Disparities in Atrial Fibrillation: Focus on Anticoagulation Related Cardiovascular Outcomes

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Disclosures

• Sanofi
• Boehringer-Ingelheim
• BMS/Pfizer
• Daichi-Sankyo
• Lake Region Medical
AF Demographic Reality

Projected number of individuals with atrial fibrillation (AF) in the United States through 2050.
Annual US cost of AF in 2005 (US $)¹

Total cost of AF in the US: $12.72 billion

Total outpatient cost $4.70 billion (37.0% total)

- Outpatient-managed AF $2.70 billion (21.2%)
- Primary AF $0.98 billion (7.7%)
- Secondary AF $3.86 billion (30.3%)
- Outpatient-managed AF $2.70 billion (21.2%)

Total hospitalization cost $8.02 billion (63.0% total)

- Primary AF $1.03 billion (8.1%)
- Secondary AF $3.92 billion (30.8%)
- Outpatient-managed AF $0.24 billion (1.9%)


¹ Based on 2005 prevalence estimates in Go et al. JAMA. 2001;285:2370-5
Incremental Cost of AF: Propensity Analysis

AF Management

Goals may include:

• Restoration of normal heart rhythm (Cardioversion)
• Control of the heart rate in AF (symptom-reduction, rate-control)
• Maintenance of normal sinus rhythm (ablation/hybrid Rx, rhythm-control)
• Reduction in stroke risk
• Control of symptoms/AF Burden (Quality of Life)
• Cardiovascular Outcomes: Treatment Targets (mortality, stroke, hospitalizations, symptoms/QOL)
Comparative Effectiveness Research: CV Outcomes

• Per the AHRQ: “designed to inform health care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options.”

• Evidence: 1) Existing clinical trials, clinical studies, and other research “aka” “Research Reviews”; 2) New evidence of effectiveness or comparative effectiveness of a test/treatment/procedure/health care service.

• “Compare” and “Effective”
AFFIRM: Management Approaches Showed No Significant Difference in Mortality

Primary End Point

35% of rate- vs 63% of rhythm-control patients were in NSR at 5 y

\[ P = 0.08 \]

Number of Deaths (%)

<table>
<thead>
<tr>
<th></th>
<th>Rhythm control</th>
<th>Rate control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 y</td>
<td>78 (4)</td>
<td>78 (9)</td>
</tr>
<tr>
<td>1 y</td>
<td>148 (7)</td>
<td>148 (11)</td>
</tr>
<tr>
<td>2 y</td>
<td>210 (13)</td>
<td>210 (16)</td>
</tr>
<tr>
<td>3 y</td>
<td>257 (13)</td>
<td>257 (16)</td>
</tr>
<tr>
<td>4 y</td>
<td>314 (13)</td>
<td>314 (16)</td>
</tr>
<tr>
<td>5 y</td>
<td>352 (24)</td>
<td>352 (21)</td>
</tr>
</tbody>
</table>

NSR = normal sinus rhythm.

Racial Diversity in AFFIRM

- 3,599 (White); 265 (Black); 132 (Hispanic)
- Overall survival the same for all 3 groups, but lower rates of event-free (all adverse events) survival for non-white groups \((p=0.02)\).

- Limitations: small numbers; post-hoc; groups not balanced at baseline

Racial Diversity and AF Outcomes: It Matters

- Limited outcomes data and investigation
- A sampling of relevant items:
  - Despite increased AF risk factors, when hospitalized for HF, blacks vs whites had less guideline recommended warfarin prescribed (AHA Get with the Guidelines HF Program; Odds ratio 0.76; p < 0.001) (Thomas K, et al. J Am Heart Assoc 2013; 2: e000200 doi: 10.1161/JAHA.113.000200)
  - Incident AF and sudden death may be higher in blacks vs non-blacks (Chen LY et al, JAMA Intern Med 2013; 173: 29-35)
  - Blacks may have more severe strokes than whites (Jones MR et al, Stroke 2000; 31: 563-567)
Catheter Ablation of AF
Thromboembolic Stroke: left temporal-parietal
RCTs of Warfarin vs Control to Prevent Stroke in AF

