Update on Atrial Fibrillation Management

Andrew H. Voigt, MD, FACC, FHRS
Director, Invasive Electrophysiology
UPMC Shadyside Hospital
Outline

- AF as a disorder of the elderly
- The great AF debate: rhythm vs rate control
- Who benefits from oral anticoagulation?
- Who are appropriate candidates for invasive approaches?
- What is on the horizon?
AF Prevalence and Age

Diamonds: Framingham Study
Circles: CV Health Study
Squares: Mayo Clinic
Triangles: Busselton, W. Australia

Allegheny County: Ground Zero?

- Aging population
- AF epidemic
  - Heart Failure
  - Obesity
- HTN
An Approach to AF

1) Should we do anything at all? (rate vs rhythm control)

2) How do we risk stratify our patients for stroke (and bleeding)?

3) If rhythm control pursued, what are the appropriate medical, catheter-based, and surgical options?
**AFFIRM**

**Trial Design:** AFFIRM was a multi-center randomized trial of rhythm control (n=2,033) vs rate control (n=2,027) in patients with atrial fibrillation and a high risk of stroke or death. Patients were followed for 5 years. The primary endpoint was all-cause mortality.

**Results**
- All cause mortality did not differ between the rate and rhythm control arms
- Hospitalization rate was higher in the rhythm control arm (80% vs 73%, p<0.001)

**Conclusions**
- There is no survival benefit to the strategy of rhythm control in elderly patients with atrial fibrillation

**Limitations**
- Trial enrolled high-risk elderly patients; extrapolation of results to other subgroups may not be appropriate

* Composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest

<table>
<thead>
<tr>
<th>Event</th>
<th>Overall (n=4060)</th>
<th>Rate-Control Group (n=2027)</th>
<th>Rhythm-Control Group (n=2033)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point (death)</td>
<td>666 (26.3)</td>
<td>310 (25.9)</td>
<td>356 (26.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Secondary end point (composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest)</td>
<td>861 (32.3)</td>
<td>416 (32.7)</td>
<td>445 (32.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>Torsade de pointes</td>
<td>14 (0.5)</td>
<td>2 (0.2)*</td>
<td>12 (0.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>15 (0.6)</td>
<td>9 (0.7)</td>
<td>6 (0.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>Cardiac Arrest Followed by Resuscitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation or ventricular tachycardia</td>
<td>19 (0.6)</td>
<td>10 (0.7)</td>
<td>9 (0.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>Pulseless electrical activity, bradycardia, or other rhythm</td>
<td>10 (0.3)</td>
<td>1 (&lt;0.1)</td>
<td>9 (0.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hospitalization after base line</td>
<td>2594 (76.6)</td>
<td>1220 (73.0)</td>
<td>1374 (80.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* One patient had crossed over to the rhythm-control group and was taking quinidine, and one patient had torsade de pointes 72 hours after mitral valve replacement.
<table>
<thead>
<tr>
<th>Covariate</th>
<th>P</th>
<th>HR</th>
<th>95% lower</th>
<th>95% upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>&lt;0.0001</td>
<td>0.54</td>
<td>0.42</td>
<td>0.70</td>
</tr>
<tr>
<td>Warfarin</td>
<td>&lt;0.0001</td>
<td>0.47</td>
<td>0.36</td>
<td>0.61</td>
</tr>
<tr>
<td>Digoxin</td>
<td>&lt;0.0001</td>
<td>1.50</td>
<td>1.18</td>
<td>1.89</td>
</tr>
<tr>
<td>AAD</td>
<td>0.0005</td>
<td>1.41</td>
<td>1.10</td>
<td>1.83</td>
</tr>
</tbody>
</table>

Corley SD et al.  Circulation 2004
Implications from AFFIRM

- Asymptomatic patients, particularly with age 70 or greater, can be managed with a rate control approach.
- Antiarrhythmic medications are marginally effective, and have significant toxicity.
- A “rhythm control” approach should be used selectively.
AF Rate Control: How Strict?

• Patients with permanent AF randomized to “strict” rate control (<80bpm avg) or “lenient” rate control (<110bpm avg).
• No significant difference in death, hospitalization, stroke, QOL

Van Gelder et al. NEJM 2010
Assessment of stroke risk: CHADS2 score

CHADS2 score, thromboembolic risk, and effect of warfarin in 11,526 patients with nonvalvular atrial fibrillation and no contraindications to warfarin therapy

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure (any history)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension (prior history)</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Secondary prevention in patients with a prior ischemic stroke or a transient ischemic attack; most experts also include patients with a systemic embolic event</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>Events per 100 person-years*</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin</td>
<td>No warfarin</td>
</tr>
<tr>
<td>0</td>
<td>0.25</td>
<td>0.49</td>
</tr>
<tr>
<td>1</td>
<td>0.72</td>
<td>1.52</td>
</tr>
<tr>
<td>2</td>
<td>1.27</td>
<td>2.50</td>
</tr>
<tr>
<td>3</td>
<td>2.20</td>
<td>5.27</td>
</tr>
<tr>
<td>4</td>
<td>2.35</td>
<td>6.02</td>
</tr>
<tr>
<td>5 or 6</td>
<td>4.60</td>
<td>6.88</td>
</tr>
</tbody>
</table>


