and for underlying cardiac disease. Restoration of sinus rhythm with cardioversion and/or suppression of atrial fibrillation with antiarrhythmic drugs is a reasonable initial strategy, particularly in younger patients. Patients should be reassessed for symptoms, side effects of treatment and recurrence of atrial fibrillation with potential reconsideration of rate control strategy if appropriate. Patient with significant symptoms associated with atrial fibrillation may warrant repeated trials with antiarrhythmic drugs, possibly in combination with permanent pacing. Ablative therapies for symptomatic atrial fibrillation refractory to pharmacological management are emerging and promising.

(Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Investigators, The, 2002 [A]; Hohnloser, 2000 [A]; Institute for Clinical Systems Improvement, 2003 [R]; Matsuda, 1991 [A]; Van Gelder, 2002 [A])

There is no observed survival advantage to strategies aimed at restoring sinus rhythm over strategies to control rate in older patients with relatively asymptomatic atrial fibrillation based on the limited data available from studies that have compared these strategies. [*Conclusion Grade II: See Conclusion Grading Worksheet B – Annotation #15 (Rhythm versus Rate Control)*] (*Institute for Clinical Systems Improvement, 2003 [R]*).

19. Other Concerns?

Despite adequate rate and symptom control, a minority of patients may express personal preference in a strategy of rhythm maintenance, and thus merit referral. Additionally, risk profiles for certain patients in regards to long-term anticoagulation may also suggest referral for alternative, emerging non-pharmacologic approaches to this problem.

20. Consultation with a Physician with Cardiology Expertise for Treatment Options

Key Points:

- Patients with recurrent atrial fibrillation should be reassessed for symptoms during atrial fibrillation, side effects to treatment and review of past therapeutic results to plan future therapy.
- Antiarrhythmic agents used for atrial fibrillation suppression are chosen based on risk of proarrhythmia related to underlying heart disease and potential side effects. Drugs should be used in adequate doses with the reduction of the frequency and severity of symptomatic atrial fibrillation episodes as the primary treatment goal.
- Cardiac pacing may allow the use of antiarrhythmic drugs that are contraindicated due to bradycardia and also may provide definitive rate control when coupled with His ablation in patients with poorly controlled ventricular response.
- Isthmus-dependent atrial flutter can be readily controlled with radiofrequency ablation.
- Catheter-based and surgically based pulmonary vein isolation procedures show great promise in the suppression of atrial fibrillation, with better outcomes expected as techniques and experience develop.

Intermittent Cardioversion

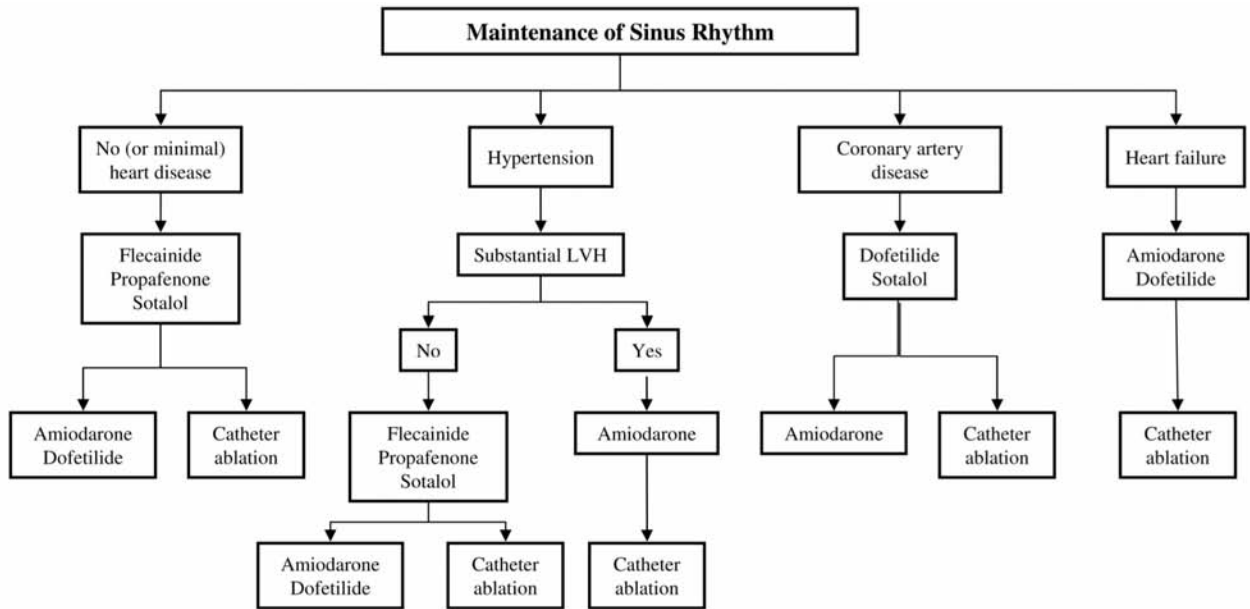
- Intermittent electrical or chemical cardioversion may be considered for:
 - infrequent recurrences,
 - hemodynamic instability (see Annotation #6, "Stabilize Patient"), or
 - failure of an antiarrhythmic agent.
- Evaluate for potentially reversible causes.
- Assess for chronic anticoagulation.
- Future treatment option: implantable atrial defibrillator.

Recurrences can be symptomatic or asymptomatic. In the Medtronic Jewel 7,250 study of the internal atrial defibrillator, 80% of recurrences were asymptomatic and could last greater than 12 hours, casting some doubt as to whether patients who otherwise are candidates for warfarin therapy should ever be removed from that agent once paroxysmal atrial fibrillation has been repeatedly identified.

Antiarrhythmics

Antiarrhythmic agents should be individualized for the patient's anticipated proarrhythmia risks, based on underlying cardiac conditions and other comorbidities while attempting to minimize organ toxicity. Optimal antiarrhythmic drug therapy should be effective in reducing symptoms, preventing recurrent atrial fibrillation and should have low incidence of toxicity and proarrhythmia. Refer to Figure 2, below, for specifics. For patients with antiarrhythmic drug therapy, monitoring for side effects such as proarrhythmia, bradycardia or other systemic side effects is essential.

Figure 2: Antiarrhythmic Drug Therapy to Maintain Sinus Rhythm



Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Within each box, drugs are listed alphabetically and not in order of suggested use. The vertical flow indicates order of preference under each condition. The seriousness of heart disease proceeds from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. LVH indicates left ventricular hypertrophy.

(Fuster, 2006 [R])

The following may guide in selection of antiarrhythmic agents:

Table 12. Drugs with a Risk of QT Prolongation and/or Torsades de Points.

Therapeutic Class of Drugs	Drugs That Have a Risk of TdP
Anti-anginal	Bepridil
Antiarrhythmic	Amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotalol
Antibiotic/anti-infective	Clarithromycin, erythromycin, pentamidine, sparflaxacin
Anti-cancer	Arsenic trioxide
Anti-psychotic	Chlorpromazine, haloperidol [†] , mesoridazine, pimozide , thioridazine
Sedative	Droperidol
Anti-malarial	Chloroquine, halofantrine
GI stimulant/heartburn	Cisapride
Opiate agonist	Levomethadyl, methadone

Bolded indicates Females > Males: Substantial evidence indicates a greater risk (usually greater than 2-fold of TdP in women

[†]when given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases

For more information, refer to <http://www.torsades.org/index.cfm>

Table 13: Antiarrhythmic Agents

All antiarrhythmics used to convert atrial fibrillation/atrial flutter to sinus rhythm can cause serious complications, including torsades de points, and require the presence of a physician or nurse with expertise in the administration of antiarrhythmics with telemetry monitoring for at least four hours, or longer if QT remains prolonged.

