OUTPATIENT MANAGEMENT OF ATRIAL FIBRILLATION: CURRENT GUIDELINES

Douglas Kopp, MD
April 30, 2010
Faculty Disclosure Declaration
Douglas E. Kopp

- I was a co-investigator at UW for the ATHENA trial, sponsored by Sanofi-Aventis.
- I have no financial relationships (>12 mo).
- I will be discussing off-label use and investigational drugs.
ACC/AHA/ESC Practice Guidelines

ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation)

Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society

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OUTLINE

• Scope of the problem
• Definitions
• Triggers/mechanisms of AF
• Treatment strategies
  – Anticoagulation
  – Rate control
  – Rhythm control
• Landmark studies
  – RE-LY
  – AFFIRM
  – ATHENA
• Treatment algorithm
ATRIAL FIBRILLATION

• AF is the most common sustained cardiac rhythm disturbance, increasing in prevalence as the population ages
  – > 80% of individuals with AF are ≥ 65 years old
  – At present, just > 50% of individuals with AF are ≥ 75
  – Soon, 50% of individuals with AF will be ≥ 80
  – Old projections of prevalence of 5.6 million could rise to as many as 16 million Americans by 2050
• Lifetime incidence of AF: 1 in 4 individuals > 40 y.o.
• Hemodynamic impairment and thromboembolic events result in significant morbidity, mortality, and cost.

DEFINITIONS

• **Paroxysmal** = self-terminating
• **Persistent** = not self-terminating
• **Longstanding persistent**
• **Permanent or chronic** = remains in AF despite attempts at rhythm control
• **Lone AF** = absence of structural heart disease
TRIGGERS OF AF

BRADYCARDIA

ISCHEMIA

PSVT

PULMONARY VEIN FOCI

AUTONOMIC STIMULATION

ACUTE ATRIAL STRETCH

SLEEP APNEA

PACs

CARDIAC SURGERY

ATRIAL FLUTTER
AF TREATMENT STRATEGIES

• Anticoagulation is paramount to prevent stroke

• Rate control – use AV nodal blockers to keep HR between 60-80 BPM at rest, and between 90-115 BPM with moderate exercise. AV junctional ablation is the ultimate form of rate control, but should be used only as a last resort (ablate and pace).

• Rhythm control – use electrical CV and AA drugs to achieve NSR and maintain it. AF ablation is currently reserved for drug refractory cases.
Risk Factors for Stroke in AF
CHADS$_2$ Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Prior Stroke or TIA</td>
<td>2</td>
</tr>
</tbody>
</table>

Gage et al JAMA 2001;285:2864-70
# AHA/ACC/ESC 2006 Guidelines
## Risk Based Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Less Validated or Weaker Risk Factors</th>
<th>Moderate Risk Factors</th>
<th>High Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>Age &gt; 75 years</td>
<td>Prior CVA, TIA, or Embolism</td>
</tr>
<tr>
<td>Age 65 to 74 years</td>
<td>HTN</td>
<td>Mitral Stenosis</td>
</tr>
<tr>
<td>CAD</td>
<td>Heart Failure</td>
<td>Mechanical Heart Valve</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>LVEF ≤ 35%</td>
<td>HOCM</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fuster et al. JACC 2006;48:854-906
## AHA/ACC/ESC 2006 Guidelines
### Risk Based Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Risk Factors</td>
<td>Aspirin 81-325 mg/d</td>
</tr>
<tr>
<td>One Moderate Risk Factor</td>
<td>Aspirin 81-325 mg/d or Warfarin (INR 2-3)</td>
</tr>
<tr>
<td>Any High or More than 1 Moderate Risk Factor</td>
<td>Warfarin (INR 2-3)</td>
</tr>
</tbody>
</table>

Fuster et al. JACC 2006;48:854-906
DABIGATRAN

• prodrug, direct thrombin inhibitor
• Half-life is 12-17 hours
• Twice daily oral dosing
• Does not require regular monitoring
• Clearance is 80% renal, 20% hepatic
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*
RE-LY

