Advances in the Management of Atrial Fibrillation

Overview of AF
Stroke risk and anticoagulation
Rate control
Antiarrhythmic Drug Therapy
Catheter ablation
Conclusion

Conflicts of Interests

- None to declare

Epidemiology of AF

- Most common sustained cardiac arrhythmia
- Currently affects 5.1 million Americans
- Prevalence expected to increase to 12.1 million by 2050 (15.9 million if increase in incidence continues)
- Preferentially affects men and the elderly
- Lifetime risk of developing AF: ~1 in 4 for adults ≥40 years of age

AF Is Associated With Increased Thromboembolic Risk

- Major cause of stroke in elderly\(^1\)
- 5-fold ↑ in risk of stroke\(^1,2\)
- 15% of strokes in US are attributable to AF\(^3\)
- Stroke severity (and mortality) is worse with AF than without AF\(^4\)
- Incidence of all-cause stroke in patients with AF: 5%\(^1\)
- Stroke risk persists even in asymptomatic AF\(^5\)


AF Is the Leading Cause of Hospitalizations for Arrhythmia

<table>
<thead>
<tr>
<th>Hospital Admissions in US</th>
</tr>
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<tbody>
<tr>
<td>AF</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>1000</td>
</tr>
</tbody>
</table>

N=517,699 (representing 10% of CV admissions).
VF, ventricular fibrillation; VT, ventricular tachycardia.

AF Increases Mortality

- 4-month HR, 9.62
- Post-4 months HR, 1.66

Survival, %

\(P<.0001\)

• 15429 subjects enrolled in ARIC study
• 5479 subjects enrolled in the CV Health Study

AF Is Associated With Dementia

AF Is Associated With Dementia

AF Reduces Quality of Life


*Higher numbers indicate higher QoL.
SF-36 = Medical Outcomes Study Short Form 36.
Pathogenesis of AF

AF Results in Atrial Remodeling
- AF begets AF -

Structural Remodeling
- LA and LAA dilation
- Fibrosis

Electro-physiologic Remodeling
- Decrease in Ca++ currents
- Shortening of atrial action potential
- Increased importance of early activating K+ channels: IKur, IKto

Fibrotic Atrial Cardiomyopathy: A Specific Disease/Syndrome Supplying Substrates for Atrial Fibrillation, Atrial Tachycardia, Sinus Node Disease, AV Node Disease, and Thromboembolic Complications

- FACM is a specific disease/syndrome supplying substrates for AF and other manifestations.
- The long help concept that “atrial begets atrial fibrillation” does not explain the variable pattern of atrial fibrosis in patients with atrial fibrillation.
- Some patients with new onset of AF have severely scarred atria.
- Other patients with longstanding AF have little fibrosis.
- Tachy-brady syndrome is likely a manifestation of FACM.
- Outcomes of ablation are impacted significantly by the extent of FACM.
- Stroke risk is related to the extent of FACM.
Conditions Frequently Associated With Nonvalvular AF

- Hypertension
- Aging
- Male sex
- Obesity/metabolic syndrome/diabetes
- Ischemic heart disease
- Heart failure/diastolic dysfunction
- Obstructive sleep apnea
- Physical inactivity
- Thyroid disease
- Inflammation?


Prevalence of AF Increases With Severity of HF

Class I – II

Class III – IV

Temporal Relations of AF and CHF and Their Joint Influence on Mortality

- 1,470 subjects, new onset AF or CHF
- AF only 539, CHF only 549, both 382
- AF first 144, CHF first 159, same day 79
- Mean f/u 5 years

Results:
- 41% of CHF patients developed AF
- 42% of AF patients developed CHF
- In AF subjects, the presence of development of CHF was associated with a 2 – 3 x increased mortality
- In CHF patients, the presence of development of AF did not impact mortality.

Time to cardiovascular death or heart failure hospitalization

AF predicted mortality for both preserved EF and depressed EF groups, and CV death or heart failure hospitalization for preserved EF group.


