Presentation Overview

• Review of the Basics
• The AFFIRM trial
• Stroke Prevention
• Rate Control
• Rhythm Control
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2011 Update on Definitions / Terminology

- Atrial Fibrillation Episode: > 30 seconds in duration
- Paroxysmal: < 7 days or self-terminating
- Persistent: > 7 days or req cardioversion
- Long-standing persistent: > 1 year
- Permanent: Forgone or failed efforts to maintain sinus
Normal rhythm
Atrial fibrillation
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The AFFIRM trial

• 4,060 patients randomized
• Rate control vs. rhythm control
• Endpoint = All cause mortality

No survival advantage with DC cardioversions and anti-arrhythmic drugs

AFFIRM investigators, NEJM 2002; 347(23):1825-33.
Why go beyond the AFFIRM trial?

• Rate ≠ Rhythm control for all
• Rhythm control strategies continually improving
• Special populations
  – Coronary artery disease
  – Heart failure
  – Valvular heart disease
Coronary Disease, Atrial Fibrillation and Mortality: The Framingham Heart Study

Quality of Life: Rhythm ≠ Rate control for all

• Quality of life improvements with sinus rhythm

• Post hoc analysis of AFFIRM
  – More symptomatic heart failure in the rate control group
  – Patients less symptomatic in sinus rhythm (Guglin et. al. *Heart Rhythm* 2010)

• Conflicting data from post hoc analyses of AFFIRM and other trials
Heart Failure

• Improvement in symptoms, LV systolic function, and chamber dimensions after catheter ablation
  — Hsu et. al. *NEJM* 2004

• No reduction in all-cause mortality with routine rhythm control strategy
  — Roy et. al. *NEJM* 2008
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Stroke Prevention: Beyond the AFFIRM trial

• Improvements in Risk Stratification
  – CHA$_2$DS$_2$-VASc scoring system

• Novel anticoagulants
  – Dabigatran (Pradaxa)
  – Rivaroxaban (Xarelto)
  – Apixaban (Eloquis)
Estimating the Risk of Stroke

CHADS$_2$ Score:

- +1 Heart failure
- +1 High blood pressure
- +1 Age $\geq$ 75 years old
- +1 Diabetes
- +2 Prior stroke or mini-stroke (TIA)

Table 2. Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by CHADS$_2$ Score*

<table>
<thead>
<tr>
<th>CHADS$_2$ Score</th>
<th>No. of Patients (n = 1733)</th>
<th>No. of Strokes (n = 94)</th>
<th>NRAF Crude Stroke Rate per 100 Patient-Years</th>
<th>NRAF Adjusted Stroke Rate, (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>2</td>
<td>1.2</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>17</td>
<td>2.8</td>
<td>2.8 (2.0-3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>23</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>25</td>
<td>6.4</td>
<td>5.9 (4.6-7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>19</td>
<td>8.0</td>
<td>8.5 (6.3-11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>6</td>
<td>7.7</td>
<td>12.5 (8.2-17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>2</td>
<td>44.0</td>
<td>18.2 (10.5-27.4)</td>
</tr>
</tbody>
</table>

*CHADS$_2$ score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. CI indicates confidence interval.
†The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.

- AF strokes twice as likely fatal than non-AF strokes
- AF-related stroke recurrence double that of non-AF strokes

Gage, et. al. JAMA 2001; 285:2864-2870
Miller, et. al. Stroke 2005; 36:360-366

Cleveland Clinic
CHA$_2$DS$_2$-VASc

+1 Heart failure  +1 Diabetes  
+1 Hypertension  +2 Stroke / TIA  
+2 Age $\geq$ 75 yrs  +1 Vascular dz.  
+1 Age 65-74 yrs  +1 Female gender

Table 6—Stroke or Other TE at 1 Year Based on the 2009 Birmingham (CHA$_2$DS$_2$-VASc) Scoring System

