The Current Management of Atrial Fibrillation

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Disclosures

• None
Objectives

• Outline the 2015 treatment of atrial fibrillation

• Update on the oral anticoagulation therapy

• Pros and cons of the antiarrhythmic drugs (AADs) vs. ablative strategies

Projected Number of Patients with AF by 2050

ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation.
MarketScan and Thomson Reuters Medicare Databases, 2009
Olmsted County Data, 2006 (assuming a continued increase in AF incidence)
Olmsted County Data, 2006 (assuming no further increase in AF incidence)
ATRIA Study Data, 2000
Atrial Fibrillation: Costs to the Health Care System/ALOT!!

35% of arrhythmia hospitalizations
Average hospital stay = 5 days
Mean cost of hospitalization = $18,800

*Does not include:*
Costs of outpatient cardioversions
Costs of drugs/side effects/monitoring
Costs of AF-induced strokes

Estimated US cost burden 15.7 billion / year

What Are the Goals of AF Therapy?

- Improve survival
- Reduce systemic thromboembolism
  - Stroke
- Reduce hospitalizations
- Improve symptoms
- Improve QoL
- Restore atrial function/reverse the remodeling process

QoL = quality of life.
Classification of Patterns of AF

- Acute illness-related
  - New onset–first episode
  - Recurrent
    - No recurrence
    - Paroxysmal (self-terminating)
      - Generally defined as within 7 days
    - Established
      - Persistent (requires cardioversion)*
      - Permanent (NSR is not/cannot be restored)

*Termination with pharmacologic therapy or DC cardioversion does not change the designation.

All forms can present with or without associated SHD


AF: TREATMENT OPTIONS

- Rate control
  - Pharmacologic
    - Class IA
    - Class IC
    - Class III
  - Nonpharmacologic
    - Ablates and pace

- Maintenance of SR
  - Pharmacologic
    - CCBs
    - ACE-I
    - ARBs
    - Statins
    - Fish oil
    - OSA
  - Nonpharmacologic
    - Catheter ablation
    - Pacing
    - Surgery mini-maze
    - + valve surgery

- Stroke prevention
  - Pharmacologic
    - Warfarin
    - Aspirin
    - Thrombin inhibitor
  - Nonpharmacologic
    - Removal/isolation LA appendage

CCB = calcium channel blocker; SR = sinus rhythm; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; LA = left atrial.
Incidence of AF Based on Presence or Absence of OSA

![Graph showing cumulative frequency of AF (%) over years for OSA and No OSA groups.]

Number at Risk
OSA
No OSA
844 709 569 478 387 333 273 214 173 134 110 94 70 46 29 8
2,209 1,502 1,616 1,317 1,057 848 641 502 356 256 217 195 130 94 69 28


Acute Rate Control in AF with RVR

- IV beta blocker or calcium channel blocker.
  - Caution in hypotension & CHF Patients

- *Digoxin* and *amiodarone* should be used in
  - AF with RVR in CHF patient
  - AF with RVR in patient with hypotension

AF = atrial fibrillation; i.v. = intravenous.
AF with RVR & Pre-excitation (WPW)

AF with Pre-excitation (WPW)
AF with RVR & Pre-excitation (WPW)

Avoid Beta blocker, CCB, Digoxin, adenosine
Procainamide or *amiodarone or cardioversion*

Electrical conversion recent-onset AF (< 48 hrs)

- Haemodynamic instability
  - Yes: *Synchronized Electrical Cardioversion*
  - No:
    - Yes: Structural heart disease
      - Yes: i.v. amiodarone
      - No: i.v. flecainide or i.v. propafenone i.v. ibutilide
    - No: IV flecainide and IV propafenone is not available in USA

TEE Prior to Cardioversion (> 48hr)
**Ibutilide**

- Activates slow inward Na channels
- Risk of TdP: 1.7 to 8%
- Only IV
- Dose:
  - ≥ 60 kg: 1mg over 10min
  - < 60 kg: 0.01mg/kg over 10min
  - May repeat once 10 min after 1st dose finished
- *Telemetry > 4 hr or until QTc at baseline*


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**Stroke is the most common complication**