• Randomized Evaluation of Long-Term Anticoagulation Therapy
• Dabigatran (2 doses) vs warfarin in > 18,000 patients with nonvalvular AF and risk for stroke (largest stroke trial to date)
• Noninferiority trial
• Primary endpoint was stroke or systemic embolism
• Average follow-up was 2 years

## RE-LY RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>1.69%</td>
<td>1.53% p&lt;0.001</td>
<td>1.11% p&lt;0.001</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>3.36%</td>
<td>2.71% p=0.003</td>
<td>3.11% p=0.31</td>
</tr>
<tr>
<td><strong>Hemorrhagic Stroke</strong></td>
<td>0.38%</td>
<td>0.12% p&lt;0.001</td>
<td>0.10% p&lt;0.001</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>4.13%</td>
<td>3.75% P=0.13</td>
<td>3.64% P=0.051</td>
</tr>
</tbody>
</table>
RE-LY
Dabigatran vs Warfarin in AF

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Major Trials Comparing Rhythm Control vs Rate Control Strategies

• **AFFIRM**  The AFFIRM Investigators. NEJM 2002;347:1825-1833
• **RACE**  Van Gelder IC, et al. NEJM 2002;347:1834-1840
• **AF-CHF**  Roy D et al. NEJM 2008;358:2667-2677

• Major overall findings
  – Rhythm-control strategy was not superior to rate-control strategy in terms of outcome (morbidity/mortality)
  – Appropriate choice of therapy should be based on each patient’s symptoms and disease
AFFIRM TRIAL

- **Atrial Fibrillation Follow-up Investigation of Rhythm Management**

- Largest AF trial at its time, the first to use mortality as the primary endpoint

- >4000 patients over age 65, or < 65 with at least one risk factor for stroke

- Recurrent AF > 6 hrs duration, able to take warfarin, in need of long term treatment, and eligible for both rate or rhythm control strategies

The AFFIRM Investigators. NEJM 2002;347:1825-1833
AFFIRM

Selected Patient Characteristics

• Age = 69.7 ± 9.0 years
• 39% female; 11% minority
• Primary diagnosis
  – HTN: 51% (prevalence = 71%)
  – CAD: 26% (prevalence = 38%)
• > 2 days of AF in 69%
• First episode in 36%
• Only 6% of patients had asx AF
• LAE in 61%
• LVF abnormal in 24%; FC ≥ II in 9%

AFFIRM Investigators. NEJM 2002;347:1825-1833
Figure 1. Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.

Time zero is the day of randomization. Data have been truncated at five years.
AFFIRM SUMMARY AND CONCLUSIONS

In patients with AF and ≥ 1 risk factor for stroke randomized to a rhythm or rate control strategy:

- The putative advantages of rhythm control over rate control (improved survival, lower risk of stroke, improved exercise tolerance, ability to stop anticoagulation, improved quality of life) were not realized in the AFFIRM patient population.
- Rate control is an acceptable primary therapeutic option for patients with AF who are at risk for stroke.
- AFFIRM data suggest that patients with AF and risk factors for stroke should receive anticoagulation indefinitely, even when sinus rhythm appears to be restored and maintained.
What is Good Rate Control?

**AFFIRM**

- Rest: $\leq 80$ BPM
- Exercise:
  - 6-minute walk test: $\leq 110$ BPM
  - 24 hour Holter:
    - Average $< 100$ BPM
    - Maximum $< 110\%$ max predicted

**RACE**

- Rest: $< 100$ BPM
- Exercise: no assessment
Pharmacological Management of AF

• Sodium Channel Blockers
  – Flecainide
  – Propafenone

• Potassium Channel Blockers
  – Sotalol
  – Dofetilide
  – Ibutilide (IV only)

• Mixed Ion Channel Blockers
  – Amiodarone
  – Dronedarone

• Atrial-Selective Potassium Channel Blockers
  – $I_{Kur}$ blockers such as Vernakalant (IV only)
INITIATION OF ANTIARRHYTHMIC DRUG THERAPY

<table>
<thead>
<tr>
<th>OUTPATIENT</th>
<th>INPATIENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>Sotalol</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Dofetilide</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Ibutilide (IV only)</td>
</tr>
<tr>
<td>Amiodarone (low dose oral)</td>
<td>Amiodarone (IV or high dose oral)</td>
</tr>
</tbody>
</table>
Figure 9. 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. See Section 8.3.3.3 in the full-text guidelines for details. LVH indicates left ventricular hypertrophy.
What Is the Measure of Successful Treatment of AF?