Figure 1b

International Normalized Ratio (INR) Level

<table>
<thead>
<tr>
<th>Category</th>
<th>&lt; 1.5</th>
<th>1.5-1.9</th>
<th>2.0-2.5</th>
<th>2.6-3.0</th>
<th>3.1-3.5</th>
<th>≥ 3.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE cases</td>
<td>128</td>
<td>121</td>
<td>73</td>
<td>41</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>TE controls</td>
<td>132</td>
<td>389</td>
<td>544</td>
<td>280</td>
<td>114</td>
<td>122</td>
</tr>
<tr>
<td>ICH cases</td>
<td>10</td>
<td>24</td>
<td>45</td>
<td>34</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>ICH controls</td>
<td>41</td>
<td>144</td>
<td>252</td>
<td>119</td>
<td>68</td>
<td>41</td>
</tr>
</tbody>
</table>

Circ CV Qual and Outcomes 2009;2:297-304
# CHA$_2$DS$_2$-VASc Scoring System

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C</strong>ongestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td><strong>H</strong>ypertension</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong>ge ≥ 75</td>
<td>2</td>
</tr>
<tr>
<td><strong>D</strong>iabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td><strong>S</strong>troke, TIA, thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td><strong>V</strong>ascular disease</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong>ge 65-74</td>
<td>1</td>
</tr>
<tr>
<td><strong>S</strong>ex <strong>c</strong>ategory (i.e. female sex)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

Note: Maximum score is 9 since age may contribute 0, 1 or 2 points.

AHA/ACCF/HRS Guideline Update (2014)

<table>
<thead>
<tr>
<th>Clinical Profile (Applies to PAF, as well)</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CHA}_2\text{DS}_2)-VASc (\geq2)</td>
<td>Warf., INR 2-3, or novel agent</td>
</tr>
<tr>
<td>( \text{CHA}_2\text{DS}_2)-VASc (=1)</td>
<td>OAC, ASA, or no AT Rx</td>
</tr>
<tr>
<td>( \text{CHA}_2\text{DS}_2)-VASc (=0)</td>
<td>No Antithrombotic Rx</td>
</tr>
</tbody>
</table>

Paroxysmal (PAF) = persistent = permanent

NOACs: Meta-Analysis of the Four Trials (RELY; ROCKET-AF; ARISTOTLE; ENGAGE-AF)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke</td>
<td>0.92 (0.83-1.02)</td>
</tr>
<tr>
<td>ICH</td>
<td>0.48 (0.39-0.59)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>1.26 (1.01-1.55)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.86 (0.73-1.00)</td>
</tr>
<tr>
<td>All cause death</td>
<td>0.90 (0.85-0.95)</td>
</tr>
</tbody>
</table>

Dabigatran; Rivaroxaban; Apixaban; Edoxaban
*High dose NOAC/warfarin

*Lancet 2013 Dec 3. doi:pii: S0140-6736(13)62343-0. 10.1016/S0140-6736(13)62343-0.*
Potential Beneficial Impact of Novel Anticoagulants

- Enlarging the % AF patients protected from ischemic stroke
  - the warfarin-reluctant
  - Lowering stroke risk threshold for anticoagulants
- Reducing intracranial hemorrhage
- Better outcomes: stroke and bleed
- Ease of use

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Warren Alpert Medical School of Brown University and the National Minority Quality Forum
Background

• Atrial Fibrillation (AF) is the most common cardiac rhythm disorder and is associated with a significant increased risk of stroke, morbidity, and mortality.
• Data support the effectiveness of warfarin in reducing AF-related stroke.
• The effect of warfarin on all-cause hospitalizations and mortality is unclear.
• Warfarin is underutilized.
• Before 2010, warfarin was the primary anticoagulant used to reduce the risk of stroke in AF patients.
• The effectiveness of warfarin on stroke and CV outcomes when stratified by patient diversity is not well described.
Purpose

• To investigate the patterns of warfarin use in Medicare beneficiaries stratified by Patient Diversity (race/ethnicity/gender) to inform the impact of warfarin anticoagulation on CV outcomes (stroke, hospitalization, and mortality).
Methods

- Data extracted from Centers for Medicare and Medicaid Services (CMS) enrollment files.
- 100% Beneficiary Annual Summary Files (BASF) for Yrs 2000 to 2010 and carrier files used.
- BASF identified AF from either 1 inpatient claim or 2 outpatient claims during the year.
- Baseline demographics, race/ethnicity, gender, and CV outcomes were recorded.
- Medicare/Administrative claims used for outcomes.
- 3 cohorts created: 2000, 2005, 2007; each followed for 4 to 5 yrs.
Methods

• Kaplan-Meier survival analyses conducted to examine warfarin use and CV outcomes (death, stroke). Life-table method.
• Cox Regression used to exam effects of warfarin and other covariates.