- AF is an independent risk factor for stroke
- AF accounts for 15%
- Stroke risk unchanged regardless if the pt has a little or a lot of AF
- Stroke risk persists even in asymptomatic AF
- If maintaining sinus rhythm with medications, stroke risk still exists and is unchanged

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**Annual stroke rate (%)**

- Low risk
- Moderate risk
- High risk

- Permanent AF
- Intermittent AF
**CHADS₂ Score**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>1</td>
</tr>
<tr>
<td>DM</td>
<td>1</td>
</tr>
<tr>
<td>Stroke / TIA / TE</td>
<td>2</td>
</tr>
<tr>
<td><strong>Maximum Score</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

**Major Risks (2 pts):**
- Prior CVA / TIA
- Systemic embolism

**Non-Major Risks (1 pt):**
- CHF / LVEF ≤ 40%
- HTN
- Age ≥ 75 yo
- DM

**Stroke Risk Related to CHADS2 Score**

- **Low, ASA**
- **Moderate, ASA or Coumadin**
- **High, Coumadin**

Coumadin “forever”, even if seemingly AAD is maintaining SR.
**CHA₂DS₂-VASc Score**

<table>
<thead>
<tr>
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<th>Score</th>
</tr>
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<tbody>
<tr>
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</tr>
<tr>
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<td>2</td>
</tr>
<tr>
<td>DM</td>
<td>1</td>
</tr>
<tr>
<td>Stroke / TIA / TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>1</td>
</tr>
<tr>
<td>Age 65 - 74</td>
<td>1</td>
</tr>
<tr>
<td>Sex (ie, female)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum Score</td>
<td>9</td>
</tr>
</tbody>
</table>

Major Risks (2 pts):
- Prior CVA / TIA
- Systemic embolism
- Age ≥ 75 yo

Non-Major Risks (1 pt):
- CHF / LVEF ≤ 40%
- HTN
- DM
- Female Sex
- Age 65-74
- Vascular Disease

**Adjusted Annual Stroke Risk Using CHA₂DS₂-VASc Score n = 7329**

**Warfarin Risk/Benefit Balance**

**INR Goal 2-3**

![Diagram of Hemostasis Pathways](http://www.neurology.org/content/78/7/501/F2.expansion.html)

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Meta-analysis: 8 studies; 41,199 patient-yrs

### On warfarin

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>AC clinic patients</th>
<th>Community patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Patients (%)</em></td>
<td>48</td>
<td>53</td>
<td>47</td>
</tr>
</tbody>
</table>

### Time in therapeutic INR range

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>AC clinic patients</th>
<th>Community patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Patients (%)</em></td>
<td>55</td>
<td>63</td>
<td>51</td>
</tr>
</tbody>
</table>


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**Dabigatran**

- RE-LY: dabigatran vs. warfarin
- RELY-ABLE: dabigatran vs. warfarin (extension)
- Brand Name Pradaxa
**RE-LY: design**

Noninferiority Trial
Randomized
Blinded/unblinded
(N = 18,113*)

- Dabigatran 150 mg
twice daily
  (110 mg twice daily)
- Warfarin
  (target INR 2-3)

*N = 12,089 excluding patients taking dabigatran 110 mg

**RE-LY: stroke or systemic embolism**

![Graph showing cumulative hazard rates for dabigatran 150 mg vs. warfarin, with hazard ratios and statistical significance.]

Dabigatran 150 mg vs. Warfarin
HR 0.66 (0.53-0.82)  p < 0.001 for noninferiority

**RE-LY: major bleeding**

- 0.93 (0.81-1.07), p = 0.31
- 0.40 (0.27-0.60), p < 0.001

**Rivaroxaban**

- ROCKET-AF: rivaroxaban vs. warfarin
- Brand name Xarelto
**ROCKET-AF: design**

Noninferiority Trial
Randomized
Double-blind
Double-dummy
(N = 14 264)

Rivaroxaban 20 mg once daily
(15 mg once daily*)

Warfarin (target INR 2-3)

*CrCl 30-49 mL/min


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**ROCKET-AF: stroke or systemic embolism**