As with heart failure or angina, success in managing AF is defined as a decrease in:

- Recurrence of AF does not equate to drug failure
- Thus, antiarrhythmic drug efficacy is not measured simply by time to first recurrence of AF
- Occasional recurrence of AF may be acceptable therapy

Waldo AL. AJC 1999;84:698-700. Prystowsky EN. JCE 2006;17
## What is Good Rhythm Control?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Assessment</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AF</td>
<td>Outstanding</td>
<td>Continue drug</td>
</tr>
<tr>
<td>Marked ↓ in AF frequency/duration</td>
<td>Excellent</td>
<td>Continue drug</td>
</tr>
<tr>
<td>Modest ↓ in AF frequency/duration</td>
<td>Good/fair</td>
<td>Consider drug change</td>
</tr>
<tr>
<td>No change</td>
<td>Poor</td>
<td>Change either drug or strategy</td>
</tr>
</tbody>
</table>
DRONEDARONE
DRONEDARONE

- A newly FDA approved type III antiarrhythmic drug, analog of amiodarone minus the iodine moiety
- Fewer side effects than amiodarone
- Only available orally; dose is 400 mg bid given with food, no dose titration
- May be started in the outpatient setting
- Low risk of torsades de pointes
Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation

Stefan H. Hohnloser, M.D., Harry J.G.M. Crijns, M.D., Martin van Eickels, M.D., Christophe Gaudin, M.D., Richard L. Page, M.D., Christian Torp-Pedersen, M.D., and Stuart J. Connolly, M.D., for the ATHENA Investigators*
ATHENA

A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter

Hohnloser SH. NEJM 2009;360:668-78
ATHENA

- Patients with paroxysmal or persistent AF or flutter and at least one risk factor for stroke were randomized to dronedarone 400 mg twice a day or placebo
- Primary outcome was CV hospitalization or death
- Secondary outcomes were death from any cause; death from CV causes; and CV hospitalization

Hohnloser SH. NEJM 2009;360:668-78
ATHENA

N = 4,628

Dronedarone = 2,301
Placebo = 2,327

42% were ≥ 75 years of age

Hohnloser SH. NEJM 2009;360:668-78
ATHENA

• Compared to placebo, patients receiving dronedarone had:
  – A 24% decrease in CV hospitalizations or death over a 21 month follow-up (p = 0.00000001)
  – A 29% decrease in the risk of death from CV causes (p = 0.03), primarily due to a 45% decrease in arrhythmic death (p = 0.01); overall mortality was similar in both arms (p = 0.17)
  – A 37% decrease in hospitalization for AF (p < 0.001), and a 30% decrease in ACS (p = 0.03)
  – A similar rate of adverse effects