**AF Is a Marker for Worse Outcomes In Heart Failure: CHARM Program**

<table>
<thead>
<tr>
<th>Year</th>
<th>No AF &amp; Low EF</th>
<th>No AF &amp; PEF</th>
<th>AF &amp; Low EF</th>
<th>AF &amp; PEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3,906</td>
<td>2,545</td>
<td>670</td>
<td>478</td>
</tr>
<tr>
<td>1</td>
<td>3,207</td>
<td>2,294</td>
<td>509</td>
<td>399</td>
</tr>
<tr>
<td>2</td>
<td>2,735</td>
<td>2,096</td>
<td>417</td>
<td>353</td>
</tr>
<tr>
<td>3</td>
<td>1,963</td>
<td>1,276</td>
<td>289</td>
<td>203</td>
</tr>
</tbody>
</table>

Preserved EF:

HR 1.72 (95% CI 1.45 – 2.06)  P < 0.001

Low EF:

HR 1.29 (95% CI 1.14 – 1.48)  P = 0.001

Number at risk

No AF & Low EF: 3,906
No AF & PEF: 2,545
AF & Low EF: 670
AF & PEF: 478

• 30 sheep on high calorie diet studies at 4 and 8 months
• 10 controls
• CMR, hemodynamic, and EP testing
• Histological examination

**Death results in progressive atrial structural and electrical remodeling: Implications for atrial fibrillation**

Mark S. Luk, MD, MBBS, FHEA, MD, FRACP, FACC, FESC, FCS, and colleagues.

AF = atrial fibrillation

HR = hazard ratio

CI = confidence interval

P = probability

**Relative optical density (Signal intensity - Background)**

**Male (n = 81)**

- Optical density: 0.000 ± 0.000 vs 0.000 ± 0.000
- Standard deviation: 0.210 ± 0.000 vs 0.210 ± 0.000
- Mean: 0.000 ± 0.000 vs 0.000 ± 0.000

**Female (n = 81)**

- Optical density: 0.000 ± 0.000 vs 0.000 ± 0.000
- Standard deviation: 0.210 ± 0.000 vs 0.210 ± 0.000
- Mean: 0.000 ± 0.000 vs 0.000 ± 0.000
Treatment

AF Guidelines

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association

Authors/Taric Furry Members: A. John Conn (Chelmsford, UK), Gregorio T.M. Gid (UK), Rafael De Caterino (Italy), Irene Sorella (UK),
Dan Azar (Norway), Stefan H. Hohler (Germany), Gorurd Vfeed (Germany),
Paulus Kirchhof (UK)

Treatment Goals and Strategies

Rate control
- Pharmacologic
  - Ca²⁺ blockers
  - β-blockers
  - Digitalis
- Nonpharmacologic
  - Abate and pace
  - Prevent Remodeling

Maintenance of SR
- Pharmacologic
  - Class IA
  - Class IC
  - β-blocker
- Nonpharmacologic
  - Catheter ablation
  - Pacing
  - Implantable devices

Stroke prevention
- Pharmacologic
  - Warfarin
  - Aspirin
  - Thrombin Inhibitor
- Nonpharmacologic
  - Removal/Isolation
  - LA appendage

Prevent Remodeling
CCB, ACE-I,ARB, Statin, Fish oil
Stroke Risk Stratification in AF

**CHADS<sub>2</sub>**
- Cardiac failure (1)
- Hypertension (1)
- Age ≥ 75 y (1)
- Diabetes (1)
- Stroke (2)

**CHA<sub>2</sub>DS<sub>2</sub>-VASc**
- Cardiac failure (1)
- Hypertension (1)
- Age ≥ 75 y (2)
- Diabetes (1)
- Stroke (2)
- Vascular disease (MI, PAD, aortic atherosclerosis) (1)
- Age 65-74 y (1)
- Sex category (female) (1)

**CHADS<sub>2</sub>-VASc Score**

- Relationship between CHADS<sub>2</sub>-VASc score and annual risk of stroke

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### Indications for Anticoagulation in AF Patients

**The 2012 ESC Guidelines**

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### Indications for Anticoagulation in AF Patients

**The 2012 ESC Guidelines**

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## ACC/AHA/ESC 2006 Atrial Fibrillation Guidelines

### Risk Stratification for AF:

#### Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Aspirin, 81-325 mg a day</td>
</tr>
<tr>
<td>No moderate-risk factors</td>
<td>CHADS$_2$ = 0</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>Aspirin, 81-325 mg a day</td>
</tr>
<tr>
<td>One moderate-risk factor</td>
<td>or warfarin (INR 2.0-3.0*)</td>
</tr>
<tr>
<td>High Risk</td>
<td>Warfarin (INR 2.0-3.0*)</td>
</tr>
<tr>
<td>Any high-risk factor or ≥2 moderate-risk factors</td>
<td>CHADS$_2$ ≥ 2</td>
</tr>
</tbody>
</table>

*INR 2.5-3.5 for prosthesis valves. What to do about "weaker" risk factors?