Medication	Usual Adult Dose	Comments
Disopyramide	<p>For maintenance: 400-800 mg daily, maximum 1,600 mg daily Immediate release is usually given 4 times daily SR form is given twice daily.</p>	<p>Precautions include renal impairment (requires dosage adjustment), urinary retention. Rate control is recommended prior to administration. Adverse reactions include negative inotropic effects, anticholinergic effects (dry mouth, blurred vision, urinary retention, constipation), nausea, torsades de pointes, heart failure, glaucoma. Drug interactions include warfarin, erythromycin, clarithromycin.</p>
Flecainide	<p>For Cardioversion: 300-400 mg once daily For Maintenance: 50-150 mg twice daily</p>	<p>Onset: for conversion: within 3-8 hrs. Precautions include avoid in patients with poor LV function, ischemic heart disease and major conduction disturbances. Renal impairment requires dosage adjustment. Rate control is recommended prior to administration. Adverse reactions include negative isotropic effects, dizziness, headache, fatigue, visual disturbances, nausea, dyspnea, tremor, heart failure exacerbation, ventricular tachycardia, enhanced AV node conduction (conversion to atrial flutter). Drug interactions include cimetidine, amiodarone, digoxin, propranolol.</p>
Propafenone	<p>For Conversion: 150-600 mg as a single dose For Maintenance: 150-300 mg 3 times daily</p>	<p>Onset for conversion within 2-48 hours. Precautions include avoid in patients with poor LV function, ischemic heart disease and major conduction disturbances, asthma/bronchospastic disease. Rate control is recommended prior to administration. Adverse reactions include nausea, vomiting, constipation, dizziness, fatigue, headache, blurred vision, positive antinuclear antibodies, bradycardia, heart block, heart failure, exacerbation, ventricular tachycardia, bronchospasm, taste disturbances, conversions to atrial flutter. Drug interactions include digoxin, quinidine, warfarin, cimetidine, theophylline, rifampin, phenobarbital, cyclosporine, ritonavir, grapefruit juice.</p>

Algorithm Annotations

Medication	Usual Adult Dose	Comments
Amiodarone	<p>For Conversion: Several regimens have been used: IV: 1.2g/hour x 24</p> <p>For Maintenance: Several regimens have been used Oral: 600-800 mg daily x 1-4 weeks, then reduced to 100-400 mg daily</p>	<p>Onset is usually relatively slow (more than 24-36 hours).</p> <p>Adverse reactions include pulmonary fibrosis, hepatic dysfunction, hypothyroidism and hyperthyroidism, photosensitivity, skin discoloration, fatigue, nausea, vomiting, constipation, ocular effects.</p> <p>Drug interactions include digoxin, quinidine, procainamide, flecainide, warfarin, phenytoin.</p> <p>Pharmacies are mandated to give patients a “Medication Guideline” with each amiodarone prescription.</p>
Sotalol	<p>Maintenance 80-160 twice daily Renal insufficiency: CrCl 40-60 mL/min change interval to every 24 hrs CrCl < 40 mL/min used contraindicated</p>	<p>Precautions include avoid in patients with poor LV function, renal impairment requires dosage adjustment, asthma (beta-blocking effects).</p> <p>Adverse reactions include torsades de pointes, fatigue, dizziness, worsening congestive heart failure, dyspnea, nausea, vomiting, visual disturbances, bradycardia, heart block, palpitations, bronchospasm, heart failure exacerbation, diarrhea.</p>
Ibutilide	<p>For Conversion: 1 mg IV (or 0.01mg/kg if less than 60 kg) over 10 minutes. May repeat 10 minutes after the end of the initial infusion if needed.</p>	<p>Onset within 30-90 minutes.</p> <p>Precautions include proarrhythmia (torsades de pointes). Requires a monitored setting.</p>
Dofetilide	<p>For Maintenance: 125-500 mcg by mouth twice daily (depending on renal function and QT/QTc measurement)</p>	<p>Precautions include proarrhythmia (torsades de pointes). Requires a hospital setting for three days. Dofetilide is available only to hospitals and prescribers who have received appropriate dosing and treatment initiation education.</p> <p>Adverse reactions include torsades de pointes, headache, dizziness, insomnia, chest pain, nausea, diarrhea, dyspnea.</p> <p>Prescribing information: http://www.tikosyn.com/pdf/full_prescribing_info.pdf</p>

Table 14: Considerations When Antiarrhythmic Drug Therapy Fails

Action Step	Considerations
Reassess patient for any change in underlying medical condition	<p>Make sure no new medical conditions have intervened that could exacerbate the patient's tendency toward A Fib. These include hyperthyroidism, worsening mitral valve disease, uncontrolled hypertension, hypokalemia, fever, anemia, obstructive sleep apnea and heart failure.</p> <p>Also look for ongoing use of known stimulants including appetite suppressants and weight-loss preparations, caffeine, nicotine, amphetamines and cocaine.</p>
If a drug level is available, assess the trough antiarrhythmic level	<p>If the drug level is low, consider patient compliance, variability in drug absorption and patient size. It is common for patients with weight greater than 150 kg to be underdosed.</p> <p>If a drug level is not readily available, search for evidence of an antiarrhythmic drug effect on the ECG via the QRS or QT intervals.</p>
Consider the duration and frequency of recurrent A Fib episodes	<p>If A Fib recurrences are infrequent (less than 1 every 1-3 months) or of short duration (less than 30-60 minutes), or produce no symptoms**, no change in prescription may be necessary. In this situation one might consider having the patient take an extra dose of medication as needed.</p> <p>** Is it certain that the patient can tell all the episodes of paroxysmal AFib when they occur? 10%-30% episodes may be asymptomatic in patients who regularly report symptoms. This has implications when considering long-term prophylaxis with ASA vs. warfarin, and when trying to assess adequacy of rate control for preventing the asymptomatic development of tachycardia-induced cardiomyopathy (TICM). If uncertain, the patient may require further Holter or telephone transmitter monitoring.</p> <p>If A Fib recurrence has been for more than 24-48 hours, refer to the algorithm to determine the need for anticoagulation and/or TEE prior to chemical or electrical cardioversion. (See discussion concerning predictors favoring successful cardioversion/maintenance.)</p>
If antiarrhythmic drug has clearly failed and patient requires further treatment	<p>Change to a different Vaughn-Williams class antiarrhythmic drug. Do not combine antiarrhythmic drugs; using more than 2-3 therapeutic drug trials is low yield. Amiodarone should be considered at some point.</p> <p>Consider patient for focal A Fib ablation (favored for younger patients with paroxysmal A Fib who have normal/near-normal LA sizes, minimal heart disease, 2-3 prior drug failures, repeated salvos of paroxysmal A Fib/paroxysmal atrial tachycardia PAT on Holter or frequent monomorphic APCs).</p> <p>Consider for surgical maze procedure. Favored for younger patients with or without other need for cardiac surgery for patients who wish to avoid implantable devices (permanent pacemaker [PPMs] or implantable cardioverter-defibrillators [ICDs]) .</p> <p>Protocols involving dual-chamber pacing systems, dual-site atrial pacing or primary atrial ICDs.</p> <p>Rate control with drugs, AVN catheter modification, or AVN ablation + PPM; issues concerning ASA or warfarin raised at the same time.</p>

Chart summarizing antiarrhythmic medications are in Annotation #20, Table 13.

Electrophysiology consult

Non-pharmacologic treatment modalities for patients requiring such therapy have expanded in the last decade and include ablation, pacing, implantable defibrillation and surgery.

Cardiac Pacing

Single-site atrial pacing

Pacing the atrium at rates of 70 to 90 beats per minute can help prevent atrial fibrillation in patients with sick sinus syndrome or severe sinus bradycardia. Cardiac pacing also allows use of rate control and antiarrhythmic drugs that could not otherwise be used in patients with tachycardia-bradycardia syndrome. Patients with sick sinus syndrome who receive an atrial or dual chamber pacemaker have a lower incidence of atrial fibrillation than those who receive a single chamber ventricular pacemaker (*Andersen, 1994 [A]; Skanes, 2001 [A]*). Continuous atrial pacing has been shown to reduce the number of days of symptomatic atrial fibrillation (*Carlson, 2003 [A]*).