![Graph showing cumulative event rates over days since randomization for Rivaroxaban vs. Warfarin.](image)

Rivaroxaban vs. Warfarin
HR 0.79 (0.66-0.96)
p < 0.001 for noninferiority

ROCKET-AF: major bleeding

1.04 (0.90-1.20), p = 0.58
3.4 3.6

0.67 (0.47-0.93), p = 0.02

Apixaban

• AVERROES: apixaban vs. aspirin
• ARISTOTLE: apixaban vs. warfarin
• Brand name: Eliquis
**ARISTOTLE: design**

Noninferiority Trial

Randomized, Double blind Double dummy 
(N = 18,201)

- Apixaban 5 mg twice daily (2.5 mg twice daily*)
- Warfarin (target INR 2-3)

*age > 80 years, < 60 kg, SCr > 1.5 mg/dL ~ 4.7% of patients

Previous use for > 30 days ~ 57% of patients

Mean time in therapeutic range of 62.2%


**ARISTOTLE: stroke or systemic embolism**

![Graph showing event rates over time for Apixaban and Warfarin with hazard ratio](image)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>9120</td>
<td>9081</td>
</tr>
<tr>
<td>12 months</td>
<td>8726</td>
<td>8620</td>
</tr>
<tr>
<td>24 months</td>
<td>8440</td>
<td>8301</td>
</tr>
<tr>
<td>30 months</td>
<td>6051</td>
<td>5972</td>
</tr>
<tr>
<td>36 months</td>
<td>3464</td>
<td>3405</td>
</tr>
<tr>
<td>42 months</td>
<td>1754</td>
<td>1768</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.79 (95% CI, 0.66–0.95) 
P = 0.01

Apixaban vs. Warfarin HR 0.79 (0.66-0.95) p < 0.01 for noninferiority

ARISTOTLE: major bleeding


Edoxaban

• ENGAGE AF-TIMI
• Approved by FDA on 01/2015
**ENGAGE AF: design**

Noninferiority Trial

Randomized
Double-blind
Double-dummy
(N = 21,105)

- High Dose Edoxaban 60 mg daily*
- Low Dose Edoxaban 30 mg daily*
- Warfarin (target INR 2-3)

*Dose reduced by 50% if:
- CrCl 30-50 mL/min
- Weight < 60 kg
- Strong P-gp inhibitor


**ENGAGE AF: stroke or systemic embolism**

Hazard ratio and 97.5% confidence intervals

- High-dose edoxaban vs. warfarin, 0.87 (0.73–1.04); P=0.08
- Low-dose edoxaban vs. warfarin, 1.13 (0.96–1.34); P=0.10

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose edoxaban</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>7016</td>
</tr>
<tr>
<td>Warfarin</td>
<td>7013</td>
</tr>
<tr>
<td>Low-dose edoxaban</td>
<td>7034</td>
</tr>
</tbody>
</table>

**ENGAGE AF: major bleeding**

![Graph showing major bleeding and intracranial bleeding rates for Warfarin, High Dose Edoxaban, and Low Dose Edoxaban with p-values](image)


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**Edoxaban**

- Edoxaban blood levels are lower in patients with better renal function

- Reduced efficacy in non-valvular AF in patients with creatinine clearance > 95 ml/min

- Assess creatinine clearance, before initiating therapy

\[
\text{CrCL} = \frac{(140-\text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times \text{creatinine in mg/dL}}.
\]

**Early discontinuation**

Black Box Warning:
“Premature discontinuation of any anticoagulant... increases the risk of thrombotic events”

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**Summary of AF Data (vs. Warfarin)**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 150 mg (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
<th>Edoxaban (Savaysa®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke and Systemic Embolism</td>
<td>Reduced</td>
<td>Equal</td>
<td>Reduced</td>
<td>Equal</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Equal</td>
<td>Equal</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>Increased</td>
<td>Increased</td>
<td>Equal (Reduced with 30 mg)</td>
<td>Equal</td>
</tr>
</tbody>
</table>

In RE-LY, ROCKET-AF, and ENGAGE-AF, patients with CrCl < 30 mL/min were excluded.

