Management of Atrial Fibrillation: Update 2010

West Virginia ACC: 11/21/09

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Objectives

- Review Atrial Fibrillation Background
- Discuss Atrial Fibrillation Guidelines
- Review Rate Control vs Rhythm Control
- Review Anticoagulation : New Drugs
- Highlight New Drugs : Rhythm Control
- Review Atrial Fibrillation Ablation
- Summary
Epidemiology of Atrial Fibrillation

• Most common sustained cardiac arrhythmia\textsuperscript{1}
• Currently affects >2.3 million Americans, or 1% of population\textsuperscript{1,2}
• Preferentially affects men and the elderly\textsuperscript{2}
• Prevalence expected to increase approximately 2.5-fold by 2050\textsuperscript{2,3}
• Lifetime risk of developing AF: 1 in 4 for men and women ≥40 years of age\textsuperscript{1}

Factors Contributing to Increasing AF Prevalence

- Growing elderly population
- Increasing prevalence of predisposing factors (i.e. diabetes, hypertension)
- Increasing rates of cardiac surgical procedures
- Improved survival with CV conditions (i.e. myocardial infarction and heart failure)
- Improved methods of detection

Increasing Hospitalizations in the U.S.
When AF Is Principal Diagnosis
(National Hospital Discharge Survey)

Prevalence per 10,000 persons

Year
1985 1987 1989 1991 1993 1995 1997 1999

Age (years)
85+ 75 to 84 65 to 74 55 to 64 35 to 54
Economic Impact and Public Health Burden of Hospitalizations in Those With AF

- AF represents a significant public health burden\(^1\)
  - Globally, the annual cost per patient is approximately $4700
- AF is associated with more hospitalizations than any other arrhythmia\(^2\)
  - Accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances\(^3\)
- Increased hospitalizations may impact both patient QOL and health care costs\(^4\)

Decreasing Atrial Fibrillation Burden is an Important Goal

• As with heart failure or angina, success in managing atrial fibrillation is defined as a decrease in:
  
  - Frequency of episodes
  - Duration of episodes
  - Symptoms during episodes

• Decreasing the atrial fibrillation burden offers potential to successfully treat atrial fibrillation by:
  
  - Decreasing mortality
  - Decreasing hospitalizations
  - Increasing Quality of Life

Therapeutic Approaches to Atrial Fibrillation

• Anticoagulation

• Antiarrhythmic suppression

• Control of ventricular response
  – Pharmacologic
  – Catheter modification/ablation of AV node

• Curative procedures
  – Surgery (maze)
  – Catheter ablation
Patterns of Atrial Fibrillation:

First Detected

Paroxysmal terminating: ≤ 7 days (most < 24 hours)

Persistent Not self-terminating: > 7 days

Permanent Cardioversion failed or not attempted
Reasons to treat AF:

- Symptomatic improvement
- Prevention of thromboembolic complications
- Prevention of tachycardia-induced cardiomyopathy
AFib Management Treatment Options

VENTRICULAR RATE CONTROL
- Pharmacologic
- Nonpharmacologic

CONVERSION AND MAINTENANCE OF SINUS RHYTHM
- Pharmacologic
- Nonpharmacologic

ANTITHROMBOTIC THERAPY
Atrial Fibrillation : Rate Control

- Ventricular Rate : Rest & Exertion
- Tachycardia Cardiomyopathy
- Rest 60-80 beats/minute
- Exertion 90-120 beats/minute
- Criteria vary with Age
- Evaluate : 24-hour ECG
## Table 1. Pharmacologic Heart-Rate Control in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control of Acute Episode</th>
<th>Control of Sustained Atrial Fibrillation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-channel blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>20-mg bolus followed, if necessary, by 25 mg given 15 min later. Maintenance infusion rate of 5–15 mg/hr.</td>
<td>Oral controlled-release formulation, 180–300 mg daily.</td>
<td>Long-term control may be better with the addition of digoxin.</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5–10 mg IV over 2–3 min, repeated once, 30 min later. Maintenance infusion rate is not reliably documented.</td>
<td>Slow-release formulation, 120–240 mg once or twice daily.</td>
<td>Causes elevation in digoxin level. May be more negatively inotropic than diltiazem.</td>
</tr>
<tr>
<td>Beta-blockers†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>0.5 mg/kg of body weight IV, repeated if necessary. Follow with infusion at 0.05 mg/kg/min, increasing as needed to 0.2 mg/kg/min.</td>
<td>Not available in oral forms.</td>
<td>Hypotension may be troublesome but responds to drug discontinuation.</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>5-mg bolus IV, repeated twice at intervals of 2 min. No data on maintenance infusion.</td>
<td>50–400 mg daily in divided doses.</td>
<td>Useful if there is concomitant coronary disease.</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1–5 mg IV, given over 10 min.</td>
<td>30–360 mg in divided doses or in long-acting form.</td>
<td>Noncardioselective: use cautiously in patients with a history of bronchospasm.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1.0–1.5 mg IV or orally over 24 hr in doses of 0.25 to 0.5 mg.</td>
<td>0.125–0.5 mg daily.</td>
<td>Renally excreted. Slow onset even if given IV, with less effective control than other agents, although may be synergistic with them. Poor efficacy for exertional heart rate control.</td>
</tr>
</tbody>
</table>

* IV denotes intravenously.