Dual-site atrial pacing

Dual-site atrial pacing attempts to depolarize enough of the right atrium simultaneously to reduce the substrate needed to maintain atrial fibrillation. Leads are placed in the right atrial appendage and near the coronary sinus os (*Default, 1998 [C]*). Larger randomized trials suggested that the benefits of dual-site pacing were limited.

Implantable atrial defibrillator

The implantable atrial defibrillator recognizes atrial fibrillation and delivers low-energy shocks between electrodes in the right atrium and the right ventricle synchronized with ventricular activity (*Gold, 2001 [D]*). Atrial cardioversion using implanted devices has not gained widespread acceptance due to painful shocks despite low energies, device costs and competitive pharmacologic and ablative strategies.

Atrial Fibrillation Ablative Therapies (Non-Atrioventricular Node)

Surgical and catheter ablative therapies have been employed for eradication of atrial fibrillation. The surgical MAZE-III operation was conceived by Cox and has served as the template and gold standard on which to base efficacy and morbidity of subsequent ablation techniques over the last three decades (*Cox, 1995 [NA]*). One-year freedom from atrial fibrillation rates of 90% has been reported in large series of patients undergoing conventional MAZE-III surgery (*Schaff, 2000 [D]; McCarthy, 2000 [D]*).

Radiofrequency catheter ablation has been utilized the last decade with the four left atrial pulmonary veins serving as the targets for the technique of pulmonary vein isolation (*Hassiguerre, 1998 [D]*). This modality has particularly served well patients who have structurally normal hearts with paroxysmal atrial fibrillation, with efficacy rates in excess of 80%. A recent single-center prospective study demonstrated freedom from atrial fibrillation at one year of approximately 90 versus 60% in a group of 67 PAF patients randomized to pulmonary vein isolation versus conventional antiarrhythmic therapy (*Wazni, 2005 [A]*).

However, additional catheter lesion sets involving lines within the right and left atria, as well as isolation involving other structures (coronary sinus, superior vena cava, Marshall ligament), have been required for more persistent/chronic patients, as well as those with advancing age and structural heart disease to insure comparative efficacies (*Oral, 2006 [A]*). Minimally invasive surgical techniques have also been developed that balance favorably with catheter techniques.

Future technologies to enhance efficacy, safety and efficiency of atrial fibrillation ablation are undergoing active investigation and include novel energy sources (cryoablation, laser, microwave and ultrasound), novel delivery systems (balloon, mesh, endoscopic, molecular and robotic-driven), and novel targets (epicardial autonomic plexuses). Prospective randomized trials of the efficacy and safety of initial treatment strate-

gies with catheter ablation versus medical therapies (CABANA), and atrioventricular nodal ablation versus medical therapies (PACIFIC) are just beginning.

The recently published guidelines by the ACC/AHA/ESC address the role of catheter ablation for the management of atrial fibrillation patients in 2006 and can be summarized in the table below.

Table 15: Atrial Fibrillation Strategy and Ablation Recommendation

A Fib Clinical Strategy	Ablation Recommendation
Pharmacological Rate Control	Ablate AV node or accessory pathway if medications ineffective or with side effects
	Ablate AV node if medication ineffective and tachycardia-mediated cardiomyopathy suspected
	Do not ablate AV node prior to medical trial
Maintenance of Sinus Rhythm	AF catheter ablate is reasonable alternative to medical therapy in symptomatic patients with little or no LA enlargement
WPW Pre-excitation Syndromes	Catheter ablation of the accessory pathway in symptomatic patients with AF, particularly in those with syncope

(Fuster, 2006 [R])

Catheter-Based Ablative Therapies

His ablation with permanent pacemaker implantation

The goal of atrioventricular junctional ablation has been to achieve "ultimate" rate control of atrial fibrillation. This technique does not restore nor maintain sinus rhythm in the atrium; therefore, patients who required anticoagulation prior to the procedure will require it thereafter for cerebrovascular vascular accident prophylaxis. However, a large group of patients with underlying structural heart disease, including those with dilated cardiomyopathy, valvular heart disease, and tachycardia-induced cardiomyopathy, have derived benefit from this procedure. Initial success rates with a single session of radiofrequency energy for achieving atrioventricular nodal block have been in excess of 95% (Brignole, 1998 [A]). Patients are paced – single-chamber atrial fibrillation if their atrial fibrillation has been permanent, or dual-chamber in the setting of paroxysmal atrial fibrillation – with a system that allows mode switching during episodes of paroxysmal atrial fibrillation between DDDR and VVIR modes. Suitable candidates for this approach include patients with atrial fibrillation who require additional rate control that has not been achieved with medications or in patients who are intolerant of multiple medications. Atrioventricular ablation has been shown to improve quality of life and exercise tolerance for patients with atrial fibrillation and rapid ventricular response. For patients with tachycardia-induced cardiomyopathy related to atrial fibrillation with rapid ventricular response, atrioventricular ablation also can be expected to improve ventricular function (Grogan, 1992 [D]). The rate of repeat hospitalization has been demonstrated to decrease following atrioventricular nodal ablation, and there does not appear to be an excess mortality in this group when compared to age-matched population controls.

Recent evidence indicates that right ventricular pacing adversely affects the sequence of cardiac depolarization and may increase the incidence of heart failure (*DAVID Trial Investigators, 2002 [A]*). This raises concern that His bundle ablation and right ventricular pacing approach may ultimately lead to the development of cardiomyopathy and heart failure. The PAVE (Post Atrioventricular nodal ablation Evaluation) clinical trial (unpublished) showed that biventricular pacing improved exercise capacity, resulted in fewer hospitalizations and lower mortality, compared with right ventricular pacing alone after His bundle ablation.

Ablation for atrial flutter

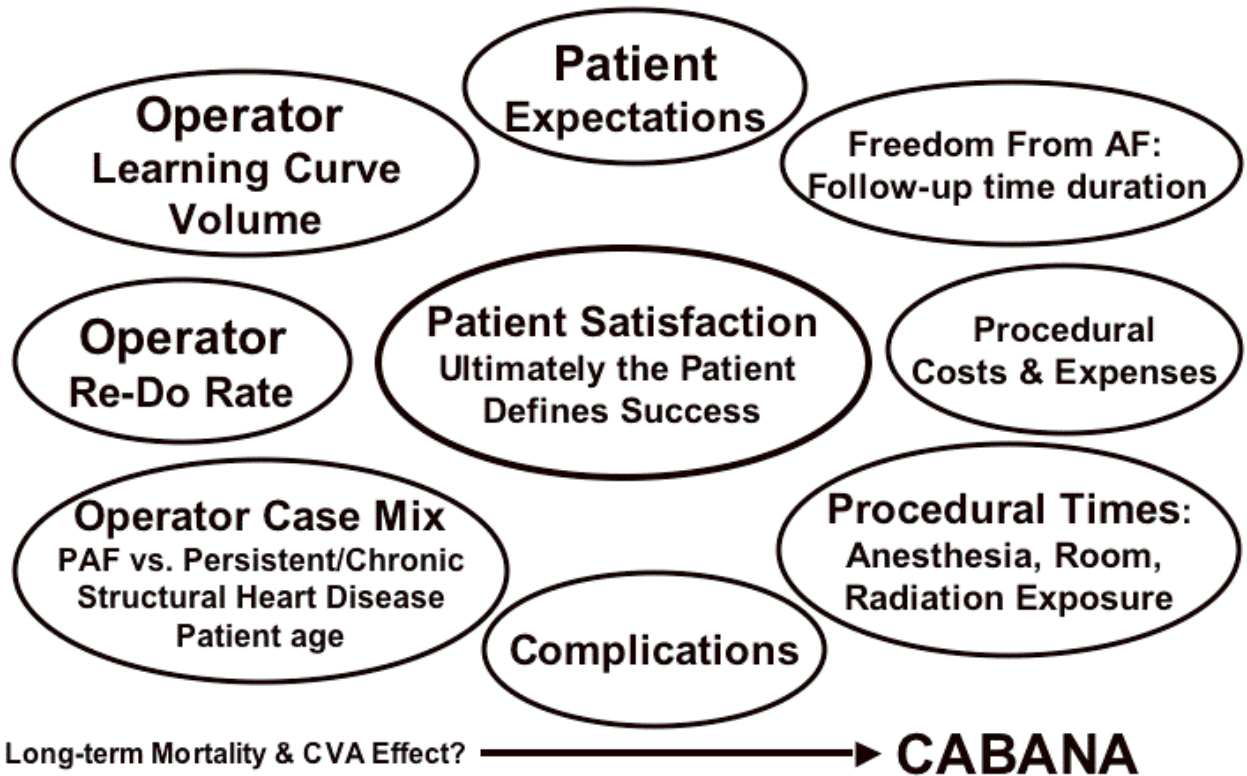
Isthmus dependent atrial flutter is a re-entrant arrhythmia within the right atrium that rotates in a counter-clockwise (typical) or clockwise (reverse flutter) direction. Both circuits use the isthmus between the inferior vena cava and inferior aspect of the tricuspid valve annulus as a critical pathway that can be confirmed at electrophysiologic studies by pacing entrainment. Linear lesions produced by radiofrequency energy application between the tricuspid valve annulus and inferior vena cava can terminate atrial flutter and prevent recurrence. When pacing techniques are used to confirm bidirectional block across the isthmus, success rates are 90%-100% in prevention recurrent atrial flutter (*Willems, 2000 [A]*). This ablation procedure has very low complication rates and is appropriate for patients with solely atrial flutter or where atrial flutter predominates over atrial fibrillation. Antiarrhythmic drug therapy, particularly flecainide and propafenone, can be associated with recurrent and often slows atrial flutter. Ablation may eliminate atrial flutter with continued drug therapy for atrial fibrillation control (*Schumacher, 1999 [C]*). Non-isthmus-dependent flutter related to prior cardiac surgery with atriotomy can be ablated, but can be technically difficult with detailed mapping to identify critical pathway that is usually associated with surgical atrial scar.