In ARISTOTLE, patients with CrCl < 25 mL/min were excluded.
FDA-Approved NOACs Indications

<table>
<thead>
<tr>
<th>NOACs</th>
<th>Prevent Stroke and Systemic embolism in non-valvular AF</th>
<th>VTE Treatment</th>
<th>VTE Secondary Prevention</th>
<th>VTE Prevention after hip and knee replacement surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>✓ (Approved 12/2012)</td>
<td>✓ (Approved 8/2014)</td>
<td>✓ (Approved 8/2014)</td>
<td></td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>✓ (Approved 1/2015)</td>
<td>(Applied for FDA approval 1/2014)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF = atrial fibrillation
VTE = venous thromboembolism, including deep vein thrombosis, pulmonary embolism

2014 AHA guidelines Risk-Based Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>SPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke, TIA, or CHA2DS2-VASc score ≥2, oral anticoagulants are recommended. Options include:</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>1- Warfarin</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>2- Dabigatran, rivaroxaban, or apixaban</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>3- Direct thrombin or factor Xa inhibitor recommended if unable to maintain therapeutic INR</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Reevaluate the need for anticoagulation at periodic intervals (pt might develops HTN…)</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

COR: Class of recommendations
SPE: strength of the evidence
2014 AHA guidelines Risk-Based Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>SOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Warfarin</em> recommended for <em>mechanical heart valves</em></td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Direct thrombin inhibitor dabigatran <em>should not</em> be used with a <em>mechanical heart valve</em></td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Direct thrombin &amp; factor Xa inhibitor are not recommended in patients with AF and <em>end-stage CKD</em> (<em>CrCl &lt;15 mL/min</em>) or on dialysis</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Evaluate renal function <em>before initiation</em> of direct thrombin or factor Xa inhibitors, and <em>reevaluate</em> when clinically indicated and at <em>least annually</em></td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

**COR: Class of recommendations**  
**SPE: strength of the evidence**

**Exclusion for use of NOAC?**

- Concurrent use of dronedarone, carbamazepine, phenytoin, ketoconazole, itraconazole, HIV protease inhibitors, rifampin
- Oncology patients
- Morbid obesity
- Concurrent MI, ASA/Plavix (triple therapy)
- Concurrent high risk thrombosis? (lupus anticoagulant disorder)
- Past hx GI bleed – avoid dabigatran / rivaroxaban?
- Advanced age – consider apixiban?
Reversal Agents

• Andexanet Alfa is Designated as Factor Xa Inhibitor Antidote

Reversal Agents

• Idarucizumab is a humanized *antibody fragment*, or Fab *Immediate reversal* of the anticoagulant effect of *dabigatran*
AFFIRM: Primary Endpoint
All-Cause Mortality

AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management.

Number of Deaths Number (%)
Rhythm 0 80 (4) 175 (9) 257 (13) 314 (18) 352 (24)
Rate 0 78 (4) 148 (7) 210 (11) 275 (16) 306 (21)

AFFIRM Results: Additional Analysis

Covariate | HR 99% CI | P Value
---|---|---
SR | | .0001
Warfarin use | | .0001
Digoxin use | | .0007
AAD use | | .0005

The toxicity of AADs (mainly amiodarone) counterbalanced the benefits of SR

HR = hazard ratio; CI = confidence interval; LVEF = left ventricular ejection fraction.
AFFIRM: Cause-Specific Mortality

CV = cardiovascular.

Long-term Rate Control in AF

- Resting HR < 110 bpm (RACE II)
- Stircker HR < 80 bpm / <110bpm (mod exercise)
- Adequate rate control is critical to avoid tachycardia-mediated cardiomyopathy
- 24 hour Holter monitor.
**AV node ablation in AF patients**

1. Rate *can not be controlled* by medications.
2. *Intolerance* for anti-arrhythmic drugs (AAD)
3. Catheter ablation or surgical intervention *is not indicated*, failed or rejected by patients.
4. *Tachycardia induced* cardiomyopathy (1-3)
5. Pacemaker has to be *implanted first*. 