† The beta-blockers listed are representative of agents in this category. Other intravenous or oral beta-blockers may be equally acceptable.
Anticoagulation Issues

- ASA 324mg/day : CHADS2 <2
- ASA 324mg/day or Warfarin : CHADS2 score =2
- Warfarin (INR 2.0-3.0) CHADS2 >2
- Document Warfarin Intolerance
- Future : Thrombin Inhibitor & Xa Inhibitor
Atrial Fibrillation and Stroke

- Risk: 5 - 8% per year in high-risk patients

- Anticoagulant therapy is clearly indicated and beneficial in rheumatic atrial fibrillation.

- In non-rheumatic atrial fibrillation, major randomized trials have provided useful guidelines for identifying and treating patients at risk.
Predictors of Thromboembolic Risk in Atrial Fibrillation

- History of hypertension
- Prior stroke or TIA
- Diabetes
- Recent heart failure
- Age > 75 years

CHADS2 INDEX

- CHF (LV Dysfunction) = 1
- Hypertension = 1
- Age >75 years = 1
- Diabetes Mellitus = 1
- Stroke or TIA = 2

(Low Risk = 0/1 and High Risk >2)
Original Article

Dabigatran versus Warfarin in Patients with Atrial Fibrillation


N Engl J Med
Volume 361(12):1139-1151
September 17, 2009
Study Overview

• In a large, randomized trial, two doses of the direct thrombin inhibitor dabigatran were compared with warfarin in patients who had atrial fibrillation and were at risk for stroke.

• At 2 years, the 110-mg dose of dabigatran was found to be noninferior, and the 150-mg dose superior, to warfarin with respect to the primary outcome of stroke or systemic embolism.
Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group

Conclusion

• In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage.

• Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.
Original Article

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators

N Engl J Med
Volume 360(20):2066-2078
May 14, 2009
Study Overview

- A randomized trial enrolled 7554 patients with atrial fibrillation who were at increased risk of stroke but not candidates for vitamin K antagonists.
- Participants were assigned to aspirin or aspirin plus clopidogrel.
- At a median of 3.6 years, the risk of major vascular events decreased significantly with clopidogrel, primarily because of reduced risk of stroke.
- The risk of major bleeding increased significantly with clopidogrel.
Cumulative Incidence of Trial Outcomes, According to Treatment Group

Conclusion

• In patients with atrial fibrillation for whom vitamin K-antagonist therapy was unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage
Recommendations for Management of Atrial Fibrillation < 48 Hours

Atrial Fibrillation < 48 hours

- Control ventricular rate
- Consider antithrombotic therapy
- Observe for spontaneous conversion

Prompt electrical or pharmacologic conversion

- Antiarrhythmic therapy if Unstable hemodynamics or frequent recurrences
- No antiarrhythmic therapy if Stable hemodynamics, infrequent recurrences, or first episode

Recommendations for Management of Atrial Fibrillation > 48 Hours

Atrial Fibrillation > 48 Hours

Control ventricular rate
Start antithrombotic therapy
(heparin and/or warfarin or aspirin)

Duration < 1 year

or

Warfarin therapy 3-4 weeks

Cardioversion or pharmacologic conversion

Antiarrhythmic therapy if
Unstable hemodynamics or frequent recurrences
Continue warfarin 1-2 months
Monitor for recurrences

No antiarrhythmic therapy if
Stable hemodynamics, infrequent recurrences, or first episode

Duration > 1 year

Chronic antithrombotic therapy
Assure control of ventricular rate

Recommendations for Management of Atrial Fibrillation > 48 Hours

Atrial Fibrillation > 48 Hours

- Control ventricular rate
- Start antithrombotic therapy (heparin and/or warfarin or aspirin)