Pulmonary Vein Isolation Techniques

Haissaguerre and coworkers reported patients with drug resistant atrial fibrillation might have atrial fibrillation triggered by focal atrial tachycardias originating within the pulmonary veins (*Haissaguerre, 1998 [D]*). Initial approaches with radiofrequency ablation on focal areas within pulmonary veins were limited by the difficulty in mapping triggering ectopy to specific pulmonary vein sites, by occurrence of pulmonary vein stenosis after ablation, and by high rates of recurrent atrial fibrillation (*Chen, 1999 [C]*; *Robbins, 1998 [D]*). Segmental ostial radiofrequency ablation was developed to isolate muscle sleeves of all four pulmonary veins venous from the left atrium (*Haissaguerre, 2000 [D]*). This technique uses radiofrequency energy applied to the left atrium at sites of early pulmonary venous potentials recorded from a ring catheter within the pulmonary vein ostia. Such techniques reduced atrial fibrillation recurrence and resulted in a decrease in pulmonary vein stenosis. Pappone and coworkers isolated the pulmonary veins from the left atrium by creating linear left atrial encircling lesions around the pulmonary vein ostia (*Pappone, 2000 [D]*). Connecting lines in the posterior atrium and to the mitral valve annulus were also used to avoid occurrence of left atrial flutter. Oral, et al. recently reported that the left atrial linear ablative approach was more effective than segmental ostial ablation in 80 patients randomized to the two approaches (*Oral, 2002 [D]*). Further investigation continues in an effort to develop quicker, safer and more effective methods of ablation to limit complications such as pulmonary vein stenosis and cardioembolism and to decrease recurrence rates of atrial fibrillation. Ongoing randomized trials of atrial fibrillation catheter ablation are examining its effects on stroke and overall mortality rates as compared to medical therapies (Cabana Trial, see Figure 3 below.)

Figure 3.

AF Ablation Patient Outcomes (What is Success & What are the Variables?)



Surgical Maze Procedure

The maze procedure involves creating multiple transmural cuts in both the right and left atria that are designed to block and interrupt the multiple reentry wavelets responsible for atrial fibrillation. The procedure is highly successful, with an acceptable morbidity and mortality (Cox, 1991 [R]; Cox, 1995 [NA]). This procedure is generally reserved for patients who are undergoing thoracotomy for correction of other lesions (e.g., valve replacement) or selected patients with severely symptomatic atrial fibrillation in whom normal sinus rhythm is felt to be preferred to rate control alone, but previous attempts at maintaining normal sinus rhythm have been unsuccessful.

Newer techniques are being employed to isolate pulmonary veins using a unipolar or bipolar radiofrequency ablation, cryoablation, microwave and ultrasonic energy. A variety of linear lesion patterns has been used in both left atrium and right atrium in an attempt to find a simpler alternative to the effective but technically challenging Cox 3 cut and sew maze. Limited surgical approaches using endoscopic techniques and/or robotics are also under development to allow pulmonary vein isolation and amputation of left atrial appendage without thoracotomy.

21. Aggressive Management of Patient Comorbidities (Hypertension)/ Monitor for Recurrence/Patient Education

Key Points:

- Patients can monitor for recurrence of atrial fibrillation and should be given a treatment plan for managing recurrence of episodes of atrial fibrillation.
- Patient education is essential for the successful management of atrial fibrillation and atrial flutter.
- Education should begin at the time of diagnosis and should occur and be documented at every visit.
- An important part of patient education is defining expectations – chronicity of disease, empiric treatment and frequent recurrences despite therapy.

Monitoring for Recurrence

- Pulse Self-Monitoring

Patients who have experienced one or more episodes of atrial fibrillation should be taught to periodically monitor their pulse. They should also be given a plan of treatment (elective versus urgent evaluation, "pill-in-the-pocket") if they detect an irregular pulse.

(Cooke, 2006 [M])

- Adjunctive Monitoring

Holter monitors and event monitors may be helpful to monitor for the recurrence of atrial fibrillation in selected patients. Adjunctive monitoring is not required for all patients with a history of atrial fibrillation.

Patient Education

Patient education is essential for the successful management of atrial fibrillation and atrial flutter. Patients should be encouraged and empowered to play an active role in the self-management of their disease. Self-management is best initiated and sustained through an education partnership between the patient and the multidisciplinary health care team.

Education should begin at the time of diagnosis, and should occur and be documented at every visit. Atrial fibrillation in and of itself is not a life-threatening arrhythmia, provided proper anticoagulation is used to prevent thromboembolic complications.

Best patient education should include:

- description of atrial fibrillation/atrial flutter including causes and symptoms
- risks associated with untreated atrial fibrillation/atrial flutter
- review of individual treatment plan
- medication education
- reason for taking medication and action
 - how to take
 - side effects
 - drug interactions
 - mechanism of action of warfarin: it depletes certain coagulation factor proteins in the blood

Algorithm Annotations

- time of day to take warfarin: it should be taken at approximately the same time each day. Due to the short half-life of factor VII and its influence on the international normalized ratio, this is especially important if the patient will have an international normalized ratio drawn the next morning
- how to take a pulse
- explanation of international normalized ratio, target range and regular testing
- when to call the clinic:
 - signs and symptoms of bleeding and that the provider should be contacted immediately if bleeding signs are present
 - need to notify provider if illness, injury or change in physical status occurs
 - need to inform all health care providers of anticoagulation therapy, especially if potentially undergoing an invasive procedure, surgery or dental work
- when to go to the hospital:
 - signs and symptoms of stroke
 - chest pain
 - loss of consciousness
 - signs of significant bleeding

