Managing Atrial Fibrillation 2016: Anticoagulation, Pharma and Ablation

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Managing Atrial Fibrillation 2016: Anticoagulation, Pharma and Ablation

• Background and Guidelines
• Decisions to anti-coagulate
• Treatment options
• Bleeding management
• Special populations
• Bridging therapy
Atrial Fibrillation
Background

• Most common cardiac arrhythmia
  • overall prevalence of ~1%

• Increased risk of mortality, heart failure and thromboembolic events.

• Hospitalization rates increased by 23% from 2000 to 2010;

• In-hospital mortality  1% and as high as 1.9% for patients >80y/o;
  Concomitant heart failure up to 8.2%
• Prevalence of atrial fibrillation increases with age
• Prevalence is higher in men than women in all age groups
The estimated US prevalence of atrial fibrillation (AF) in the year 2050 ranges from 5.6 million to as high as 15.9 million individuals.

Lifetime risk for developing atrial fibrillation (AF) from the Framingham Heart Study.

Therapy for AF

Prevent Thromboembolism

Control ventricular response

Restore/Maintain sinus rhythm
DUAL SUBSTRATES FOR AF

TRIGGERING

PV PACs
OTHER PACs
AT / SVT

MAINTENANCE

LOCAL ANISOTROPY
FIBROSIS / SCARRING
REPEETITIVE TRIGGERING

MODULATORS

STRETCH
AUTONOMIC TONE
ELECTRICAL
REMODELING

PAROXYSMAL AF
PERSISTENT AF
Permanent AF
# Types of Atrial Fibrillation

## TABLE 3 Definitions of AF: A Simplified Scheme

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paroxysmal AF</strong></td>
<td>• AF that terminates spontaneously or with intervention within 7 d of onset.</td>
</tr>
<tr>
<td></td>
<td>• Episodes may recur with variable frequency.</td>
</tr>
<tr>
<td><strong>Persistent AF</strong></td>
<td>• Continuous AF that is sustained &gt;7 d.</td>
</tr>
<tr>
<td><strong>Long-standing persistent AF</strong></td>
<td>• Continuous AF &gt;12 mo in duration.</td>
</tr>
<tr>
<td><strong>Permanent AF</strong></td>
<td>• The term &quot;permanent AF&quot; is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.</td>
</tr>
<tr>
<td></td>
<td>• Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF.</td>
</tr>
<tr>
<td></td>
<td>• Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.</td>
</tr>
<tr>
<td><strong>Nonvalvular AF</strong></td>
<td>• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation.

*J Am Coll Cardiol. 2014; 64 (21): 2246-2280*
CLINICAL PRACTICE GUIDELINE

2014 AHA/ACC/HRS Guideline 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 Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons
Prevention of Thromboembolism

Decision to anti-coagulate comes down to risk of embolism versus bleeding.

Guideline recommendation:

3. In patients with nonvalvular AF, the CHA$_2$DS$_2$-VASc* score is recommended for assessment of stroke risk (68-70).

*(Level of Evidence: B)*

J Am Coll Cardiol. 2014; 64 (21): 2246-2280
CHADS2-Vasc Score

• CHADS2-VASC increases the number of patients who meet criteria for anticoagulation therapy and more accurately identifies truly low risk patients

• More people who were considered low risk before (ie females, age 65-74, vascular dx) are moved to the higher risk categories to better reflect risk of embolization.