Duration < 1 year

- Warfarin therapy 3-4 weeks
- Cardioversion or pharmacologic conversion

Antiarrhythmic therapy if

Unstable hemodynamics or frequent recurrences

Continue warfarin 1-2 months

Monitor for recurrences

No antiarrhythmic therapy if

Stable hemodynamics, infrequent recurrences, or first episode

Duration > 1 year

Chronic antithrombotic therapy

Assure control of ventricular rate

Management of Recurrent Paroxysmal AF

Recurrent Paroxysmal Atrial Fibrillation

- Minimal or No Symptoms
  - Anticoagulation and Rate Control as Needed
  - No Drug for Prevention of AF

- Disabling Symptoms
  - Anticoagulation and Rate Control as Needed
  - Antiarrhythmic Drug Therapy (see flow sheet)
  - AF Ablation, if AAD Fails
AA Drug Therapy to Maintain SR (Recurrent Paroxysmal or Persistent AF)

No or Minimal Heart Disease:

- Flecainide
- Propafenone
- Sotalol

Amiodarone
Dofetilide

Catheter Ablation

Disopyramide
Procainamide
Quinidine
AA Drug Therapy to Maintain SR (Recurrent Paroxysmal or Persistent AF)

Hypertension:

Substantial LVH

No

Flecainide
Propafenone
Sotalol

Yes

Amiodarone

Amiodarone
Dofetilide

Catheter Ablation

Catheter Ablation

Disopyramide
Procainamide
Quinidine
AA Drug Therapy to Maintain SR (Recurrent Paroxysmal or Persistent AF)

Coronary Artery Disease:
- Dofetilide
- Sotalol
- Amiodarone
- Catheter Ablation
AA Drug Therapy to Maintain SR (Recurrent Paroxysmal or Persistent AF)

Heart Failure:

Amiodarone, Dofetilide

Catheter Ablation
MULTAQ (dronedarone)

- **Mechanism of action**
  - The exact mechanism of action of dronedarone is unknown
  - Dronedarone has antiarrhythmic properties belonging to all four Vaughan-Williams classes, but the contribution of each of these activities to the clinical effect is unknown

- **Chemical structure**
  - A benzofuran derivative: N-{2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl] benzofuran-5-yl} methanesulfonamide, hydrochloride

- **Pharmacokinetic properties**
  - Elimination half life is 13-19 hours
  - After repeated administration of 400 mg twice daily, steady state is reached within 4 to 8 days of treatment
  - Extensively metabolized, mainly by CYP3A
  - Bioavailability is increased by meals
  - Binds mainly to albumin

ATHENA Trial: Background

- Atrial fibrillation (AF) impairs patients’ lives, leading to increased risks of cardiovascular complications.

- Over the course of 20 years of clinical drug trials in AF no drug has demonstrated a significant reduction in the risk of cardiac death.

- ATHENA set out to evaluate the effect of Multaq® (dronedarone), a multi-channel blocker with anti-adrenergic properties, on a composite primary endpoint of all-cause mortality and cardiovascular hospitalization in patients with AF.
ATHENA Trial: Study Design

4,628 patients ≥75 years with atrial fibrillation or 70-75 years with atrial fibrillation and at least one additional cardiovascular risk factor prior to randomization. Double blind. Randomized. Placebo controlled. International multicenter. Mean follow-up 21 months.

- Multaq® (dronedarone) 400 mg BID
- Placebo

12-30 mos. follow-up

- Primary Endpoint: composite of all-cause mortality combined with cardiovascular hospitalization
- Secondary Endpoint: death from any cause, cardiovascular death, hospitalization for cardiovascular reasons
ATHENA Trial: Primary Endpoint Results

Multaq® (dronedarone) decreased the risk of cardiovascular hospitalizations or death from any cause by 24% (p<0.001).
ATHENA Trial: Secondary Endpoint Results

- Compared to placebo, Multaq® (dronedarone) significantly decreased the risk of cardiovascular death by 30% (p=0.034).

- Multaq® (dronedarone) was associated with numerically fewer deaths from any cause (16%, p=0.17).

- First cardiovascular hospitalization was reduced by 25% (p=<0.001).
ATHENA Trial: Other Outcomes

• Death from arrhythmias was reduced by 45% (p=0.01) when patients were treated with Multaq® (dronedarone).

• Multaq® (dronedarone) demonstrated a lower risk of pro-arrhythmia than placebo and no excess of hospitalizations for congestive heart failure.

• The rate of study drug discontinuation was similar between the two study arms.
ATHENA Trial: Adverse Events

- There was a higher frequency of reported gastro-intestinal complications in the Multaq® (dronedarone) group than in the placebo arm.
Multaq® (dronedarone) was associated with a more frequent occurrence of skin disorders as compared to placebo.
Patients treated with Multaq® (dronedarone) demonstrated increased serum creatinine more frequently than those given placebo.
ATHENA Trial: Limitations

• Future trials should consider patients under 75 years of age without additional cardiovascular risk factors and those with decompensated heart failure.