---

**AV node ablation in AF patients**

![Illustration of the AV node ablation procedure](image)
AV node ablation in AF patients

- Anticoagulation *is needed* if not contra-indicated.
- Pacemaker *regulate heart rate*

**Objective Benefits of AV nodal Ablation**

A. Left ventricular ejection fraction (%)

B. Left ventricular end systolic diameter (mm)

Rhythm Control Strategy

- Anti-arrhythmic drugs or ablation to restore SR.
- The aim is not to restore SR and discontinue anticoagulation.
- Needs anticoagulation if indicated by CHADS2 or CHA2DS2-Vasc score

Benefits of Sinus Rhythm

- Reduce symptoms and improve QoL
- Improve ejection fraction and reduce HF in patients with SHD
- Reduce LA size
- Reduce CV morbidity and mortality (may be patient- and therapy-specific)

SHD = structural heart disease.
Antiarrhythmic Classification
Vaughn Williams

Class I: fast Na+ blocker

- Class IA- Procainamide, quinidine, disopyramide
- Class IB- Lidocaine, mexillitine (ventricle)
- Class IC- Propafenone, flecainide
- Class II- Beta-blockers
- Class III (K+ blocker) sotalol and dofetilide
- Class IV- Calcium-channel blockers

Amiodarone, ibutilide and dronedarone

Rhythm Control for AF: Commonly Used Oral Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Class IA</th>
<th>Class IC</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>Propafenone</td>
<td>Sotalol</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Propafenone SR</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Flecainide</td>
<td>Dofetilide</td>
</tr>
</tbody>
</table>

Procainamide, disopyramide, and amiodarone are not FDA-approved for treatment of AF.

**AF Efficacy: Maintaining NSR > 6 Months**

Canadian Trial of AF Medications Rarely Provide Long Term Efficacy

**At 1 yr, Recurrence rate 60%**

### AF Antiarrhythmic Therapy

- Treatment goals
  - ↓ frequency of recurrences
  - ↓ duration of recurrences
  - ↓ severity of recurrences
  - Not to abolish every episode
- *Safety is primary concern*
- Minimize risk of *pro-arrhythmia*

### Factors Which Influence Ventricular Pro-arrhythmia Risk

- Hypokalemia, hypomagnesemia
- Long QT at baseline
- CHF / Decreased EF
- Ventricular hypertrophy
- Bradycardia
- Female gender
- Reduced drug metabolism or clearance
- *Amiodarone has lowest risk*
Antiarrhythmic Therapy
ORGAN TOXICITY

- Examples:
  - Lupus, agranulocytosis, thrombocytopenia, optic neuritis, pulmonary fibrosis, hepatitis, etc.

- Negligible:
  - Dofetilide, flecanide, propafenone, sotalol

- High:
  - Amiodarone, procainamide, quinidine

Sotalol- Baseline Assessment

- QT interval (EKG)
  - Contraindicated: QT >450 ms

- Avoid in:
  - Asthma/COPD
  - Overt CHF
  - Long QT syndromes
  - Severe bradycardia
  - 2nd or 3rd degree block
### Dofetilide - Drug Interactions

- **Contraindicated**
  - Cimetidine
  - *Trimethoprim (including Bactrim)*
  - Ketoconazole
  - *Verapamil*
  - Prochlorperazine
  - Megestrol
  - *HCTZ*

- **Avoid if possible Any drug that prolongs QT interval**
  - Tricyclic antidepressants
  - Phenothiazines
  - *Metformin*
  - *(fluoroquinolones, macrolides)*

### Amiodarone

- **Multiple channel blockade**
  - K, Na, Beta, Ca, Alpha
- **Effective for most arrhythmias**
- **Drawbacks: toxicity, drug interactions**
- **Comparatively more effective than other AARx**
Amiodarone- Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>↑</td>
<td>↓ Digoxin by 50%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>↑</td>
<td>↓ Warfarin by 30 to 50%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑</td>
<td>Avoid &gt;20mg/day</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>↑</td>
<td>Avoid &gt;40mg/day</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>↑</td>
<td>Check levels</td>
</tr>
</tbody>
</table>

Amiodarone Monitoring- OSU Ross Heart Hospital Antiarrhythmic Clinic Protocol

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>CXR, ECG, LFT, PFT, TFT</td>
</tr>
<tr>
<td>Q6 Months</td>
<td>ECG, LFT, TFT</td>
</tr>
<tr>
<td>Q12 Months</td>
<td>CXR, PFT</td>
</tr>
<tr>
<td>PRN</td>
<td>Ophthalmology</td>
</tr>
</tbody>
</table>

Amiodarone and Dronedarone
Less thyroid and lung toxicity

Iodine molecules were removed from the amiodarone chemical structure


Liver toxicity and the concern in CHF in patient who are taking Dronedarone?

