Stroke Prevention in Atrial Fibrillation: Medical Therapy

Jonathan P. Piccini, MD, MHS
Associate Professor of Medicine
Director, Duke Center for Atrial Fibrillation
Duke University Medical Center
jonathan.piccini@duke.edu
Disclosures

Grants
- AHA
- Abbott
- ARCA biopharma
- Boston Scientific
- Gilead
- Janssen
- NHLBI

Consulting
- Abbott
- Allergan
- ARCA Biopharma
- Bayer
- Biotronik
- Johnson & Johnson
- Medtronic
- Sanofi
- Phillips

Duke Heart Center
Warfarin is inferior to NOAC therapy
Non vitamin K antagonists versus warfarin for stroke prevention in nonvalvular AF

- RE-LY [Dabigatran 150 mg]
  - Risk Ratio (95% CI): 0.66 (0.53 - 0.82)

- ROCKET AF [Rivaroxaban]
  - Risk Ratio (95% CI): 0.88 (0.75 - 1.03)

- ARISTOTLE [Apixaban]
  - Risk Ratio (95% CI): 0.80 (0.67 - 0.95)

- ENGAGE AF-TIMI 48 [Edoxaban 60 mg]
  - Risk Ratio (95% CI): 0.88 (0.75 - 1.02)

- Combined [Random Effects Model]
  - N=58,541
  - Risk Ratio (95% CI): 0.81 (0.73 - 0.91)
  - P<0.0001

Overview of 4 Trials of NOACs vs Warfarin

Risk Ratio (95% CI)

Hemorrhagic Stroke
- Favors NOAC: 0.49 (0.38 - 0.64) p<0.0001
- Favors Warfarin: 0.90 (0.85 - 0.95) p=0.0003

All-Cause Mortality
- Favors NOAC: 0.2
- Favors Warfarin: 0.5

ICH Volumes Are Smaller in NOAC Treated Patients

2.4 mL for NOAC vs 8.9 mL for warfarin
(p =0.0028)

Wilson D. Neurology. 2016;86:360-6
DNA TESTING AUTHORIZATION
Coumadin®/Warfarin CYP2C9 and VKORC1

STEP 2 REVIEW

- Our records indicate that WARFARIN SODIUM 5 MG was prescribed on 08/30/2017. Genetic testing may provide valuable information about your patient's drug metabolism to help you determine the proper dosing, achieve therapeutic goals, and avoid adverse events.

- On January 28, 2010, the FDA updated the warfarin label to provide guidance for the initial prescribing of warfarin, taking into account clinical factors including the patient's age, race, weight, sex, concomitant medications and comorbidities, and genetic factors (CYP2C9 and VKORC1 genotypes). The update includes specific dosing recommendations. Refer to the warfarin label for the range of expected therapeutic warfarin doses based on CYP2C9 and VKORC1 genotypes.

- This testing is at no cost to your patient. The program is paid by Express Scripts's clients and not billed to Medicare. If you have any questions about this program call 800.838.5233 and follow the prompts for warfarin, 9:00 a.m. to 5:30 p.m., eastern time, Monday to Friday or visit www.express-scripts.com/personalizedmedicine.

STEP 3 AUTHORIZE AND RETURN BY FAX

TO AUTHORIZE THIS GENETIC TEST, COMPLETE, SIGN, AND FAX THE FORM WITHIN 48 HOURS.
Primary Endpoint: Percent Out-of-Range INRs

54% of OOR values were subtherapeutic; 46% were supratherapeutic.

## Coumagen, Secondary Endpoints

<table>
<thead>
<tr>
<th>End point</th>
<th>Genomics</th>
<th>Standard care</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first supratherapeutic INR, days</td>
<td>53.4</td>
<td>47.1</td>
<td>0.53</td>
</tr>
<tr>
<td>Time within goal range, %</td>
<td>69.7</td>
<td>68.6</td>
<td>0.74</td>
</tr>
<tr>
<td>Goal INR by day 5, %</td>
<td>69.7</td>
<td>68.3</td>
<td>0.85</td>
</tr>
<tr>
<td>Dose adjustments per patient, mean (SD)</td>
<td>3.0 (2.0)</td>
<td>3.6 (2.0)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Only 1/3 of patients with stable INR values continue to have stable values

100% INRs 2.0-3.0 >> 100% INRs 1.5-4.0  
C-index 0.533

Duke Heart Center

Pokorney SD. JAMA. 2016;316:661-663
Indications for Warfarin in AF

- Mechanical valve
- CrCl <30 mL/min
- Cannot afford NOAC
Warfarin use & stroke in patients with AF undergoing dialysis

Aggregate evidence does not suggest clear benefit

Shah M. Circulation. 2014;129:1196-1203
RENAL-AF Trial: Study Overview

Selected inclusion criteria
- Atrial fibrillation
- CHA2DS2-VASc ≥2
- Hemodialysis
- Candidate for OAC

Selected exclusion criteria
- Moderate or severe mitral stenosis
- OAC needed for reason other than AF
- Need for aspirin > 100 mg
- Need for dual antiplatelet therapy
- Life expectancy < 3 months

Apixaban 5 mg oral twice daily
(2.5 mg BID in patients ≥ 80 years of age and/or ≤ 60 kg)

Warfarin
(target INR 2–3)

Randomize
(n ≈ 760)

Primary outcome: ISTH major and clinically relevant non-major bleeding

Secondary outcomes:
- PK/PD
- Stroke and systemic embolism
- Death
- Tolerability/persistence/adherence parameters

Open label with blinded event adjudication

Slide courtesy of Sean Pokorney.