Drug interactions

- What to do if a new medication is initiated or a medication is discontinued, especially if the interaction with warfarin is unknown: check international normalized ratio within three to four days
- Drugs that affect the absorption of warfarin
- Drugs that increase or decrease the effect of warfarin
- Common over-the-counter medication interactions including aspirin, non-steroidal anti-inflammatory drugs, acetaminophen, natural or herbal remedies, laxatives, antacids and multivitamin preparations containing vitamin K
 - Role of vitamin K and the importance of consistency of vitamin K-rich foods in the diet rather than avoidance of vitamin K-rich foods
 - Importance of minimizing trauma risk associated with activities at high risk for injury
 - Effect of exercise: increased activity results in decreased effect of the drug
 - Effect of personal habits: alcohol, chewing tobacco, etc.
 - Effect of certain conditions: congestive heart failure, thyroid disease, gastroenteritis and diarrhea
 - Importance of self-monitoring: maintain a log of international normalized ratios, dose of warfarin, etc.
 - Medic Alert bracelet/necklace and warfarin identification card

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Original Work Group Members

Shelly Bartsch, RN
Nursing
Park Nicollet Clinic

Spring Davis, RN
Health Education
HealthPartners

David Hale, MD, PhD, FACEP
Emergency Medicine
HealthPartners Medical Group

Diane Jacobsen, MPH
Measurement Advisor
ICSI

Jim Lehmann, MD
Internal Medicine
Lakeview Clinic

Peter Marshall, PharmD
Pharmacy
HealthPartners Medical Group
Mark Morrow, MD
Internal Medicine, Work Group Leader

Aspen Medical Group
Thomas Munger, MD
Cardiology/Electrophysiology
Mayo Clinic

Jeff Shultz, MD
Electrophysiology
Park Nicollet Clinic

Mary Stadick, MA
Facilitator
ICSI

Joseph Van Kirk, MD
Family Practice
Lakeview Clinic

Contact ICSI at:

8009 34th Avenue South, Suite 1200; Bloomington, MN 55425; (952) 814-7060; (952) 858-9675 (fax)
Online at <http://www.ICSI.org>

Brief Description of Evidence Grading

Individual research reports are assigned a letter indicating the class of report based on design type: A, B, C, D, M, R, X.

A full explanation of these designators is found in the Foreword of the guideline.

II. CONCLUSION GRADES

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system defined in the Foreword and are assigned a designator of +, -, or \emptyset to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

The symbols +, -, \emptyset , and N/A found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

+ indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;

- indicates that these issues have not been adequately addressed;

\emptyset indicates that the report or review is neither exceptionally strong or exceptionally weak;

N/A indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

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Conclusion Grading Worksheet A – Annotation #9 (Transesophageal Echocardiography and Anticoagulation Therapy)

Work Group's Conclusion: At this time, there is insufficient evidence to recommend routine transesophageal echocardiography (TEE) to guide anticoagulant therapy prior to or following cardioversion (CV).

Conclusion Grade: III

Author/Year	Design Type	Class	Quality +,-,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Manning et al. (1995)	Case Series	D	Ø	<p>-Patients admitted – diagnosis included atrial fibrillation (AF)</p> <p>-Excluded: long-term anticoagulation with warfarin, estimated duration of AF <2 days, spontaneous reversion to sinus rhythm before consent, CV not indicated, TEE contraindicated</p> <p>-Heparin anticoagulation in 211 (91%) to maintain PTT 1.4-1.9 X baseline (22 were not candidates for heparin therapy)</p> <p>-Warfarin in 163 patients suitable for post-CV anticoagulation (target PTT 1.4-1.6 X baseline)</p> <p>-Conventional transthoracic examination (all subjects); if no definite thrombus, TEE within 48 hours; if no atrial thrombi seen, attempted chemical CV in patients receiving heparin; if sinus rhythm not achieved in 12-36 hrs, attempted direct current (DC) CV; continued heparin for ≥24 hrs after CV in those receiving no warfarin and until PTT therapeutic in those who did; continued warfarin for 1 month after CV; those who didn't receive heparin had DC CV immediately after TEE</p> <p>-If atrial thrombus was identified, patient received >3 wks warfarin with target PTT of 1.5-1.8 X baseline</p>	<p>-Follow-up daily during hospital stay and by office visit or phone call at 3-4 wks after CV</p> <p>-Of 1,299 patients screened, 270 were eligible and 233 agreed to participate (105 M, 128 F, mean age 73, range 30-98); clinically estimated duration of AF was 3.4±6 wks (indeterminate in 48 patients)</p> <p>-No patient lost to follow-up</p> <p>-233 had transthoracic echocardiography followed by TEE in 230 (3 could not be intubated)</p> <p>-5 atrial thrombi suspected by transthoracic echocardiography (2 atrial thrombi confirmed by TEE)</p> <p>-40 atrial thrombi identified by TEE in 34 patients; all thrombi identified in vertical plane</p> <p>-Left atrial thrombi more frequent in patients with rheumatic mitral valve disease (p=0.02), abnormal left ventricular systolic function (p=0.01), recent thromboembolism (p=0.01), and spontaneous left atrial echo contrast (p=0.0002); there was substantial overlap between groups; age, gender, duration of AF, and left atrial dimension were not different between groups</p> <p>-CV was deferred in all 34 patients with evidence of thrombi; 3 of these patients died suddenly; 18 of the surviving 31 had uneventful CV after prolonged anticoagulation; 13 remained in AF</p> <p>-196 (85% of total) had no atrial thrombus (with TEE); 186 (95%) had successful CV without chronic anticoagulation and without clinical embolic event; 10 failed CV</p>	<p>-This study documents the safety of TEE in concert with short-term anticoagulation to facilitate early cardioversion for hospitalized patients with atrial fibrillation of unknown or prolonged duration. The approach is as safe as conventional therapy and minimizes the total durations of anticoagulation, atrial fibrillation, and atrial mechanical dysfunction.</p> <p>NOTES: authors do not advocate the use of TEE in all patients with AF (this study included patients hospitalized for treatment of AF); study was not designed to compare sensitivity or specificity of different TEE imaging planes for detection of atrial thrombi (data corroborate the superiority of biplane examination)</p>

**Conclusion Grading Worksheet A – Annotation #9
(Transesophageal Echocardiography and Anticoagulation Therapy)**

Author/Year	Design Type	Class	Quality	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Black et al. (1994)	Case Reports	D	+,-,0	-Requested that investigators from hospitals performing TEE provide information about embolic events after CV in patients screened by TEE -Collected clinical data, echocardiographic data, CV data and data regarding embolic event	-Obtained data on 17 patients (2.4% of 712 patients screened by TEE at the participating centers) -All patients had nonvalvular AF; duration of AF ranged from 2 days to 3 years; etiology varied -TEE did not detect thrombus in the 17 patients prior to CV; only 3 of 17 were therapeutically anticoagulated at the time of TEE (10 were receiving therapy) -16 underwent DC CV; 1 pharmacological CV; no immediate complications of CV in any patient; only 2 of 17 were therapeutically anticoagulated at the time of CV (12 were receiving therapy) -13 had cerebral embolic events and 4 had brachial embolism; embolism occurred 2 hrs to 7 days after CV; there were 2 deaths; none of the 17 patients was therapeutically anticoagulated at the time of embolism (11 were receiving therapy)	-Embolism may occur despite apparent exclusion of preexisting atrial thrombus by TEE. -The most characteristic feature of patients in the series was inadequate anticoagulation. NOTES: the precise incidence of embolism after TEE-guided CV cannot be determined from this study; it is not possible to determine whether emboli occurred because of pre-existing thrombi missed by TEE or <i>de novo</i> atrial thrombosis after CV
Moreya et al. (1995)	Meta Analysis	M	N/A	-Included studies with patients with AF and atrial flutter for >48 hours; CV was spontaneous, pharmacologic or electrical -7 studies used TEE to exclude patients with atrial thrombus and CV was done without prophylactic anticoagulation -18 studies (control) did CV without TEE screening; some received prophylactic anticoagulation and some did not	-Endpoint was reported episode of systemic embolic event (stroke, TIA, or peripheral embolus) occurring in ≤10 days of CV -Of 374 patients screened with TEE and with no evidence of atrial thrombus, there were 5 embolic events (1.34%) -Of 3,271 control patients: a. 1,221 were anticoagulated; there were 4 embolic events (0.33%) b. 2,050 were not anticoagulated; there were 41 embolic events (2.00%) -The incidence of embolic events did not differ between the TEE group and the non-anticoagulated group (p=0.26); the incidence of events in the TEE group was significantly higher than in the anticoagulated group (p=0.04)	-The results from the pooled data revealed that TEE-guided CV for non-anticoagulated patients was not safer than blind CV of non-anticoagulated patients and was associated with a higher risk of an embolic event than blind CV of patients receiving prophylactic anticoagulation. NOTES: included only English-language, published manuscripts or abstracts with >10 patients; included only patients who were screened with TEE and then had CV without anticoagulation <i>Work Group's Comments: potential publication bias due to inclusion of only published reports and abstracts</i>