Liver toxicity
Acute liver failure
and worsening of heart failure

were reported during post marketing Multaq therapy
Dronedarone: Labeling Changes

- 6 Label changes in 2011
  - Liver injury
  - New/worsening CHF
  - ↑ INR with warfarin
  - Reports of interstitial lung disease
  - ↑ Serum Creatinine beyond initiation
  - Updated Black Box Warning and warnings regarding use in permanent AF

Accessed 1/11/2012
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

Comorbidities to Avoid/Adjust AADs

<table>
<thead>
<tr>
<th>CAD/MI</th>
<th>CHF</th>
<th>Hepatic Failure</th>
<th>Renal Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IC</td>
<td>Class I (especially IC)</td>
<td>Class I</td>
<td>Dofetilide</td>
</tr>
<tr>
<td></td>
<td>Dronedarone</td>
<td>Amiodarone</td>
<td>Sotalol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dronedarone</td>
<td>Flecainide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disopyramide</td>
</tr>
</tbody>
</table>
Drug-Induced Proarrhythmia - Torsades

Indications for Catheter AF Ablation

- Symptomatic AF refractory or intolerant to at least 1 class I or III AAD
- Selected symptomatic patients with HF and/or reduced ejection fraction
- As an alternative to device implantation to support AAD therapy in bradycardic patients
- Presence of an LA thrombus is a contraindication to catheter ablation of AF

Beginnings of “Non Drug” Therapies for AFib

- Minneapolis Feb 1999
- Haisseguerra – Bordeaux, France
- Designed a *circular catheter* to map the pulmonary veins
- “Pulmonary Vein Isolation”
  - Atrial muscle bundles span the *transition zone* from the pulmonary veins into the atria – trigger for AFib

Focal Origin of Atrial Fibrillation
*Hassaiguerre M, NEJM, 1998*

- 94% of AF triggers from Pulmonary Veins
- “90 – 95% of all AF is initiated by PV ectopy”
- *Pulmonary vein isolation is the target of the RF ablation or cryo-ablation*
Prior to RF ablation we need

- TEE to rule out LAA thrombus
- Cardiac CT/ MRI to assess:
  - The pulmonary vein anatomy
  - Adjacent structure next to the posterior wall “the esophagus”

Atrial Fibrillation Ablation
Atrial Shell and Cardiac CT
A4 study: Catheter Ablation vs Anti-Arrhythmic drug therapy for PAF

Paroxysmal AF resistant to ≥1 AAD, n = 112

<table>
<thead>
<tr>
<th>Follow-up (days)</th>
<th>Freedom from recurrent AF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td>50</td>
<td>100.0</td>
</tr>
<tr>
<td>100</td>
<td>90.0</td>
</tr>
<tr>
<td>150</td>
<td>80.0</td>
</tr>
<tr>
<td>200</td>
<td>70.0</td>
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<tr>
<td>250</td>
<td>60.0</td>
</tr>
<tr>
<td>300</td>
<td>50.0</td>
</tr>
<tr>
<td>350</td>
<td>40.0</td>
</tr>
<tr>
<td>400</td>
<td>30.0</td>
</tr>
</tbody>
</table>

Logrank P < 0.0001

Radiofrequency Ablation

Antiarrhythmic Medications

Comparison of Antiarrhythmic Drug vs. RF Ablation in Patients With Paroxysmal AFib
Randomized Controlled Trial
D. Wilber, MD, C. Pappone, MD, F. Marchlinski, MD, A. Natale, MD, L. Macle, MD, E. Daoud, MD, H. Calkins, MD; *JAMA*, 2010