Limitations of Warfarin

<table>
<thead>
<tr>
<th>Limitations</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset of action</td>
<td>Overlap with parenteral anticoagulant</td>
</tr>
<tr>
<td>Genetic variation in metabolism</td>
<td>Variable dose requirements</td>
</tr>
<tr>
<td>Multiple food and drug interactions</td>
<td>Frequent coagulation monitoring</td>
</tr>
<tr>
<td>Narrow therapeutic window</td>
<td>Frequent coagulation monitoring</td>
</tr>
</tbody>
</table>


Courtesy of PR Kowey, MD.

Targets of New Anticoagulant Agents

Beckstein Throm Res 2012 33
Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY)

- 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 was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.


Rivaroxaban vs Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF)

- 14,264 patients with atrial fibrillation were randomly assigned to receive either rivaroxaban or warfarin.
- Rivaroxaban was noninferior to warfarin with respect to the primary end point of stroke or systemic embolism.


Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE)

- Apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and lowered mortality.

New Oral Anticoagulant Agents

<table>
<thead>
<tr>
<th>Drug Characteristics</th>
<th>Comparison</th>
<th>New Agent 1</th>
<th>New Agent 2</th>
<th>New Agent 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral Available</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Oral route</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>INR maintenance</td>
<td>0.5-1.4</td>
<td>0.8-1.2</td>
<td>0.9-1.2</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>RI/LF ratio</td>
<td>1</td>
<td>1.2</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>17</td>
<td>15</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>95%</td>
<td>80%</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>60%</td>
<td>55%</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Molecular weight (kDa)</td>
<td>1550</td>
<td>1400</td>
<td>1300</td>
<td>1200</td>
</tr>
</tbody>
</table>

Which New Agent Should We Recommend?

- Raise the issue / Pop the question
- Variables to consider:
  - coumadin experience
  - approach to new drugs
  - cost considerations
  - h/o GI symptoms
  - renal function
  - compliance issues

Can We Use These New Agents in Patients on ASA or Clopidogrel?

- Concomitant use of an antiplatelet drug leads to a significant rise in bleeding when combined with any anticoagulant.
- The risk is increased by approximately 50% with a single antiplatelet drug and is doubled when dual antiplatelet therapy is used.
- Concomitant antiplatelet therapy has little impact on the relative advantages of dabigatran and apixaban in comparison with warfarin.
Treatment Goals and Strategies

Rate control
- Maintenance of SR
- Stroke prevention
- Pharmacologic
  - Ca²⁺ blockers
  - ß-blockers
  - Dilatiazem
  - Amiodarone
  - Dronedarone
- Nonpharmacologic
  - Ablation and pace

Pharmacologic
- Warfarin
- Aspirin
- Thrombin Inhibitor
- Nonpharmacologic
- Removal/isolation
- LA appendage

Prevent Remodeling
- CCB
- ACE-I, ARB
- Statins
- Fish oil

Rate Control
- End point
  - Resting and ambulatory ventricular rates similar to those expected in sinus rhythm
  - Best assessed with Holter monitoring
  - Determining pulse on exam and heart rate on ECG are not sufficient
- Methods
  - Digitalis: in sedentary patients or CHF
  - ß-blockers and/or CCBs (verapamil, dilatiazem): needed in most active individuals
  - AVN ablation plus pacemaker: in resistant patients
- Special considerations
  - Brady-tachy syndrome (pindolol, or pacer plus drugs)
  - Preexcitation (focus on the BT as well as the AVN)

Treatment Goals and Strategies

Rate control
- Maintenance of SR
- Stroke prevention
- Pharmacologic
  - Class I
  - Class IC
  - Class III
- Nonpharmacologic
  - Catheter ablation
  - Pacing
  - Surgery
  - Implantable devices

Pharmacologic
- ß-blocker
- Nonpharmacologic
- Ablation and pace

Prevent Remodeling
- Only in patients with nonpermanent AF
- The antiarrhythmic drug classes are based on the Vaughan Williams classification.
**AAD Treatment Goals**

- Remember to keep goals realistic!
- AF is rarely life-threatening and is usually recurrent
- Thus, goals should be to:
  - Reduce the frequency of recurrences
  - Reduce the duration of recurrences
  - Reduce the severity of recurrences
  - Minimize intolerance and risk of therapy

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**Catheter Ablation**
What Do We Know About AF Ablation?