Hohnloser SH. NEJM 2009;360:668-78
### EFFECT OF DRONEDARONE ON CARDIOVASCULAR EVENTS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (N=4268)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yr</td>
<td>942/2703</td>
<td>0.76 (0.67–0.87)</td>
<td>0.93</td>
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<tr>
<td>≥75 yr</td>
<td>709/1925</td>
<td>0.75 (0.65–0.87)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>Male</td>
<td>850/2459</td>
<td>0.74 (0.64–0.85)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>801/2169</td>
<td>0.77 (0.67–0.89)</td>
<td></td>
</tr>
<tr>
<td>Presence of atrial fibrillation or flutter</td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Yes</td>
<td>396/1155</td>
<td>0.74 (0.61–0.91)</td>
<td></td>
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<tr>
<td>No</td>
<td>1255/3473</td>
<td>0.76 (0.68–0.85)</td>
<td></td>
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<td>Structural heart disease</td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Yes</td>
<td>1115/2732</td>
<td>0.76 (0.67–0.85)</td>
<td></td>
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<tr>
<td>No</td>
<td>524/1853</td>
<td>0.77 (0.65–0.92)</td>
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<tr>
<td>Any congestive heart failure</td>
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<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Yes</td>
<td>603/1365</td>
<td>0.75 (0.64–0.88)</td>
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<tr>
<td>No</td>
<td>1048/3263</td>
<td>0.76 (0.68–0.86)</td>
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<td>LVEF</td>
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<td></td>
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<tr>
<td>&lt;35%</td>
<td>86/179</td>
<td>0.68 (0.44–1.03)</td>
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</tr>
<tr>
<td>35 to &lt;45%</td>
<td>145/361</td>
<td>0.66 (0.47–0.92)</td>
<td></td>
</tr>
<tr>
<td>≥45%</td>
<td>1387/4004</td>
<td>0.78 (0.70–0.86)</td>
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<tr>
<td>Use of ACE or ARB</td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Yes</td>
<td>1175/3216</td>
<td>0.74 (0.66–0.83)</td>
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<tr>
<td>No</td>
<td>476/1412</td>
<td>0.79 (0.66–0.95)</td>
<td></td>
</tr>
<tr>
<td>Use of beta-blocker</td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>Yes</td>
<td>1226/3269</td>
<td>0.78 (0.69–0.87)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>425/1359</td>
<td>0.71 (0.58–0.86)</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 3](image150x36.png)

**Figure 3.** Hazard Ratios for the Primary Outcome, According to Selected Baseline Characteristics.

Complete data for structural heart disease were available for 4585 of the 4628 study patients, and data for left ventricular ejection fraction (LVEF) for 4544. P values are given for the interaction between baseline characteristics and study group, calculated with the use of Cox regression analysis. The x axis is shown on a log_{10} scale. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.
Analysis of Stroke in ATHENA: A Placebo-Controlled, Double-Blind, Parallel-Arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter

Stuart J. Connolly, MD; Harry J.G.M. Crijns, MD; Christian Torp-Pedersen, MD; Martin van Eickels, MD; Christophe Gaudin, MD; Richard L. Page, MD; Stefan H. Hohnloser, MD; for the ATHENA Investigators

Circulation 2009;120:1174-80.
Figure 2. Cumulative risk of stroke (A) and composite outcome of stroke, acute coronary syndrome, or cardiovascular death (B). HR indicates hazard ratio.
DIONYSOS

Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation

• Dosing:
  – Dronedarone 400 mg bid
  – Amiodarone 600 mg daily for 28 days, then 200 mg daily

• Primary composite endpoint = AF recurrence or premature drug discontinuation
DIONYSIS

AF Recurrence

Droned: 63%
Amio: 42%
P < 0.001

Drug Discontinuation

Droned: 10.4%
Amio: 13.3%
P = NS
# Dronedarone Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Dose</th>
<th>Population Studied</th>
<th>Mean Follow-Up</th>
<th>Primary Efficacy End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAFNE (n = 142)</td>
<td>Dronedarone 400 to 800 mg bid vs. placebo</td>
<td>Nonpermanent AF/AFL (low risk)</td>
<td>6 months</td>
<td>Time to recurrence of AF/AFL</td>
</tr>
<tr>
<td>EURIDIS (n = 612)</td>
<td>Dronedarone 400 mg bid vs. placebo</td>
<td>Nonpermanent AF/AFL (low risk)</td>
<td>12 months</td>
<td>Time to recurrence of AF/AFL</td>
</tr>
<tr>
<td>ADONIS (n = 625)</td>
<td>Dronedarone 400 mg bid vs. placebo</td>
<td>Nonpermanent AF/AFL (low risk)</td>
<td>12 months</td>
<td>Time to recurrence of AF/AFL</td>
</tr>
<tr>
<td>ERATO (n = 174)</td>
<td>Dronedarone 400 mg bid vs. placebo</td>
<td>Permanent AF (low risk)</td>
<td>6 months</td>
<td>Rate control</td>
</tr>
<tr>
<td>ANDROMEDA (n = 627)</td>
<td>Dronedarone 400 mg bid vs. placebo</td>
<td>Worsening CHF (high risk)</td>
<td>13 months</td>
<td>ACM or CHF hospitalization</td>
</tr>
<tr>
<td>ATHENA (n = 4,628)</td>
<td>Dronedarone 400 mg bid vs. placebo</td>
<td>Stable (low to moderate risk)</td>
<td>21 months</td>
<td>ACM or CV hospitalization</td>
</tr>
<tr>
<td>DIONYSOS (n = 504)</td>
<td>Dronedarone 400 mg bid vs. amiodarone 200 mg</td>
<td>Nonpermanent AF/AFL</td>
<td>6 months</td>
<td>Recurrence of AF/AFL or discontinuation due to intolerance</td>
</tr>
</tbody>
</table>