### Comparison of the CHADS$_2$ and CHA$_2$DS$_2$-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

<table>
<thead>
<tr>
<th>Definition and Scores for CHADS$_2$ and CHA$_2$DS$_2$-VASc</th>
<th>Stroke Risk Stratification With the CHADS$_2$ and CHA$_2$DS$_2$-VASc Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHADS$_2$</strong></td>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq$75 y</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Maximum score</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CHA$_2$DS$_2$-VASc</strong></th>
<th><strong>Score</strong></th>
<th><strong>CHA$_2$DS$_2$-VASc</strong></th>
<th><strong>Adjusted Stroke Rate (% per y)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive HF</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Age $\geq$75 y</td>
<td>2</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>Age 65-74 y</td>
<td>1</td>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>Sex category (i.e., female sex)</td>
<td>1</td>
<td>7</td>
<td>9.6</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
<td>15.20</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol. 2014; 64 (21): 2246-2280
**Prevention of Thromboembolism**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure or left ventricular dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq 75$ yrs</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke, transient ischemic attack, or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 yrs</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e., female)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum total points</td>
<td><strong>9</strong></td>
</tr>
<tr>
<td>Letter</td>
<td>Clinical Characteristic</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal Liver or Renal Function</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
</tr>
<tr>
<td>L</td>
<td>Labile INR</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (age &gt; 65)</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or Alcohol</td>
</tr>
</tbody>
</table>

**Maximum Score**: 9
• Anticoagulation recommended

5. For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA₂DS₂-VASc score of 2 or greater, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (68–70) (Level of Evidence: A), dabigatran (74) (Level of Evidence: B), rivaroxaban (75) (Level of Evidence: B), or apixaban (76). (Level of Evidence: B)

J Am Coll Cardiol. 2014; 64 (21): 2246-2280
Anticoagulant Mechanisms of Action

Initiation

Warfarin

Propagation

Fondaparinux
Heparin LWMH

Rivaroxaban
Apixaban

Fibrin formation

Dabigatran

### TABLE 2 Summary of Selected DOACs Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (33)</th>
<th>ROCKET-AF (34)</th>
<th>ARISTOTELE (35)</th>
<th>ENGAGE AF-TIMI 48 (36)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug, dose</strong></td>
<td>Dabigatran, 150 mg bid</td>
<td>Rivaroxaban, 20 mg daily</td>
<td>Apixaban, 5 mg bid</td>
<td>Edoxaban, 60/30 mg daily</td>
</tr>
<tr>
<td><strong>Adjusted dose?</strong></td>
<td>No</td>
<td>Yes, at randomization only: 15 mg daily if CrCl 30-49 mL/min</td>
<td>Yes, at randomization only: 2.5 mg bid if 2 or &lt; age 80 yrs, weight &lt; 60 kg, SCr &gt; 1.5 mg/dL</td>
<td>Yes, at randomization and during study: both doses halved if any 1 of the following: CrCl 30-50 mL/min, weight &lt; 60 kg, use of verapamil, quinidine, or dromedarine</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Randomized open-label</td>
<td>Randomized double-blind, double-dummy</td>
<td>Randomized double-blind, double-dummy</td>
<td>Randomized double-blind, double-dummy</td>
</tr>
<tr>
<td><strong>Mean age, yrs</strong></td>
<td>71.5</td>
<td>73</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td><strong>Prior stroke/ transient ischemic attack/systemic embolism</strong></td>
<td>20%</td>
<td>55%</td>
<td>19%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Mean CHADS2</strong></td>
<td>2.2</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Warfarin-naïve</strong></td>
<td>50.4%</td>
<td>37.6%</td>
<td>43%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Comparator warfarin INR 2-3</strong></td>
<td>67% TTR (median)</td>
<td>58% TTR (median)</td>
<td>56% TTR (median)</td>
<td>68% (median)</td>
</tr>
<tr>
<td><strong>Comparator Warfarin INR 2-3</strong></td>
<td>54% TTR (mean)</td>
<td>55% TTR (mean)</td>
<td>62% TTR (median)</td>
<td>65% (median)</td>
</tr>
<tr>
<td><strong>Outcome, RR (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke/systemic embolism</td>
<td>0.66 (0.53–0.82)</td>
<td>0.88 (0.75–1.03)</td>
<td>0.79 (0.66–0.95)</td>
<td>0.88 (0.75–1.03)</td>
</tr>
<tr>
<td>ischemic stroke</td>
<td>0.76 (0.60–0.98)</td>
<td>0.94 (0.75–1.17)</td>
<td>0.92 (0.74–1.13)</td>
<td>1.00 (0.83–1.19)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.25 (0.14–0.49)</td>
<td>0.59 (0.37–0.93)</td>
<td>0.51 (0.35–0.75)</td>
<td>0.54 (0.38–0.77)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.93 (0.81–1.07)</td>
<td>1.04 (0.90–1.20)</td>
<td>0.69 (0.60–0.80)</td>
<td>0.80 (0.71–0.91)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.40 (0.27–0.60)</td>
<td>0.67 (0.47–0.93)</td>
<td>0.42 (0.30–0.58)</td>
<td>0.47 (0.34–0.63)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.50 (1.19–1.89)</td>
<td>1.39 (1.19–1.61)</td>
<td>0.89 (0.70–1.15)</td>
<td>1.23 (1.02–1.50)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.85 (0.72–0.99)</td>
<td>0.89 (0.73–1.10)</td>
<td>0.89 (0.76–1.04)</td>
<td>0.86 (0.77–0.97)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.88 (0.77–1.00)</td>
<td>0.87 (0.70–1.02)</td>
<td>0.89 (0.80–0.998)</td>
<td>0.92 (0.83–1.01)</td>
</tr>
</tbody>
</table>