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Risk stratification
2014 AHA/ACC/HRS Guidelines

In patients with nonvalvular AF, the CHA$_2$DS$_2$-VASc score is recommended for assessment of stroke risk. (*Class I, Level of Evidence: B*)

### How good are we at discriminating stroke risk in AF?

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome</th>
<th>C-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRACE Score</td>
<td>6-month survival after ACS</td>
<td>0.75-0.81</td>
</tr>
<tr>
<td>Seattle Heart Failure Model</td>
<td>1-year survival in HF</td>
<td>0.73</td>
</tr>
<tr>
<td>APACHE III</td>
<td>Survival to discharge following ICU admission</td>
<td>0.90</td>
</tr>
<tr>
<td>Model for End-Stage Liver Disease (MELD)</td>
<td>3-month survival in end-stage liver disease</td>
<td>0.80-0.87</td>
</tr>
</tbody>
</table>

**CHA₂DS₂VASC** C-statistic 0.55-0.64

Agreement between Doctors and Models

Impact of New 2014 ACC/AHA/HRS Guidelines Recommendations

<table>
<thead>
<tr>
<th>Category</th>
<th>2011 Guideline</th>
<th>2014 Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>7274 9199</td>
<td>10131 10131</td>
</tr>
<tr>
<td>&lt;65</td>
<td>882 1240</td>
<td>2047 2047</td>
</tr>
<tr>
<td>≥65</td>
<td>6394 7963</td>
<td>8084 8084</td>
</tr>
<tr>
<td>Women</td>
<td>3290 4190</td>
<td>4289 4289</td>
</tr>
<tr>
<td>Men</td>
<td>3990 5012</td>
<td>5842 5842</td>
</tr>
</tbody>
</table>

Bleeding scores are not helpful
HAS-BLED Bleeding Risk Score

- **HAS-BLED**
  - Hypertension
  - Abnormal renal/liver function (1 pt for each)
  - Stroke
  - Bleeding hx or prone
  - Labile INR
  - Elderly (>65)
  - Drugs/alcohol (1 pt for each)

- Predicts ISTH major bleeding (c-index 0.72)

HAS-BLED scores and Outcomes by Treatment

Bleeding scores *may* be helpful selecting patients for LAA occlusion.
Factor XI Inhibition

- Hemophilia C
- FXI-deficient individuals rarely suffer from spontaneous bleeding
- Lower risk of ischemic stroke & DVT

L-Horani RA. *Expert Opin Ther Pat.* 2016;26:323-45
Aspirin is a problem
Stroke Prevention Across Risk Strata: NCDR PINNACLE Registry

Aspirin: Two Problems

1. Aspirin is used with oral anticoagulation

2. Aspirin is used instead of oral anticoagulation
Concomitant Aspirin Use (In Addition to OAC) By Vascular History

<table>
<thead>
<tr>
<th>Any Vascular History (CAD, PAD, or CVD)</th>
<th>OAC Alone (n=4804)</th>
<th>OAC+ASA (n=2543)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Vascular History (CAD, PAD, or CVD)</td>
<td>37</td>
<td>61</td>
</tr>
<tr>
<td>CAD</td>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>Prior MI</td>
<td>9.7</td>
<td>23</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>9.1</td>
<td>24</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>9.2</td>
<td>24</td>
</tr>
<tr>
<td>Prior DES</td>
<td>2.4</td>
<td>8.9</td>
</tr>
<tr>
<td>Prior Cerebrovascular Events (stroke or TIA)</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Stroke – non-hemorrhagic</td>
<td>7.8</td>
<td>10</td>
</tr>
<tr>
<td>Stroke – hemorrhagic</td>
<td>0.5</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Major Bleeding by Subgroup

## Adjusted 6-Month Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OAC Alone (n=4239)</th>
<th>OAC+ASA (n=2301)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>74 (1.8)</td>
<td>68 (3.0)</td>
<td>1.53 (1.20 - 1.96)</td>
</tr>
<tr>
<td><strong>Nuisance Bleeding</strong></td>
<td>428 (10)</td>
<td>250 (11)</td>
<td>1.09 (0.96 - 1.25)</td>
</tr>
<tr>
<td><strong>All-cause Hospitalization</strong></td>
<td>815 (19)</td>
<td>523 (23)</td>
<td>1.08 (1.00 - 1.17)</td>
</tr>
<tr>
<td><strong>Cardiovascular Bleeding</strong></td>
<td>463 (10.9)</td>
<td>306 (13.3)</td>
<td>1.08 (0.97-1.21)</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>69 (1.6)</td>
<td>60 (2.6)</td>
<td>1.52 (1.17 - 1.97)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>366 (8.6)</td>
<td>220 (9.6)</td>
<td>0.98 (0.87 - 1.11)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>80 (1.9)</td>
<td>59 (2.6)</td>
<td>1.26 (0.98 - 1.63)</td>
</tr>
</tbody>
</table>