**Conclusion Grading Worksheet A – Annotation #9
(Transesophageal Echocardiography and Anticoagulation Therapy)**

Author/Year	Design Type	Class	Quality	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Klein et al. (2001)	RCT	A	+	<p>-Patients >18 yrs old with AF (or atrial flutter with history of AF) of >2 days; DC cardioversion prescribed</p> <p>-Excluded: hemodynamic instability, warfarin >7 days, contraindications to warfarin or TEE, childbearing potential, potential need for discontinuation of anticoagulation</p> <p>-Randomly assigned to:</p> <p>a. conventional approach – 3 wks warfarin, CV, 4 wks warfarin</p> <p>b. TEE approach – anticoagulation began at initial visit; goal was therapeutic anticoagulation at CV and 4 wks after; heparin for inpatients with CV within 24 hrs; warfarin for outpatients with CV 5 days later; if thrombi detected with TEE CV postponed and warfarin given for 4 wks, TEE repeated and CV done if no thrombus, otherwise another 4 wks of warfarin with no CV</p> <p>-8-wk follow-up</p>	<p>-Study terminated early (with 1,222 enrolled) due to low rate of recruitment and low number of events</p> <p>-619 in TEE group, 603 in conventional tx group</p> <p>-Groups comparable at enrollment; significant differences at time of cardioversion in use of warfarin and heparin, antiarrhythmic therapy</p> <p>-Of 619 in TEE group: 69% had early CV (mean of 3 days); 81% were successful</p> <p>-Of 603 in conventional tx group: 55% had CV (mean of 31 days); 80% were successful</p> <p>-Time to cardioversion differed (p=0.001)</p> <p>-Embololic events: total number low; no difference between groups (5 in TEE group vs. 3 in conventional group)</p> <p>-Thrombus: revealed by TEE in 76 patients (13.8%) of 549 who had TEE; among the 76 – no embolic events, 4 died, 2 major hemorrhage complications (not different from those without thrombus)</p> <p>-Hemorrhagic events: overall fewer in TEE group (2.9% vs. 5.5%; p=0.03)</p> <p>-Deaths: trend toward higher all-cause death in TEE group (2.4% vs. 1.0%; p=0.06)</p> <p>-Sinus Rhythm: higher percent restored within 8 wks in TEE group (71% vs. 65%; p=0.03); no difference in % restored immediately or % maintained at 8 wks</p> <p>-Functional status: no difference at 8 wks</p>	<p>-The use of transesophageal echocardiography to guide the management of atrial fibrillation may be considered a clinically effective alternative strategy to conventional therapy for patients in whom elective cardioversion is planned.</p> <p>NOTES: sample size estimation called for n=3,000 to achieve 92% power (at $\alpha=0.05$) for analysis of all embolic events; 95% of all patients who died had serious coexisting conditions such as coronary artery disease, congestive heart failure, diabetes, dilated cardiomyopathy</p>

**Conclusion Grading Worksheet A – Annotation #9
(Transesophageal Echocardiography and Anticoagulation Therapy)**

Author/Year	Design Type	Class	Quality +,-,∅	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Weigner et al. (2001)	Case Series	D	∅	-539 patients with AF of unknown or ≥2 days duration; not receiving chronic therapeutic warfarin; given IV heparin to maintain PTT 1.5-2X control plus oral warfarin; TEE attempted before planned elective CV; 54% male; ages 23-90 years -TEE performed: A) if no evidence of thrombus patients underwent CV with heparin until INR ≥2.0 and warfarin for ≥1 month B) if thrombus present CV deferred and warfarin continued at least 3-4 wks, follow-up TEE suggested before attempted CV, if thrombus on follow-up TEE then CV canceled and warfarin given indefinitely -Followed daily in hospital, at 1 month (office visit or phone call), and 1 year (review of records over 12-month period)	-TEE completed in 98.8%; 70 patients (13%) had 76 atrial thrombi (70 in left atrium); 5 of the 70 died during index admission (2 related to acute thromboembolism); 28 had follow-up TEE with thrombus resolution in 22 (79%); 18 of 22 were cardioverted with no clinical thromboembolic events; 5 with thrombus on initial TEE were cardioverted after 4-12 wks of warfarin with no clinical events -463 patients with no atrial thrombi; CV successful in 413 (89%); 386 had DC CV; 27 spontaneously reverted -Of 413, 93% received anticoagulation treatment and achieved therapeutic PTT or INR at time of TEE and CV; 71% of these patients were discharged on warfarin -1 patient with "negative" TEE had thromboembolic event in 1st month after cardioversion (recovered) -Follow-up data from 278 patients; 57% developed recurrent AF during 1st yr post-CV; 57% in sinus rhythm at 1 yr; recurrent AF lower and number of patients in sinus rhythm higher if duration of AF <3 wks at time of CV (both p<0.01); 12 "late" (>1 month, <1 year) clinical thromboembolic events	-Early cardioversion facilitated by transesophageal echocardiography has a favorable safety profile and provides the associated benefit of reduced recurrence of atrial fibrillation for patients in whom the duration of atrial fibrillation is <3 weeks. NOTES: study conducted over 9 year period; 95% of patients received heparin or warfarin at time of initial TEE; 73% of these patients prescribed warfarin at discharge; aspirin prescribed for 20%; follow-up data from 278 patients included 92% of subjects who reached 1-yr post-CV

Conclusion Grading Worksheet B – Annotation #15 (Rhythm versus Rate Control)

Work Group's Conclusion: There is no observed survival advantage to strategies aimed at restoring sinus rhythm over strategies to control rate in older patients with relatively asymptomatic atrial fibrillation, based on the limited data available from studies that have compared these strategies.

Conclusion Grade: II

Author/Year	Design Type	Class	Quality	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Wyse et al., (2002) AFFIRM trial	RCT	A	+	<ul style="list-style-type: none"> -4,060 patients (mean age 69.7 years) enrolled in study (70.8% history of hypertension and 38.2% had coronary artery disease) -patient inclusion: 65 years of age or older or other risk factors for stroke or death; recurrent AF likely to cause illness or death; long-term treatment of AF warranted; and anticoagulation therapy could not be contraindicated -drugs chosen by the treating physician and cardioversion used as necessary 	<ul style="list-style-type: none"> -women: 40.6% in rate control group and 37.9% in rhythm control group (p=0.08) -prevalences of sinus rhythms in rhythm control group 82.4%, 73.3%, and 62.6% after 1, 3, and 5 years follow-up, respectively -356 deaths in rhythm control group and 310 deaths in rate control group (mortality at 5 years 23.8% and 21.3%; hazard ratio 1.15 [95%CI 0.99 to 1.34]; p=0.08) -rhythm control group had more hospitalizations (80.1% vs 73.0%, p<0.001) and more adverse drug effects than rate control group ->85% of the rate control group was taking warfarin at all assessments as compared to approximately 70% in rhythm control group; majority strokes occurred after warfarin was stopped -combination secondary endpoint (death, disabling stroke or anoxic encephalopathy, major bleeding, or cardiac arrest) similar in both groups (32.0% vs 32.7%) -64.5% of all patients had recurrent AF 	<ul style="list-style-type: none"> -Management of atrial fibrillation with the rhythm control strategy offers no survival advantage over the rate control strategy, and there are potential advantages, such as a lower risk of adverse drug effects, with the rate control strategy. -Anticoagulation should be continued in this group of high-risk patients.