CHADS2-VASc adds the Following risk factors:
- age 65-74
- female sex
- any vascular disease
Assessment of Bleeding Risk: HAS-BLED score

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Clinical Feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension (uncontrolled, SBP&gt;160)</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal/liver fxn</td>
<td>2 (one for each)</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding history</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (&gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs/alcohol</td>
<td>2 (one for each)</td>
</tr>
</tbody>
</table>

Pisters et al. CHEST November 2010
HAS-BLED Predictive Value

Roldan et al. CHEST 2013.
# Antiarrhythmic Armamentarium for AF in 2013

<table>
<thead>
<tr>
<th>Class Ic: Sodium Channel Blockers</th>
<th>Class III: Potassium Channel Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• flecainide (Tambocor)</td>
<td>• dofetilide (Tikosyn)</td>
</tr>
<tr>
<td>• propafenone (Rhythmol)</td>
<td>• sotalol (Betapace)</td>
</tr>
<tr>
<td></td>
<td>• amiodarone (Cordarone)</td>
</tr>
</tbody>
</table>

**All agents (except for amiodarone/dronedarone) are usually started in hospital on cardiac telemetry. Proarrhythmia is a major concern.**
## AAD side effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Cardiac Effects</th>
<th>Side Effects</th>
<th>Avoid In</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>Ic</td>
<td>QRS prolongation; negative inotropy</td>
<td>Dizziness, H/A, nausea</td>
<td>Structural heart disease</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Ic</td>
<td>QRS prolongation; negative inotropy</td>
<td>Unusual taste sensation, dizziness</td>
<td>Structural heart disease</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>III</td>
<td>QT prolongation</td>
<td>Generally well tolerated</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Sotalol</td>
<td>III</td>
<td>QT prolongation; bradycardia</td>
<td>fatigue</td>
<td>Bradycardia; renal insufficiency</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>III</td>
<td>Mild QT prolongation</td>
<td>Pulmonary, hepatic, thyroid, neurological</td>
<td>Bradycardia, pulmonary disease with low DLCO</td>
</tr>
</tbody>
</table>

**Other class IA and IB drugs (disopyramide, procainamide, quinidine, mexelitine) are very rarely used for AF in 2013**
Dronedarone (Multaq): A New Hope?

- Amiodarone-like structure without the notorious toxicity
- Outpatient initiation
- Modest antihypertensive effects
- Few important drug interactions
Dronedarone clinical data

• ANDROMEDA (2008)- increase in mortality in patients admitted for heart failure vs placebo
• ATHENA (2009)– decrease in combined endpoints of cardiovascular hospitalization and death vs placebo, mostly in patients >70 without HF
• FDA approval in late 2009
Dronedarone Caution

• March 2011: reports of rare cases of severe liver injury; FDA warning issued

• PALLAS (2011) – halted prematurely due to increase in cardiovascular events and death in patients with permanent AF

• Efficacy and GI tolerability questionable
Next Candidate?

- Vernakalant: “atrially selective” transient outward potassium current inhibitor
- Phase III clinical trials of oral form for paroxysmal AF ongoing
- Approved in Europe in 2010
Choosing an antiarrhythmic drug to prevent atrial fibrillation

**Minimal or no heart disease**
- Possible prevention of remodeling with ACEI/ARB/statin
- β blockade where appropriate

**Significant underlying heart disease**
- Treatment of underlying condition
- Possible prevention/reversal of remodeling with ACEI/ARB/statin
- β blockade where appropriate

**HTN**
- No LVH
  - Dronedarone/Flecainide/Propafenone/Sotalol
  - Amiodarone

- LVH
  - Amiodarone

**CAD**
- Dronedarone
  - Sotalol
  - Amiodarone

- Amiodarone

**HF**
- NYHA III/IV or "unstable" NYHA II
  - Dronedarone

Within each box, the antiarrhythmic drugs are listed alphabetically. The vertical flow represents the order of preference for each condition.

HTN: hypertension; CAD: coronary artery disease; HF: heart failure; LVH: left ventricular hypertrophy; NYHA: New York Heart Association class; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

AF Drug Summary

• “If many drugs are used for a disease, all are insufficient.” –Sir William Osler
• In 2013, antiarrhythmic drugs for AF are marginally effective and sometimes toxic
• Each patient with AF should undergo stroke and bleeding risk stratification by some measure
A Recent Paradigm Shift

- “Catheter ablation era” began in late 1990s with observation that high frequency electrical potentials from the pulmonary veins can trigger AF

Evolution of AF Ablation

• 1998-2001: Focal ablation in proximal PVs
• 2002-2005: Segmental ablation at os of PVs
• 2006-present: wide area circumferential ablation
• 2010-present: cryoballoon ablation
• Other investigational technologies
Who is the “Ideal” AF Ablation Candidate?