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc Score</th>
<th>No.</th>
<th>Number of TE Events</th>
<th>TE Rate During 1 y (95% CI)</th>
<th>TE Rate During 1 y, Adjusted for Aspirin Prescription, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>103</td>
<td>0</td>
<td>0% (0-0)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>162</td>
<td>1</td>
<td>6.6% (0.0-3.4)</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>164</td>
<td>3</td>
<td>1.6% (0.3-4.7)</td>
<td>1.9</td>
</tr>
<tr>
<td>3</td>
<td>203</td>
<td>5</td>
<td>3.9% (1.7-7.6)</td>
<td>4.7</td>
</tr>
<tr>
<td>4</td>
<td>206</td>
<td>4</td>
<td>1.9% (0.5-4.9)</td>
<td>2.3</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
<td>3</td>
<td>3.2% (0.7-9.0)</td>
<td>3.9</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>2</td>
<td>3.6% (0.4-12.3)</td>
<td>4.5</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>2</td>
<td>5.0% (1.0-36.0)</td>
<td>10.1</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>1</td>
<td>11.1% (0.3-48.3)</td>
<td>14.2</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>1</td>
<td>100% (25-100)</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>1,054</td>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$P$ Value for trend 0.003

Lip, et. al. Chest 2010; 137(2):263-72
Chao, et. al. JACC 2011; 59(23): 2380-5
**Warfarin (Coumadin)**

- Antagonist for Vitamin K dependent clotting factors
- **Pros**
  - Established safety profile over decades of clinical use
  - Readily reversible with Vitamin K (1mg IV, 10mg PO)
  - Quickly overcome by transfusing fresh frozen plasma
  - Cheap (1 month supply $13.99 on drugstore.com)
  - Used for both valvular and non-valvular AF
- **Cons**
  - Nuisance bleeds very common (bruising, nose bleeds, etc.)
  - Need for PT/INR monitoring (Goal INR 2-3)
  - Strict dietary consistency needed (green leafy vegetables)
  - Drug interactions (amiodarone, bactrim, azithromycin, etc.)
  - Typically 3-5 days to become therapeutic
Dabigatran (Pradaxa)

• Direct thrombin inhibitor

• Pros
  – ‘Non-inferior’ to warfarin for stroke prevention
  – Does not require PT/INR monitoring
  – Lower major bleeding (2.7%/year vs. 3.4%/year with warfarin)
  – ‘One dose for all’ 150mg twice daily (controversial concept)

• Cons
  – GI side effects and bleeding
  – No pharmacologic reversal agent available
  – Expensive (1 month supply $245.99 on drugstore.com)
  – FDA approval limited to non-valvular AF

Rivaroxaban (Xarelto)

• Direct Factor Xa inhibitor

• Pros
  – ‘Non-inferior’ to warfarin for stroke prevention
  – Once daily dosing 20mg, no monitoring required
  – Slightly lower risk of intracranial hemorrhage and fatal bleeding

• Cons
  – Very new to the market – only FDA approved November 2011
  – Expensive (~$200/month by GoodRx.com)

ROCKET AF trial. *New England Journal of Medicine* 2011; 365(10)
Apixaban (Eliquis)

• Direct Factor Xa Inhibitor

• Pros
  – Superiority to warfarin in major bleeding (2.13% vs. 3.09% per year)
  – Slight decrease in mortality at ~2 yrs (3.52% vs. 3.94%)
  – Hemorrhagic stroke lower (0.24% vs. 0.47% per year)

• Cons
  – Newest kid on the block yet; FDA approved Dec 2012
  – Twice daily dosing (5mg); Renal dose 2.5mg
  – Non-valvular AF indication
  – Expensive (no pricing info yet available on drugstore.com)

Anticoagulation Intolerant Patients

- Aspirin is better than nothing at all (81mg – 325mg)

- Aspirin / clopidigrel (plavix) is superior to aspirin alone (ACTIVE A trial)

- Warfarin is superior to aspirin / clopidigrel (plavix) combination (ACTIVE W trial)


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Rate Control: Beyond the AFFIRM trial

• In AFFIRM, goal was resting HR <80 and <110 with moderate exercise (Considered Strict rate control)

• In RACE II trial, goal resting HR <110 / min for patients with normal LV systolic function (Lenient rate control)