<table>
<thead>
<tr>
<th>Follow Up (mos)</th>
<th>Freedom from AFib (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td>1</td>
<td>90.0</td>
</tr>
<tr>
<td>2</td>
<td>80.0</td>
</tr>
<tr>
<td>3</td>
<td>70.0</td>
</tr>
<tr>
<td>4</td>
<td>60.0</td>
</tr>
<tr>
<td>5</td>
<td>50.0</td>
</tr>
<tr>
<td>6</td>
<td>40.0</td>
</tr>
<tr>
<td>7</td>
<td>30.0</td>
</tr>
<tr>
<td>8</td>
<td>20.0</td>
</tr>
<tr>
<td>9</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Log rank, p < 0.001

Radiofrequency Ablation, n = 106

Antiarrhythmic Medications, n = 61
Catheter Ablation vs Antiarrhythmic Drug Therapy for AF
Meta-analysis of 4 randomized clinical trials

<table>
<thead>
<tr>
<th>Source</th>
<th>AAD more effective</th>
<th>Ablation more effective</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pappone et al, 2006</td>
<td></td>
<td></td>
<td>3.86 (2.65-5.63)</td>
<td>25.5</td>
</tr>
<tr>
<td>Stabile et al, 2006</td>
<td></td>
<td></td>
<td>6.43 (2.91-14.21)</td>
<td>16.1</td>
</tr>
<tr>
<td>Wazni et al, 2005</td>
<td></td>
<td></td>
<td>4.22 (2.14-8.32)</td>
<td>12.0</td>
</tr>
<tr>
<td>Krittayaphong et al, 2003</td>
<td></td>
<td></td>
<td>2.00 (1.02-3.91)</td>
<td>14.4</td>
</tr>
<tr>
<td>Jais et al, 2008</td>
<td></td>
<td></td>
<td>2.85 (2.24-5.71)</td>
<td>14.2</td>
</tr>
<tr>
<td>Wilber et al, 2010</td>
<td></td>
<td></td>
<td>6.35 (3.1-10.2)</td>
<td>17.8</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td></td>
<td></td>
<td>4.73 (2.87-6.63)</td>
<td></td>
</tr>
</tbody>
</table>

Complications, OSU Experience

- Major complications 1.4%
  - Pericardial Effusion/Tamponade
  - Stroke
  - Vascular access complication
  - Phrenic nerve injury
- No deaths
- No inadvertent damage to the esophagus
Atrial Fibrillation: Ablation vs Drug Rx.

<table>
<thead>
<tr>
<th>Ablation</th>
<th>Drug Rx.</th>
</tr>
</thead>
<tbody>
<tr>
<td>80% success</td>
<td>50% success</td>
</tr>
<tr>
<td>PV stenosis</td>
<td>Proarrhythmia</td>
</tr>
<tr>
<td>AE fistula</td>
<td>End Organ Toxicity</td>
</tr>
<tr>
<td>TIA/CVA</td>
<td></td>
</tr>
<tr>
<td>PV stenosis</td>
<td></td>
</tr>
<tr>
<td>AE fistula</td>
<td></td>
</tr>
</tbody>
</table>

**Pick Your Poison**

Torsades

**Maintenance of Sinus Rhythm**

- No/Minimal Heart Disease
- Hypertension
- Coronary Artery Disease
- Heart Failure

- Dorendarone
- Flecanidine
- Propafenone
- Sotalol
- Amiodarone
- Dofetilide
- Catheter Ablation

- Yes
  - Amiodarone
  - Catheter Ablation

- No
  - Amiodarone
  - Dofetilide
  - Catheter Ablation

- Left Ventricular Hypertrophy
- Dronadarone
- Dofetilide
- Sotalol

- Amiodarone
- Catheter Ablation

- Amiodarone
- Dofetilide
- Catheter Ablation
### Conclusion

- AF is a common disease that is increasing in prevalence.
- Decision regarding *Rate control strategy* Vs. *Rhythm control strategy* and *antithrombotic therapy* are patient specific.
- Anticoagulation is essential in AF patients with risk markers, regardless of any *restoration of SR*.
- Guidelines provide *recommendations* for the management of patients with AF.