ACM = all-cause mortality; ADONIS = American-Australian Trial With Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm; AF = atrial fibrillation; AFL = atrial flutter; ANDROMEDA = Antiarrhythmic Trial With Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease; ATHENA = A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter; bid = twice a day; CHF = congestive heart failure; CV = cardiovascular; DAFNE = Dronedarone Atrial Fibrillation Study After Electrical Cardioversion; DIONYSOS = Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation; ERATO = Efficacy and Safety of Dronedarone for the Control of Ventricular Rate During Atrial Fibrillation; EURIDIS = European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Dronedarone</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>p Value</th>
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<tbody>
<tr>
<td>DAFNE*</td>
<td>60</td>
<td>5.32</td>
<td>0.45 (0.28-0.72)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>35/54 (65%)</td>
<td>43/48 (90%)</td>
<td>0.72 (0.58-0.90)</td>
<td>0.004</td>
</tr>
<tr>
<td>EURIDIS</td>
<td>96</td>
<td>41</td>
<td>0.78 (0.64-0.96)</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>150/411 (37%)</td>
<td>95/201 (47%)</td>
<td>0.77 (0.64-0.94)</td>
<td>0.009</td>
</tr>
<tr>
<td>ADONIS</td>
<td>158</td>
<td>59</td>
<td>0.73 (0.59-0.89)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>154/417 (37%)</td>
<td>89/208 (43%)</td>
<td>0.86 (0.71-1.06)</td>
<td>0.151</td>
</tr>
<tr>
<td>ATHENA</td>
<td>498</td>
<td>737</td>
<td>0.75 (0.65-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>779/1,732 (45%)</td>
<td>950/1,741 (55%)</td>
<td>0.75 (0.68-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DIONYSOS</td>
<td>158/249 (63%)</td>
<td>107/255 (42%)</td>
<td>1.51 (1.27-1.80)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Dronedarone dose 400 mg twice a day; time to recurrence is shown in median days. The control arm in all trials was placebo except for the DIONYSOS study, where dronedarone was compared with amiodarone.

Abbreviations as in Table 1.
Increased Mortality after Dronedarone Therapy for Severe Heart Failure

Lars Køber, M.D., Christian Torp-Pedersen, M.D., John J.V. McMurray, M.D., Ole Gøtzsche, M.D., Samuel Lévy, M.D., Harry Crijns, M.D., Jan Amlie, M.D., and Jan Carlsen, M.D., for the Dronedarone Study Group*
Figure 1. Kaplan–Meier Cumulative Incidence of All-Cause Mortality or Hospitalization for Worsening Heart Failure.

Panel A shows the Kaplan–Meier cumulative incidence of all-cause mortality or hospitalization for worsening heart failure among patients in the dronedarone and placebo groups. Panel B shows the Kaplan–Meier cumulative incidence of all-cause mortality among patients in the dronedarone and placebo groups.
Box Warning

Contraindications

WARNING: HEART FAILURE

Dronedarone is contraindicated in patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.
Important Safety Information

• As with amio, serum Cr increases by about 10% on dronedarone, but this does not represent a ↓ in GFR
• Modest increase in QT interval (average of 10 ms), but torsades rare
• Increased digoxin levels, but less than amio
• Minimal interaction with warfarin
• Treatment with Class I or Class III antiarrhythmics or drugs that are strong inhibitors of CYP3A must be stopped before starting dronedarone
• Avoid grapefruit juice
Figure 1 | Proposed treatment algorithm for the use of dronedarone in the therapy of patients with atrial fibrillation. Abbreviation: LVH, left ventricular hypertrophy. Modified from Fuster, V. et al. J. Am. Coll. Cardiol. 48, e149–e246 (2006).