**Conclusion Grading Worksheet B –
Annotation #15 (Rhythm versus Rate Control)**

Author/Year	Design Type	Class	Quality + , - , \emptyset	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Van Gelder et al., (2002) RACE trial	RCT	A	\emptyset	<p>-patients randomly received rate control (n=256) or rhythm control (n=266)</p> <p>-patients included for persistent atrial fibrillation or flutter (7% of patients) after previous electrical cardioversion and if anticoagulation not contraindicated</p> <p>-patients excluded: if arrhythmia had lasted longer than one year; if they had heart failure; current or previous treatment with amiodarone; or a pacemaker</p> <p>-patients in rate control group received oral anticoagulant and rate-slowing medication; patients in rhythm-control group underwent serial cardioversions and received antiarrhythmic and oral anticoagulant drugs</p> <p>-anticoagulation could stop at 1 month if patient in sinus rhythm</p>	<p>-patients with hypertension significantly higher in rhythm control group as compared to rate control group (55% vs 43%, p<0.007)</p> <p>-39% of rhythm control group had sinus rhythm as compared with 10% in rate control group</p> <p>-primary endpoint (death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, and severe adverse effects of drugs) occurred in 44 patients (17.2% in rate control group and in 60 (22.6%) in the rhythm control group (absolute difference -5.4, 90%CI -11.0 to 0.4)</p> <p>-hazard ratio for the risk of primary endpoint was 0.73 (90%CI 0.53 to 1.01, p=0.11)</p> <p>-6 patients had thrombotic complications after discontinuation of anticoagulants and 23 after inadequate anticoagulant therapy</p>	<p>-Rate control is not inferior to rhythm control for the prevention of death and morbidity from cardiovascular causes and may be appropriate therapy in patients with a recurrence of persistent atrial fibrillation after electrical cardioversion.</p>
Hohnloser et al., (2000) PIAF trial	RCT	A	\emptyset	<p>-randomized 252 patients (18-75 years) with persistent AF of 7-360 days duration to rate control (group A, 125 patients) or rhythm control (group B, 127 patients)</p> <p>-diltiazem used as first-line therapy in group A and amiodarone used in group B</p> <p>-patients followed for 1 year</p> <p>-all patients received anticoagulation throughout study period</p> <p>-patients excluded for congestive heart failure; unstable angina; acute myocardial infarction (MI) within 30 days; AF fewer than 50 beats per minute; sick sinus syndrome; Wolff-Parkinson-White syndrome; coronary bypass; valve replacement within 3 months; intracardiac thrombus; embolization within 3 months; hypertrophic cardiomyopathy; amiodarone within 6 months; acute thyroid dysfunction; pacemaker; contraindications to anticoagulation; or pregnancy</p>	<p>-more patients with hypertension (54% rate vs 46% rhythm) and recurrent AF (59% rate vs 51% rhythm) in rate control group</p> <p>-over 1 year, similar proportion of patients reported improvement in symptoms in both groups (76 responders in group A vs 70 responders in group B, p=0.317)</p> <p>-amiodarone administration resulted in pharmacological restoration of sinus rhythm in 23% of patients</p> <p>-at one-year follow-up, 56% of patients in rhythm group were in sinus rhythm compared to 10% in rate control group</p> <p>-walking distance in 6-minute walk test better in group B compared with group A (p=0.008 at one-year), but quality of life showed no differences between groups</p> <p>-incidence of hospital admission higher in group B (69% vs 24% group A, p=0.001)</p> <p>-adverse drug effects more frequently led to change in therapy in group B (25% vs 14% group A, p=0.036)</p>	<p>-With respect to symptomatic improvement in patients with atrial fibrillation, the therapeutic strategies of rate versus rhythm control yielded similar clinical results overall. However, exercise tolerance is better with rhythm control, although hospital admission is more frequent. These data may serve as a basis to select therapy in individual patients.</p>

This section provides resources, strategies and measurement specifications for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Priority Aims and Suggested Measures
 - Measurement Specifications
- Key Implementation Recommendations
- Knowledge Resources
- Resources Available

Priority Aims and Suggested Measures

1. Increase the percentage of adult patients (age 18 years and older) who are accurately diagnosed with atrial fibrillation/flutter. (*Annotation #2*)

Possible measure for accomplishing this aim:

- a. Percentage of adult patients (age 18 years and older) with documentation in the medical record of an electrocardiogram confirming a diagnosis (of atrial fibrillation/flutter).
2. Improve the consistency of anticoagulation therapy in adult patients (age 18 years and older) with non-valvular paroxysmal, persistent or permanent atrial fibrillation/flutter. (*Annotation #14*)

Possible measures for accomplishing this aim:

- a. Percentage of adult patients (age 18 years and older) with non-valvular atrial fibrillation/flutter with a CHADS2 score of 2 or greater (without contraindications to anticoagulation therapy) who are taking warfarin.
 - b. Percentage of adult patients (age 18 years and older) with non-valvular atrial fibrillation/flutter not taking warfarin (without contraindications to aspirin) who are taking daily aspirin.
3. Improve rate control in adult patients (age 18 years and older) with permanent atrial fibrillation/flutter. (*Annotation #17*)

Possible measure for accomplishing this aim:

- a. Percentage of adult patients (age 18 years and older) with a diagnosis of permanent atrial fibrillation/flutter with documentation in their medical record indicating adequate rate control both at rest and during exercise was achieved:
 - Less than 80 to 90 beats per minute at rest, and during exercise in those patients who are physically active
 - Walking ventricular response less than 120 beats per minuteOR
 - Average ventricular response on 24 hour Holter less than 100 beats per minute
4. Increase the percentage of adult patients (age 18 years and older) with a confirmed diagnosis of atrial fibrillation/flutter who, along with their family, have received patient education around atrial fibrillation/flutter and anticoagulation therapy. (*Annotation #21*)

Inpatient and outpatient:

Possible measures for accomplishing this aim:

- a. Percentage of adult patients (age 18 years and older) with a confirmed diagnosis of atrial fibrillation/flutter seen within the last month who have documentation in their medical record indicating they have received education that includes:
 - the importance of follow-up monitoring
 - compliance/self management issues
 - dietary restrictions
 - potential for adverse drug reactions and interactions.

(2008/2009 Joint Commission National Safety Goal)

Priority Aims and Suggested Measures

5. Reduce the percentage of patient harm associated with the use of anticoagulation therapy. (*Annotation #14*)

Possible measures for accomplishing this aim:

Inpatient and Outpatient:

- a. Percentage of adult patients (age 18 years and older) who are initially prescribed warfarin with documentation in the medical record indicating a baseline INR was obtained.
- b. Percentage of adult patients (age 18 years and older) who receive ongoing warfarin with documentation in the medical record indicating a current INR is available and is used to monitor and adjust therapy.

(2008/2009 Joint Commission National Safety Goal)

6. Increase the percentage of adult patients (age 18 years and older) with a confirmed diagnosis of atrial fibrillation/flutter, receiving dietary monitoring. (*Annotation #21*)

Possible measure for accomplishing this aim:

Inpatient

- a. Percentage of adult patients (age 18 years and older) with a confirmed diagnosis of atrial fibrillation/flutter prescribed warfarin therapy with documentation in their medical record indicating dietary services was notified and responded according to the organization's food/drug interaction program.

(2008/2009 Joint Commission National Safety Goal)

7. Increase the percentage of adult patients (age 18 years and older) with a confirmed diagnosis of atrial fibrillation/flutter who have a medication communication/reconciliation plan throughout the continuum of care. (*Annotations #7, 15, 21*)

Possible measures for accomplishing this aim:

Inpatient and Outpatient

- a. Percentage of adult patients (age 18 years and older) with a confirmed diagnosis of atrial fibrillation/flutter with documentation in their medical record indicating a complete list of medication was communicated to the next provider of service when the patient is referred or transferred to another setting, service, practitioner or level of care within or outside the organization.
- b. Percentage of adult patients (age 18 years and older) with a confirmed diagnosis of atrial fibrillation/flutter with documentation in their medical record indicating a complete list of medications was provided to the patient along with review of the list upon discharge.