*For nuisance bleeding odds ratios are presented, as dates of events are not included in the analysis.*
In high-risk patients NOACs are more effective than ASA without increased bleeding
Dosing of Non Vitamin K Antagonists (NOAC)

• Safety & efficacy of NOAC agents have been demonstrated with specific doses

• Dose selection is based on several patient factors
  – Renal function
  – Concomitant medications
  – Markers of frailty

• NOAC dose-selection & outcomes in community practice are not well described
# US Prescribing Information for Stroke Prevention in AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard Dose</th>
<th>Adjustment</th>
</tr>
</thead>
</table>
| Dabigatran| 150 mg bid   | CrCl 30-50 & Dronedarone: 75 mg bid  
CrCl 15-30 mL/min: 75 mg bid  
CrCl 15-30 & Dronedarone: Avoid  
CrCl <15 mL/min: No recommendation |
| Rivaroxaban| 20 mg daily | CrCl 15-50 mL/min: 15 mg daily  
CrCl <15 mL/min: Avoid# |
| Apixaban  | 5 mg bid     | 2.5 mg bid if >2 of following  
Age ≥80, weight ≤60 kg, Cr >1.5 mg/dL  
ESRD: No adjustment except above |

*Additional adjustment for certain concomitant medications  
#Following the study period (May, 2016), rivaroxaban USPI revised to state 15 mg will result in similar concentrations in hemodialysis patients.
Dosing by Agent

Dabigatran

- 91% dosage at 150 mg bid
- Not tested in RELY

Rivaroxaban

- 83% dosage at 20 mg daily
- 20% in ROCKET AF

Apixaban

- 81% dosage at 5 mg bid
- 5% in ARISTOTLE

## Renal Function Across NOAC Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Creatinine Clearance, mL per minute (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>75 mg bid</td>
<td>66±40</td>
</tr>
<tr>
<td></td>
<td>150 mg bid</td>
<td>97±40</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>15 mg daily</td>
<td>54±24</td>
</tr>
<tr>
<td></td>
<td>20 mg daily</td>
<td>100±42</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.5 mg bid</td>
<td>50±26</td>
</tr>
<tr>
<td></td>
<td>5 mg bid</td>
<td>90±41</td>
</tr>
</tbody>
</table>

Estimated with Cockcroft Gault

Dosing Distribution

- 5,738 patients, 242 sites in ORBIT-AF II
  - Appropriate: n=5000 (87%)
  - Under-dosed: n=541 (9.4%)
  - Over-dosed: n=197 (3.4%)

# Underdosing: “inappropriate dose reduction”

<table>
<thead>
<tr>
<th>Drug</th>
<th>Event Rate per 100 person-years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced dose</td>
<td>Standard dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>n=550</td>
<td>n=550</td>
</tr>
<tr>
<td></td>
<td>S/SE</td>
<td>2.57</td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>6.01</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>n=412</td>
<td>n=412</td>
</tr>
<tr>
<td></td>
<td>S/SE</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>4.99</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>n=815</td>
<td>n=815</td>
</tr>
<tr>
<td></td>
<td>S/SE</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>5.42</td>
</tr>
</tbody>
</table>

Overdosing: “failure to reduce for CKD”

<table>
<thead>
<tr>
<th>Event Rate per 100 person-years</th>
<th>Reduced dose</th>
<th>Standard dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOACs (pooled)</td>
<td>n=410</td>
<td>n=410</td>
</tr>
<tr>
<td>S/SE</td>
<td>1.85</td>
<td>2.32</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5.06</td>
<td>11.29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard versus reduced dose</td>
<td>1.66 (0.40, 6.88)</td>
</tr>
<tr>
<td></td>
<td>2.19 (1.07, 4.46)</td>
</tr>
</tbody>
</table>

Favor reduced dose

In Summary

• Warfarin is inferior to NOAC therapy
  – Less ICH, lower mortality
• There are many challenges to stroke prevention
• Aspirin is not effective and often causes harm
• Dosing is really important
  – Under-dosing does not help
Duke Center for Atrial Fibrillation

Thank you
OAC discontinuation after ablation is common and is associated with increased cardioembolism

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation use</td>
<td></td>
</tr>
<tr>
<td>Low risk patients (CHA2DS2-VASc 0 or 1)</td>
<td></td>
</tr>
<tr>
<td>Continuation</td>
<td>Reference</td>
</tr>
<tr>
<td>≥3 mo off OAC</td>
<td>0.34 (0.04–2.62)</td>
</tr>
<tr>
<td>High risk patients (CHA2DS2-VASc ≥2)</td>
<td></td>
</tr>
<tr>
<td>Continuation</td>
<td>Reference</td>
</tr>
<tr>
<td>≥3 mo off OAC</td>
<td>2.48* (1.11–5.52)</td>
</tr>
</tbody>
</table>

Noseworthy PA. JAH. 2015 Nov 5;4(11