Problems with Drug Treatment of AF

- Poor long-term efficacy
  - Recurrences likely in absence of reversible cause
  - Total prevention with AADs is unlikely
  - Palliative, not curative

- Adverse effects often require discontinuation
  - Nuisance subjective adverse effects
  - End-organ toxicity
  - Proarrhythmia and increased risk of death
  - Increased mortality with structural heart disease, esp. HF

- Decreased quality of life

- Long-term risks of anticoagulation
IDEALIDE: for AF Suppression

• Greater than 95% efficacy
• Safe in all patients, including those with SHD
  – Atrial selective
  – No proarrhythmia or organ toxicity
  – No drug, food, or device interactions
• Parenteral preparation available
• Once daily dosing
• Outpatient initiation
• Moderate price

Waldo, Albert L.
CASE 1

• 53 y.o. man with history of HTN, sleep apnea, AF treated with flecainide and warfarin who returns to the clinic for follow-up.

• 12 lead ECG in clinic on 1/8/08 is shown.
53 yrs - Male

PR: 172  *Atrial flutter, rate 200 with 2:1 AV conduction
QRS: 92  (ST/TN): Inferior ST-T abnormalities
QT: 446  *Flutter rate is slowed due to flecainide
QTc: 446  (NUAFL): Appearance of atrial flutter since the previous record

-ABNORMAL ECG-

AFIB, FLUTTER

PREVIOUS ECG: 14 AUG 2007 8:37:23, CONFIRMED BY MKN - BO

DOUGLAS KOPP, M.D. - 10 JAN 2008 8:54:44

UWHC EAST CARDIOVASCULAR - CPD/CVM

Requested by
DR. KOPP
Tech BJS

Edited C-HF708
ATRIAL FLUTTER

• Typical form is a macroreentrant circuit in the right atrium
• Rate control is often difficult to achieve
• Thromboembolism is a concern
• No therapeutic role for adenosine, but may unmask flutter waves
TYPICAL ATRIAL FLUTTER

• Counterclockwise rotation around TV annulus (as viewed from RV) has a “sawtooth” appearance with negative flutter waves in inferior leads
• Clockwise rotation has positive flutter waves in inferior leads
• Both utilize the cavotricuspid isthmus (between TVA and IVC) which is the vulnerable portion of the circuit
ACUTE TREATMENT OF AFL WITH IBUTILIDE

- Type III drug useful for chemical CV of recent onset atrial flutter, and as a pretreatment to aid in CV of AF
- Dose is 1 mg IV over 10 minutes, may repeat dose if persistent flutter 10 minutes after first dose is in
- Adverse effects: QT prolongation, torsades de pointes in 4.3%
- Need continuous ECG monitoring for 4 hours
- Do not give if hypokalemic or hypomagnesemic
CHRONIC TREATMENT OF TYPICAL ATRIAL FLUTTER

- Type Ia, Ic, and III drugs can suppress
- Electrical CV at low energies is effective – must be anticoagulated
- Catheter ablation is curative for typical (counterclockwise and clockwise) forms
Figure 4. Right anterior oblique (panel A, top) and left anterior oblique (panel B, bottom) fluoroscopic projections showing the intracardiac positions of the right ventricular (RV), His bundle (HIS), coronary sinus (CS), Halo (HALO), and mapping/ablation catheter (RF). Note that the Halo catheter is positioned around the tricuspid valve annulus, with the proximal electrode pair (HALOP) at 1 o'clock and the distal electrode pair (HALOD) at 7 o'clock. The mapping/ablation catheter is positioned in the SE isthmus, midway between the interatrial septum and low lateral right atrium, with the distal ablation electrode near the tricuspid valve annulus.
Can Common-Type Atrial Flutter Be a Sign of an Arrhythmogenic Substrate in Paroxysmal Atrial Fibrillation?