*Estimate creatinine clearance (CrCl) using Cockcroft-Gault formula ([140 – age] x weight [in kg] x 0.85 if female)/(72 x creatinine [in mg/dL]). *Results are shown for dabigatran 150 mg bid. *Results are shown for edoxaban 60 mg daily. 
CHADS2 — Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, Stroke or transient ischemic attack; CI — confidence interval; CrCl — creatinine clearance, DOAC — direct-acting oral anticoagulant; INR — international normalized ratio; RR — risk ratio; SCr — serum creatinine; TTR — time in therapeutic range.*
Bleeding Risk

- Annual rate of major bleeding range between 2.1% to 3.6%
- Fatal bleeding occurs in up to 0.5%
- Major bleeding is associated with higher mortality
  - 30-day mortality after major bleeding episode
    - 13% with warfarin and 9% with dabigatran

J AM Coll Cardiol. 2015; 65 (13): 1340-1360
Bleeding management

Agents to reverse anticoagulation

- More complicated as DOAC reversal is limited (*until recently*)
- Develop institutional plan
- Consult hematology
Bleeding management: Warfarin

- **Vitamin K**
  - Vit K 5-10mg slow IV infusion
    - IV Vitamin K does not begin to reduce INR for 6hrs (usually longer than 24hrs)
    - IV vitamin K allergic reaction if given as bolus
  - Subcutaneous and IM Vitamin K not recommended
  - PO Vitamin K used in minor bleeding
  - Does not work for DOAC

- **Fresh frozen plasma**
  - Along with blood transfusion provide volume
    - >1500 ml of FFP
  - Does not work for DOAC
Bleeding management: DOAC

- Prothrombin complex concentrate (PCC)
  - 10-30min infusion improves INR within minutes and last 24-48hrs
    ♠ Use Vitamin K along with this
  - Limited reversal of dabagatran and rivaroxiban in 2hrs in healthy volunteers
  - Small concern about myocardial infarction and arterial thromboembolism
  - Some have heparin therefore cautious use in patients with heparin-induced thrombocytopenia

Bleeding management, reversal: *Dabigatran*

- antibody fragment developed to reverse the anticoagulation effects of dabigatran
Bleeding management, reversal:  
*Factor Xa inhibitors*

- Andexanet
  - Recombinant factor Xa with minor amino acid deletions; Therefore lacks pro or anticoagulation affects on its own
  - Active binding site of Andexanet functions as a decoy and binds to factor Xa inhibitors with high affinity
  - Overall factor Xa inhibitors concentration is reduced
  - Phase 3 ANNEXA trial
Bleeding management, reversal: *Factor Xa inhibitors*

- Aripazine
  - synthetic small molecule with broad activity against heparin, LMWH, and DOAC
  - IV dosing
  - reversal seen in 10 minutes in the phase I study
Thromboembolism Prevention Conclusions

• Decision to anti-coagulate should be guideline driven but individualized to the patient

• Use objective assessment tools for bleeding and embolic risk calculation.