• The exclusion of these patients from this study limits the applicability of the results.
• Multaq® (dronedarone) has been discovered as the first safe drug to benefit patients with atrial fibrillation.

• Findings include decreased rates of cardiovascular hospitalization and mortality.
Rhythm Control: Ablation Considerations

• Highly Symptomatic
• AA Drug Failure >2 (Class I or III)
• Ideal AF Type: Paroxysmal
• LA Size < 5.0cm
• Minimal Heart Disease: LVEF >50%
• Abscess: OSA, Obesity, TIA
• Understands: Risk/Benefits/Efficacy
RF Ablation of Atrial Flutter

• Atrial flutter involves a macro-reentry circuit within the right atrium and driving the left atrium.

• Critical areas of conduction within the right atrium are necessary to sustain atrial flutter.

• RF ablation of conduction within such critical sites (most commonly the inferior vena cava-tricuspid valve isthmus) abolishes atrial flutter.

Diagram of Atrial Flutter Circuit Within Right Atrium


Inferior vena cava - tricuspid valve isthmus

HA, MA, LA, HPS, MPS, LPS
ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: Maintenance of Sinus Rhythm

• Class IIa recommendation: “Catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no LA enlargement.” (Level of Evidence: C) *

• Typically utilized after 1st line antiarrhythmic agents fail or are not tolerated, with or without LAE, paroxysmal or even persistent (symptomatic)
Expert Consensus Statement on Ablation of AF –
Indications for Catheter Ablation

- Symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication
- “In rare clinical situations, it may be appropriate to perform AF ablation as first line therapy”
- “Selected symptomatic patients with heart failure and/or reduced ejection fraction”
Development of AF requires trigger + susceptible substrate

Goal of ablation:
Eliminate triggers and/or alter substrate

PVI isolation

From AF consensus document
Atrial Fibrillation Initiated From Focal Triggers (Most Commonly Localized to Pulmonary Veins)
Intracardiac Echo to Define Anatomy

Anatomic Variability of PV Location and Number: LA Electroanatomic Map of SR Activation & MRA

Marchlinski Penn 2002

Ren et al, J of Echo 2002
Limitations: Ablation Data

- Small Sample: Single Centers
- No Standard Success Definition
- No Standard Follow-up <12 months
- Post-Ablation AAD use
- Single Procedure Success Rate
- Complications: No Standards
Atrial Fibrillation Ablation: Reality

- Efficacy Rates Vary: Learning Curve
- Optimal Success: 70% Paroxysmal
- Optimal Success: 50% Persistent
- Multiple Procedures: 20-30%
- Major Complications: 2-8%
- CABANA Trial
Permanent Pacing for Prevention of Atrial Fibrillation

- Evidence that AAI pacing is associated with less atrial fibrillation than VVI pacing.¹
- Chronic dual-site right atrial pacing may also prevent recurrent atrial fibrillation.²

¹ Andersen HR. Lancet. 1994;344:1523-1528.
Prevention of Recurrent Atrial Fibrillation with Chronic Dual-Site Right Atrial Pacing

Patient Selection Criteria

- Symptomatic drug-refractory atrial fibrillation
- 2 or more episodes of sustained atrial fibrillation before device insertion
- Coexisting bradyarrhythmia in absence or presence of drug therapy and requiring rate support

Saksena S. J Am Coll Cardiol. 1996;28(3);687-694.
Mean Arrhythmia-Free Intervals

- Saksena S. J Am Coll Cardiol. 1996;28(3);687-694.

Days

- Preimplantation period
- Dual-site pacing
- High right atrial pacing

P = 0.10

Days:
0 20 40 60 80 100 120

Intervals:
14 76 89

P < 0.001
AF Classification and Progression

**Paroxysmal**
- Intermittent periods of AF that terminate spontaneously
- Between episodes, predominant baseline rhythm is sinus rhythm

**Persistent**
- Rhythm disturbance does not resolve spontaneously
- Requires an intervention (e.g. electrical cardioversion) to be converted back to sinus rhythm

**Permanent**
- Longstanding and resistant to cardioversion

**Recurrent***
- Two or more paroxysmal or persistent episodes

*Termination with pharmacologic therapy or direct-current cardioversion does not change the designation.

Summary Points

• AF is a progressive disease\(^1\)
• AF worsens the prognosis of patients with CV comorbidities\(^1\)
• AF is a driver of CV hospitalizations\(^1,2\)
• AF is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality\(^3\)
  - Mortality rate of patients with AF is approximately double that of those in sinus rhythm\(^1\)