(2008/2009 Joint Commission National Safety Goal)

Measurement Specifications

Possible Suggested Measurement #2a

Percentage of patients (without contraindications to anticoagulation) with paroxysmal, persistent or permanent atrial fibrillation/flutter with risk factors for thromboembolism who are taking warfarin.

Population Definition

Adult patients (age 18 years of age or older) who have had an electrocardiogram that confirms a diagnosis of atrial fibrillation/flutter.

Data of Interest

Adult patients (age 18 years of age or older) with the following:

- Paroxysmal atrial fibrillation/flutter
- Persistent atrial fibrillation/flutter
- Permanent atrial fibrillation/flutter
- Risk factors for thromboembolism
- Without contraindication to anticoagulation
- Receiving warfarin

of adult patients (age 18 years of age or older) with paroxysmal, persistent or permanent atrial fibrillation/flutter whose medical records are reviewed.

Numerator/Denominator Definitions

Numerator: Among the atrial fibrillation/flutter patients in the denominator, the number of patients with atrial fibrillation/flutter who have paroxysmal, persistent or permanent atrial fibrillation/flutter with risk factors for thromboembolism without contraindications to anticoagulation who are receiving warfarin.

Denominator: Adult patients (18 years of age or older) with paroxysmal, persistent or permanent atrial fibrillation/flutter as defined by one or more visits with any (primary or secondary) diagnosis of atrial fibrillation/flutter (ICD-9 code 427.31 or 427.32) in the last month or measurement time frame under review.

Method/Source of Data Collection:

This measure may be collected electronically through claims data using the ICD-9 codes 427.31 or 427.32 to identify the patients. Charts will be reviewed to determine if patients have risk factors for thromboembolism without contraindications (see assess risk for bleeding or thromboembolism on pages 11 and 12 of guideline) to anticoagulation therapy are on warfarin.

Select a random sample of the eligible population for data collection. The suggested sample size for each medical group is at least 10 charts each month. If the medical group identifies a total of less than 10 atrial fibrillation/flutter patients, all identified patients are to be included.

Time Frame Pertaining to Data Collection

The sample would be drawn quarterly; data would be abstracted monthly.

Priority Aims and Suggested Measures

Possible Suggested Measurement #3a

Improve the consistency of anticoagulation therapy in adult patients (age 18 years and older) with non-valvular atrial fibrillation/flutter.

Population Definition

Adult patients (age 18 years and older) who have had an electrocardiogram confirming a diagnosis of atrial fibrillation/flutter.

Data of Interest

of patients (age 18 years and older) with a confirmed diagnosis of non-valvular atrial fibrillation/flutter.

of patients (age 18 years and older) with non-valvular atrial fibrillation/flutter whose medical record was reviewed.

Numerator/Denominator Definitions

Numerator: Among atrial fibrillation/flutter patients in the denominator, the number of patients with non-valvular atrial fibrillation/flutter with risk factors for thromboembolism having a CHADS2 score of 2 or greater (without contraindications to anticoagulation therapy) who are receiving warfarin.

Denominator: Adult patients (age 18 years of age and older) with non-valvular atrial fibrillation/flutter as defined by one or more visits with any (primary or secondary) diagnosis of atrial fibrillation/flutter ICD-9 code 427.31 or 427.32) in the last month or measurement time frame under review.

Method/Source of Data Collection

This measure may be collected electronically through claims data using the ICD-9 codes 427.31 or 427.32 to identify the patients. Charts will be reviewed to determine if patients have risk factors for thromboembolism, and without contraindications to anticoagulation therapy who are taking warfarin.

Time Frame Pertaining to Data Collection

The sample would be drawn quarterly, data would be abstracted monthly.

Key Implementation Recommendations

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Develop a process for accurate diagnosis of atrial fibrillation/flutter:
 - Documentation of an electrocardiogram along with results in the medical record.
 - Process for communicating to physicians that a diagnosis of atrial fibrillation/flutter was confirmed by electrocardiogram.
2. Develop a process for implementing the five key steps in the management of atrial fibrillation/flutter (SALT-E):
 - Stabilize (*Annotation #6*)
 - Assess (*Annotation #7*)
 - Label (*Annotations #9, 14, 15, 18, 19, 20*)
 - Treat (*Annotations #9, 14, 15, 20*)
 - Educate (*Annotation #21*)
3. Patient education is essential in the treatment of atrial fibrillation/flutter. Patients and caregivers should be informed of signs and symptoms that require contact with their health care provider.

(*Annotations #1, 21*)
4. Develop a process to assure that patients who are diagnosed with atrial fibrillation/flutter and are initiated on warfarin have a baseline international normalized ratio that is documented in the medical record.
5. Develop and implement a defined anticoagulation management program.
6. Develop a process for appropriate referral to specialty; this should include a process for communication across the continuum of care.
7. Develop a process that will assure the completion of a patient medication list for the purpose of communicating to the next provider of service, when the patient is referred, or transferred to another setting, service, practitioner or level of care within or outside the organization.

Knowledge Products and Resources

Criteria for Selecting Resources

The following resources were selected by the Atrial Fibrillation guideline work group as additional resources for providers and/or patients. The following criteria were considered in selecting these resources.

- The site contains information specific to the topic of the guideline.
- The content is supported by evidence-based research.
- The content includes the source/author and contact information.
- The content clearly states revision dates or the date the information was published.
- The content is clear about potential biases, noting conflict of interest and/or disclaimers as appropriate.

Resources Available to ICSI Members Only

ICSI has a wide variety of knowledge resources that are *only* available to ICSI members (these are indicated with an asterisk in far left-hand column of the Resources Available table). In addition to the resources listed in the table, ICSI members have access to a broad range of materials including tool kits on CQI processes and Rapid Cycling that can be helpful. To obtain copies of these or other Knowledge Resources, go to http://www.icsi.org/improvement_resources. To access these materials on the Web site, you must be logged in as an ICSI member.

The resources in the table on the next page that are not reserved for ICSI members are available to the public free-of-charge.

Resources Available

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	American Heart Association	Their mission is to reduce disability and death from cardiovascular diseases and stroke. National and local chapter information is available, as well. To access information on atrial fibrillation, type "atrial fibrillation" in the search box.	Health Care Professionals; Patients and Families	http://www.americanheart.org
	The Arizona CERT Clinical Path Institute	An independent research and education center whose mission is to improve therapeutic outcomes and reduce adverse events caused by drug interactions and drugs that prolong the QT interval, especially those affecting women.	Health Care Professionals	http://www.torsades.org/index.cfm
	Center for Cardiovascular Education, Inc.	Founded by a person with heart disease and a physician, the site provides information on many heart diseases, including atrial fibrillation/flutter symptoms, therapies and guides for patient questions for their providers.	Health Care Professionals; Patients and Families	http://www.heartinfo.org
	Heart Rhythm Society	Comprehensive site includes research updates, guidelines and a reference center for professionals. Patient and public links include a heart information center, electrophysiology referral information, and patient stories. Education materials available. Spanish and English.	Health Care Professionals; Patients and Families	http://www.hrsonline.org
	Journal of the American Medical Association – Patient Page	The JAMA Patient Page is a public service of The Journal of the American Medical Association. The key objective of JAMA is to promote the science and art of medicine and the betterment of the public health.	Health Care Professionals; Patients and Families	http://www.jama.ama-assn.org/cgi/collection/patient_page
	Mayo Foundation for Medical Education and Research	Mayo Clinic patient-oriented Web site. The basics of heart disease, how heart disease is diagnosed, heart disease screening tests, heart disease risk factors and heart disease prevention.	Health Care Professionals; Patients and Families	http://www.mayoclinic.com/health/heart-disease/HB99999

* Available to ICSI members only.