• Direct oral anticoagulants (DOAC) provide good anticoagulation options to warfarin

• Bridging therapy in high risk patients remains controversial but new evidence suggests bridging might not necessary. However, additional trials are needed to validate this.
Lots to know... without lots of consensus

- Strategies
  - Focal
  - Segmental
  - WACA/LACA/WEPV
  - Lines lines lines
  - Non-PV triggers, CFAE, rotors, GPs

- Procedure/Techniques
  - Irrigated v. non-irrigated RF
  - Non-RF energy sources
  - Imaging/mapping
  - Sheaths
  - Anesthesia
  - Peri-procedural anticoagulation

- Endpoints
  - Entrance block
  - Exit block
  - Organization/conversion to SR
  - Inducibility

Pulmonary veins are the “cornerstone”

Avoid complications!

“I” is for isolation
Isolation of RCPV

Atria remain in AF
RSPV dissociated potential initially after isolation
RCPV isolation site
Rate Control vs. Rhythm Control

**AFFIRM**

AFFIRM Investigators, NEJM 2002

**RACE**

Van Gelder, et al. NEJM 2002
Many strategies for AF ablation evolved; most studied in 1-2 centers

• CFAE ablation
  
  Nademanee et al. *JACC* 2004; 43(11): 2044
  
  - CFAEs mapped with CARTO
  - AF terminated w/o DCCV in 95%
    (concomitant ibutilide in 28%)
  - 76% symptom free at 1-yr with 1 procedure; 91% with 2

• Stepwise: PVI + CS/SVC + LA +/- lines (roof, MI, CTI)
  

![Graph showing cumulative incidence of AF termination]
Many strategies for AF ablation evolved; most studied in 1-2 centers

• **FIRM ablation**

  Narayan et al. *JACC* 2012; 60(7): 628

  - 92 patients, 107 consecutive ablation procedures, 72% with persistent AF
  - FIRM-guided + conventional, versus conventional alone (WACA, + roof line in persistent AF)
  - 2.1 ± 1 localized rotor or focal impulse sources (in 97% of cases)
  - AF termination or slowing in 86% of FIRM-guided cases, with median time to termination of 2.5 min (versus 20%)
  - 82.4% freedom from AF at median 273 days in FIRM-guided cases (versus 45%)
Many strategies for AF ablation evolved; most studied in 1-2 centers

- FIRM ablation

  Narayan et al. *JACC* 2012; 60(7): 628
FIRM ablation

Entire population

Population off AAD’s

Narayan et al. JACC 2012; 60(7): 628
Regardless of technique or endpoint, stay cognizant of universal risks

Endocarditis symptoms 2-3d post-op; extensive septic/air emboli +/- hematemesis over next weeks


Courtesy F. Garcia, MD
One problem with targeting APDs inside PVs...

Pre-ablation

Post-ablation

Courtesy M. Hutchinson, MD
Which RF catheter to use?

- Multiple demonstrations of irrigated RF superiority in other clinical situations (flutter, VT); limited comparative data in AF

Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation

A Randomized Controlled Trial

David J. Wilber, MD
Carlo Pappone, MD, PhD
Pete Naccari, MD
Angelo De Paola, MD
Frank Marchinski, MD
Andrea Natali, MD
Laurent Natale, MD
Emile G. Daoud, MD
Hugh Calkins, MD
Mark Field, MD
Virend Reddy, MD
Giuseppe Angelillo, MD
Matthew H. Reynolds, MD, MSc
Chandan Vinikar, MS
Christine Y. Lau, MPH
Scott M. Barry, PhD
Donald A. Berry, PhD
for the ThermoCool AF Trial Investigators

- Funded by Biosense Webster
- NaviStar ThermoCool used for all procedures (2004-2007) in 19 centers
- 66% of ablation pts v. 16% of AAD pts were “free of treatment failure” at 9 months
Therapy for AF

- Prevent Thromboembolism
- Control ventricular response
- Restore/Maintain sinus rhythm
Thank You for Your Attention