Clinical and Ablative Consequences in Patients With Coexistent Paroxysmal Atrial Fibrillation/Atrial Flutter

Wendel Moreira, MD; Carl Timmermans, MD, PhD; Hein J.J. Wellens, MD, PhD; Yuka Mizusawa, MD; Suzanne Philippens, RN; David Perez, MD; Luz-Maria Rodriguez, MD, PhD

Background—The coexistence of atrial fibrillation (AF) and atrial flutter (AFL) is well recognized. AF precedes the onset of AFL in almost all instances. We evaluated the effect of 2 ablation strategies in patients with paroxysmal AF (PAF) and AFL.

Methods and Results—Ninety-eight patients with PAF/AFL were prospectively recruited to undergo pulmonary vein cryoisolation (PVI). Those with at least 1 episode of sustained common-type AFL were assigned to cavitricuspid isthmus cryoablation followed by a 6-week monitoring period and a subsequent PVI (n=36; group I). Patients with PAF only underwent PVI (n=62; group II). The study included 76 men with a mean age of 50±10 years. Most patients (76 [78%]) had no structural heart disease. When the 2 groups were compared, residual AF after a blanking period of 3 months after PVI occurred in 24 patients (67%) in group I versus 7 (11%) in group II (P<0.05).

Conclusions—In patients with PAF and no documented common-type AFL, PVI alone prevented the occurrence of AF in 82%, whereas in patients with AFL/PAF, cavitricuspid isthmus cryoablation and PVI were used successfully to treat sustained common-type AFL but appeared to be insufficient to prevent recurrences of AF. In this population, AFL can be a sign that non–pulmonary vein triggers are the culprit behind AF or that sufficient electrical remodeling has already occurred in both atria, and thus a strategy that includes substrate modification may be required. (Circulation. 2007;116:2786-2792.)

Key Words: atrial fibrillation ■ atrial flutter ■ electrophysiology ■ pulmonary veins ■ catheter ablation
CASE 2

• 50 year old right handed male farmer with a history of AF who presented with acute onset of left sided weakness on 4/16/10.

• He fell after getting out of his car and was unable to move his left arm or leg at all. Using his right hand, he got his cell phone and phoned a friend who took him to the ER. Initial CT showed no bleed.
CASE 2

• MRA later that day showed an acute infarct in the right subcortex with an occluded proximal right MCA. He was transferred to UW to the Stroke Service.

• Initially, he described his left leg strength was back to baseline, but his left arm was still weak.

• Other than AF, no cardiac history.
MEDICATIONS

• Home medications:
  – Aspirin 81 mg daily
  – Metoprolol

• He stated that he was on Warfarin in the past, but was taken off of it. He does not recall the reason why.
PHYSICAL EXAM

• BP 156/93, HR 113 BPM, irregular
• Awake and alert
• No carotid bruits. JVP increased.
• No pulmonary congestion.
• Murmur of MR present.
• Dysarthric speech, left lower facial weakness
• Mild weakness LUE, decreased sensation
• Plantar reflexes: upgoing left, downgoing right
LABS

- Hgb 14.7
- Platelets 175K
- Troponin < 0.02
- Glucose 133
- Cr 0.9
- TSH 0.99
- INR 1.3
ECG
HOSPITAL COURSE

• He was felt to have a cardioembolic stroke from his AF. Initial improvement (due to presence of collaterals to the right MCA territory) and being outside the time window for t-PA led to conservative management.

• The next morning, however, he worsened with increasing lethargy and left sided weakness.

• Emergent CT showed hemorrhagic conversion requiring neurosurgical intervention with ventriculostomy, right hemicraniectomy for decompression
ECHOCARDIOGRAM

- Biatrial enlargement
- LV moderately dilated with severely reduced systolic function, LVEF 35%.
- Moderate to severe MR
- Estimated peak PAP 45 mm Hg
- TEE was obtained the following day
CASE 2 SUMMARY

• AF can sometimes go unrecognized and if ventricular rates remain elevated, a tachycardia-mediated cardiomyopathy can develop.

• We were of course unable to anticoagulate this patient due to his intracranial bleed, and use of beta blockers was limited by the need to maintain a higher BP to ensure cerebral perfusion.

• Coumadin should be continued indefinitely in patients with persistent AF, especially if structural heart disease is present.