<table>
<thead>
<tr>
<th>Ideal Patient</th>
<th>Less Ideal Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal AF</td>
<td>Continuous AF</td>
</tr>
<tr>
<td>Severe Symptoms</td>
<td>No Symptoms</td>
</tr>
<tr>
<td>Failed Amiodarone</td>
<td>No Drugs Tried</td>
</tr>
<tr>
<td>Young</td>
<td>Elderly</td>
</tr>
<tr>
<td>Frequent atrial premature beats</td>
<td>No atrial premature beats</td>
</tr>
<tr>
<td>Small left atrium</td>
<td>Large left atrium</td>
</tr>
<tr>
<td>No structural heart disease</td>
<td>CHF / Hypertension</td>
</tr>
</tbody>
</table>

Source: Cardiosource © 2006 by the American College of Cardiology Foundation
Imaging for Atrial Fibrillation Ablation

Contrast CT at Level of LA

3D CT Reconstruction of LA with esophagus
Where do we ablate?

Right PV Vestibule

Left PV Vestibule

Lines of Ablation
Achieving PV Electrical Isolation

Green icon= RFA site where PVI achieved
Validation of PV Electrical Isolation
AF Ablation Outcomes

Complications from AF Ablations

- Death, Pericardial Effusion, Atrial-Esophageal Fistula, Pseudoaneurysm, Phrenic Nerve Block, CVA/TIA

AF Catheter Ablation Complications

- Johns Hopkins experience, 2001-2010
- 1190 AF ablation procedures
- Vascular injury (1.5%)
- Pericardial tamponade (1.1%)
- CVA (1.1%)
- No atrioesophageal fistulæ or deaths
- Independent predictors of major complications: CHADS>2 and female gender

Catheter Ablation of Atrial Fibrillation in Octogenarians: Safety and Outcomes

Journal of Cardiovascular Electrophysiology
Meta-analysis of trials evaluating circumferential pulmonary vein ablation (CPVA) vs antiarrhythmic drug therapy (ADT) for AF recurrence-free survival during follow-up

AF Ablation and Quality of Life

AF RFA: Simplified Guidelines

New Directions in Catheter Ablation: Cryoballoon Technology

- STOP-AF trial (2011)
  - Comparable results to RFA
  - Technically simpler
  - Achilles heel was risk of phrenic nerve injury (10%)
Cryoballoon at ostium of Left Superior Pulmonary Vein
Catheter ablation with the cryoballoon
Ablate/pace approach

• A reasonable palliative option when AF rates cannot be controlled pharmacologically or when such treatment is poorly tolerated (class II recommendation)

• Often improves QOL, especially in the elderly

• Up to 2/3 patients have a ventricular escape rhythm post AVN ablation
Amplatzer LA Appendage Occluder Device

TEE Pre and Post Deployment
PLAATO

Trial Design: PLAATO was a registry of patients with atrial fibrillation at high-risk for embolization and stroke treated with the PLAATO device for percutaneous left atrial appendage occlusion (n=111). Patients were followed for mean of 9.8 months. Primary endpoint was major adverse events at 30 days.

Results
• CHADS risk score for predicting stroke, averaged 2.5, which corresponds to expected annual stroke risk of stroke of 6.3%
• Mortality 5.4%
• Total cardiac tamponade in 2 patients and pericardial effusion in 2 patients
• 3 TIAs occurred in 2 patients
• Observed annual stroke rate ↓ than expected based on CHADS risk score (Figure)

Conclusions
• Among patients with atrial fibrillation at high-risk for embolization and stroke, use of PLAATO device for percutaneous left atrial appendage occlusion was feasible and was associated with a lower than expected stroke rate based on baseline stroke risk estimate
• Randomized trial need to assess efficacy of PLAATO device

J Am Coll Cardiol 2005;46:9-14
PROTECT AF Study (2009)

Patients randomized to long term warfarin vs. WATCHMAN (nitinol LA appendage occluder device)
LAA occlusion non inferior to warfarin
Tamponade a concern
PREVAIL Trial

- Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy
- Presented at ACC meeting March 2013
- Avg age 74.0 +/- 7.4 years; CHADS 2.6 +/- 1.0
- LAA occlusion device had similar outcomes w/r/t stroke, systemic embolism, and death at 18 months as compared to warfarin
- Rate of vascular/cardiac complications (mostly tamponade) 4.5% at 7 days
Conclusions

• AF management remains a serious challenge in 2013
• Its prominence as a public health problem will intensify as our population ages
• Assessment (and mitigation) of stroke risk is crucial
• More medical and interventional advances are on the horizon