• Lenient rate control non-inferior and more convenient (fewer outpatient visits) EXCEPT in certain scenarios (e.g., mitral stenosis, heart failure)

B-Blockers

- Slows down AV nodal conduction
- Common side effects: Bradycardia, fatigue, depressed mood, loss of libido, erectile dysfunction, shortness of breath
- Bronchospasm in Asthma/COPD and worsening claudication for patients with PAD
Calcium channel blockers

- Slows down AV nodal conduction (NDHP)
- Common side effects: Bradycardia, constipation, fatigue, hypotension (particularly orthostatic)
- No concern for bronchospasm in COPD / emphysema
Digoxin

• Use as an adjunct to a calcium channel blocker or B-blocker
• Contraindicated as a solo agent for rate control
• Beware of renal disease and drug interactions (lots of them)
• Dose 0.125mg – 0.25mg PO daily
• Beware of those dig toxic rhythms (both fast and slow)
• Low potassium = Increased digoxin effect!
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Drugs for the Non-Electrophysiologist

- Amiodarone
- Dronedarone (Multaq)
- Sotalol (Betapace)*

* QT prolonging effect -- should be started in the hospital on monitor
Drugs used by the Electrophysiologist

- Class Ic drugs: Flecainide (Tambacor), Propafenone (Rhythmol)
- Class Ia drugs: Procainamide (IV only), Disopyramide (Norpace), Quinidine
- Class III drugs: Sotalol (Betapace), Dofetilide (Tikosyn), Ibutilide (IV use only, a pure cardioversion drug)
Choice of drug by underlying heart condition:

- No structural heart disease:
  - Flecainide, Propafenone, Sotalol, Dronedarone

- Hypertension and ‘substantial’ LVH
  - Amiodarone

- Coronary artery disease / heart failure
  - Amiodarone, dofetilide, sotalol, dronedarone (except NYHA class IV)
Exclusions / Precautions:

• Impaired Renal function
  – Sotalol, Dofetilide

• Liver dysfunction
  – Amiodarone, Flecainide (partially liver metabolized)

• QT prolonging drugs – can cause torsades
  – Sotalol, Dofetilide >> Amiodarone

• NYHA functional class IV heart failure
  – Dronedarone
Common side effects

Flecainide: Dizziness

Propafenone: Dizziness, metallic taste, bronchospasm (slow metabolizers)

Disopyramide: Urinary retention, blurred vision, constipation, ataxia, tremor, pupil dilation, increased body temp – avoid in pts with BPH, myasthenia gravis and glaucoma

Procainamide: Nausea, Lupus-like reaction, Agranulocytosis

Amiodarone: Nausea, Pulmonary fibrosis, Hepatitis, Thyroid (hyper and hypo), Photosensitivity, Ocular deposits

→ Major adverse event rate with amiodarone is 2% per year
Don’t forget about CYP and P-glycoprotein

• CYP 2C19: Metabolizes warfarin. Inhibited by amiodarone
• CYP 3A4: Metabolizes amiodarone, dofetilide, dronedarone, diltiazem, verapamil. Inhibited by grapefruit juice, ketoconazole.
• CYP 2D6: Metabolizes propafenone, metoprolol, carvedilol, flecainide. Inhibited by quinidine and SSRIs
• P-Glycoprotein: Substrates digoxin, dofetilide, verapamil, dabigatran. Inhibited by grapefruit juice, amiodarone, dronedarone, cyclosporine, verapamil and quinidine.
Pregnancy

Sotalol is the ONLY class B drug, but is excreted in breast milk.
Amiodarone

• Great short term drug; bread-and-butter for post-op AF

• Load 10 grams orally, then 200mg daily maintenance dose. My regimen is Amiodarone 400mg BID x 10 days, 400mg QD x 5 days, then 200mg daily.