- How to perform it.
- How to avoid PV stenosis and phrenic nerve injury.
- How to avoid esophageal injury.
- Results in elimination of symptomatic AF in most patients.
- Improves quality of life.
- More effective than antiarrhythmic drug therapy.
- Associated with a moderate risk of complications.
Efficacy of Catheter Ablation in Patients With AF

Meta-analyzed Proportion of Patients, %


Catheter Ablation of AF: Meta-analysis of 4 Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Risk Ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pappone et al, 2006</td>
<td>3.86 (2.65-5.63)</td>
<td>37.5</td>
</tr>
<tr>
<td>Stable et al, 2006</td>
<td>6.43 (2.91-14.21)</td>
<td>18.1</td>
</tr>
<tr>
<td>Waziri et al, 2005</td>
<td>4.22 (2.14-8.32)</td>
<td>22.0</td>
</tr>
<tr>
<td>Krittayaphong et al, 2003</td>
<td>2.00 (1.02-3.91)</td>
<td>22.4</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>3.73 (2.47-5.63)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Risk Ratio


Ablation Catheters
Treatment Success

RF
CRYO

AF Ablation Outcomes in 2013

<table>
<thead>
<tr>
<th></th>
<th>Single Procedure</th>
<th>Multiple Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal Candidate</td>
<td>60-80%</td>
<td>70-90%</td>
</tr>
<tr>
<td>Moderate Candidate</td>
<td>45-65%</td>
<td>55 – 75%</td>
</tr>
<tr>
<td>Poor candidate</td>
<td>35 – 50%</td>
<td>45 – 60%</td>
</tr>
</tbody>
</table>

*Success is defined as freedom from symptomatic AF at 12 months of follow-up*

Complications in 2013

**Overall Complication Rate:**

1% - 3%

- Stroke /TIA – 0.2% - 1%
- Cardiac perforation / tamponade – 0.2% - 1%
- Vascular injury / bleeding – 0/5% - 1%
- Phrenic nerve injusy 0.1% - .3%
- Atrial esophageal fistula - < 1/1000
- Gastroparesis – 0.1% - 0.2%
- Death - < 1/1000
Where Are the Knowledge Gaps?

- Safety and efficacy of the catheter ablation in:
  - very elderly
  - heart failure
  - long standing persistent AF
- Impact of AF ablation on stroke risk.
- Impact of AF ablation on survival.
- Technical questions.
  - optimal ablation strategy for long standing persistent AF
  - relative efficacy of cryo ablation, RF ablation, and laser ablation

What is the impact of AF ablation on stroke and mortality?

- The CABANA Trial
  - Prospective randomized clinical trial of 3500 patients to compare catheter ablation with pharmacologic therapy of atrial fibrillation.
  - 3500 patients, > 65 years of age or > 1 stroke risk factor
  - Endpoints: death and stroke

Indications for AF Ablation in 2013
### Indications for Catheter Ablation of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Highly symptomatic</th>
<th>Minimally symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Paroxysmal</td>
<td>Persistent</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

#### Patient Selection for Ablation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Highly symptomatic</th>
<th>Minimally symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF type</td>
<td>Paroxysmal</td>
<td>Persistent</td>
</tr>
<tr>
<td>Age</td>
<td>Younger (&lt;75 years)</td>
<td>Older (≥75 years)</td>
</tr>
<tr>
<td>LA size</td>
<td>Smaller (&lt;5.0 cm)</td>
<td>Larger (≥5.0 cm)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Other cardiac disease</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Obesity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Courtesy of Hugh Calkins, MD.*
Treatment Goals and Strategies

**Rate control**
- Pharmacologic
  - Ca²⁺ blockers
  - β-blockers
  - Digoxin
  - Amiodarone
- Nonpharmacologic
  - Ablate and pace

**Maintenance of SR**
- Pharmacologic
  - Class IA
  - Class IC
  - Class III
  - β-blocker

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

**Prevent Remodeling**
- CCB
- ACE-I, ARB
- Statin
- Fish oil

Conclusion

- Atrial fibrillation is an important arrhythmia.
- Stroke prevention is the primary goal of treatment.
- Anticoagulation is indicated for all patients except the extremely low risk.
- Rhythm control strategies may improve quality of life in symptomatic patients.
- Catheter ablation plays an important role in the treatment of AF.
- Selection of antiarrhythmic agents is largely based on side effect profiles.

Thank You