• Amiodarone 150mg IV bolus, then 1mg/min x 6 hours, then 0.5mg/min x 18 hours

• Efficacy rates 60-70% at 1 year

• Prolongs QT – not a problem when by used itself – but when mixed with other QT prolonging drugs
Procedure Treatments

• Cardioversion –
  – Therapeutic anticoagulation: 3 weeks prior and 4 weeks post
  – TEE guided DC cardioversion, therapeutic anticoagulation that day

• Surgical based treatments
  – Open heart surgery / MAZE procedure
  – Mini-MAZE procedure / pulmonary vein isolation
  – Left atrial appendage removal or clipping

• Catheter ablation
  – Pulmonary vein isolation
  – AV nodal ablation plus a pacemaker
Single procedure outcomes: Cleveland Clinic

Outcomes, cont.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Age, y</th>
<th>Parox, %</th>
<th>SHD, %</th>
<th>Tool(s)</th>
<th>End Point</th>
<th>AF Free (Off Drugs), %</th>
<th>Follow-Up, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouyang et al</td>
<td>2004</td>
<td>41</td>
<td>63±9</td>
<td>100</td>
<td>NA</td>
<td>CARTO</td>
<td>PV Isolat’n</td>
<td>76*</td>
<td>178</td>
</tr>
<tr>
<td>Haissaguerre et al</td>
<td>2004</td>
<td>70</td>
<td>53±8</td>
<td>NA</td>
<td>43</td>
<td>Fluoro</td>
<td>PV Isolat’n</td>
<td>79</td>
<td>210</td>
</tr>
<tr>
<td>Mansour et al</td>
<td>2004</td>
<td>40</td>
<td>55±10</td>
<td>80</td>
<td>13</td>
<td>CARTO</td>
<td>PV Isolat’n</td>
<td>75</td>
<td>330</td>
</tr>
<tr>
<td>Marrouche et al</td>
<td>2003</td>
<td>259</td>
<td>54±11</td>
<td>51</td>
<td>21</td>
<td>ICE</td>
<td>PV Isolat’n</td>
<td>87†</td>
<td>347</td>
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<tr>
<td>Oral et al</td>
<td>2003</td>
<td>40</td>
<td>54±11</td>
<td>100</td>
<td>3</td>
<td>CARTO</td>
<td>EGM Red’n</td>
<td>88</td>
<td>365</td>
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<tr>
<td>Pappone et al</td>
<td>2003</td>
<td>589</td>
<td>65±9</td>
<td>69</td>
<td>6</td>
<td>CARTO</td>
<td>EGM Red’n</td>
<td>79</td>
<td>861</td>
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<tr>
<td>Total</td>
<td></td>
<td>1039</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>81.0</td>
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## Complications: National Data

<table>
<thead>
<tr>
<th>Event</th>
<th>Approximate Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-arrhythmia</td>
<td>5 - 25%</td>
</tr>
<tr>
<td>Thrombo-embolism</td>
<td>5 – 7%</td>
</tr>
<tr>
<td>Groin Hematoma / fistula</td>
<td>4% / 1%</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>2 – 6 %</td>
</tr>
<tr>
<td>Phrenic nerve injury</td>
<td>0.5%</td>
</tr>
<tr>
<td>Pulmonary vein stenosis</td>
<td>0.3 % (previously up to 38%)</td>
</tr>
<tr>
<td>Esophageal injury / fistula</td>
<td>0.25%</td>
</tr>
</tbody>
</table>

### Complications: Cleveland Clinic

<table>
<thead>
<tr>
<th>Event</th>
<th>Approximate Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major complications</td>
<td>2-3%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.5%</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>1%</td>
</tr>
<tr>
<td>Pulmonary vein stenosis</td>
<td>1%</td>
</tr>
<tr>
<td>Esophageal injury</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Vascular complications</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

AV nodal ablation + Biventricular Pacing: Improved Mortality Outcomes in Heart Failure

Ganesan et. al. *J Am Coll Cardiol* 2012

**Figure 2**

**Risk Ratios for All-Cause Mortality in CRT-AF Patients Undergoing AVNA versus Medical Therapy with Rate-Controlling Drugs**

All-cause mortality data were available for 3 studies, comprising 450 patients. The risk ratio for all-cause mortality was 0.42 (95% confidence interval: 0.26 to 0.68; p < 0.001), favoring patients undergoing AVNA. Abbreviations as in Figure 1.