• Poisson Regression Model (age, gender, race, CHADS2, consumption cluster in prior year, and warfarin use) used to assess all-cause hospitalizations rather than first hospitalization.
## 20% Sample Cohorts

<table>
<thead>
<tr>
<th>Year</th>
<th>Overall</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
<th>Asian</th>
<th>Other</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>38.10%</td>
<td>38.60%</td>
<td>28.40%</td>
<td>32%</td>
<td>31.90%</td>
<td>30.20%</td>
<td>40.50%</td>
<td>36.10%</td>
</tr>
<tr>
<td>2005</td>
<td>44.50%</td>
<td>45.10%</td>
<td>35.10%</td>
<td>39.60%</td>
<td>38.60%</td>
<td>39.40%</td>
<td>46.70%</td>
<td>42.70%</td>
</tr>
<tr>
<td>2007</td>
<td>46.80%</td>
<td>47.30%</td>
<td>38.90%</td>
<td>42.90%</td>
<td>41.10%</td>
<td>43.80%</td>
<td>49.20%</td>
<td>44.70%</td>
</tr>
</tbody>
</table>

### AF Stroke

<table>
<thead>
<tr>
<th>Year</th>
<th>Overall</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
<th>Asian</th>
<th>Other</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>3.90%</td>
<td>3.75%</td>
<td>6.89%</td>
<td>5.33%</td>
<td>4.77%</td>
<td>4.55%</td>
<td>3.22%</td>
<td>4.44%</td>
</tr>
<tr>
<td>2005</td>
<td>2.98%</td>
<td>2.85%</td>
<td>5.51%</td>
<td>4.13%</td>
<td>3.54%</td>
<td>3.35%</td>
<td>2.40%</td>
<td>3.47%</td>
</tr>
<tr>
<td>2007</td>
<td>2.70%</td>
<td>2.59%</td>
<td>4.87%</td>
<td>3.50%</td>
<td>3.18%</td>
<td>2.77%</td>
<td>2.15%</td>
<td>3.17%</td>
</tr>
</tbody>
</table>

*P = 0.01 for both (Chi-Square)*
Warfarin Effect: Stroke

*\(p<0.01\)
Warfarin Effect: Mortality

*p<0.01
2007 AF Cohort (n = 470K): Annual # of Hospitalizations as Outcome Variable

- Black RR = 1.26*
- Hispanic RR = 1.03
- Asian RR = 0.83*
- (White is Reference)

- Female RR = 1.02*

- Warfarin Use RR = 0.71*

- *p < 0.0001
CV Outcomes Summary

• Compared to Whites, Black pts were 40 % more likely to have a stroke even after adjustment for warfarin use (p < 0.0001).
• Significant reduction in mortality with use of Warfarin (> 70 %; p < 0.0001).
  Black pts, however, had a 25 % (p < 0.0001) higher mortality risk than White pts even after adjusting for warfarin.
• 5 year survival for all AF beneficiaries was about 50 %.
• Asians had better CV outcomes.
• Women had lower death rate than men, but slightly higher rate of stroke and hospitalization.
Conclusions

• Overall, increased warfarin utilization in AF pts over 10 yrs has resulted in clinical CV outcomes benefits.
  – Reduction in Stroke
  – Reduction in All-Cause mortality and hospitalizations

• Significant differences in CV outcomes exist depending on race/ethnicity and gender.

• Black Pts had worse outcomes.

• Further investigation on the disparity in CV outcomes is needed.
Implications

- Patient Diversity should be a focus for future trials in AF-related CV Outcomes
Anticoagulation of AF

• There is no controversy regarding AC in AF pts at risk for stroke whereas there is controversy around other AF therapies.

• ACC PINNACLE (9/2013): 57 %
ACTIVE-W VKA arm: Time in Therapeutic Range (TTR)

<table>
<thead>
<tr>
<th>Country</th>
<th>Mean TTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>46.3</td>
</tr>
<tr>
<td>Brazil</td>
<td>47.1</td>
</tr>
<tr>
<td>Russia</td>
<td>53.4</td>
</tr>
<tr>
<td>Poland</td>
<td>55.3</td>
</tr>
<tr>
<td>Belgium</td>
<td>58.7</td>
</tr>
<tr>
<td>United States</td>
<td>62.9</td>
</tr>
<tr>
<td>Netherlands</td>
<td>64.0</td>
</tr>
<tr>
<td>Argentina</td>
<td>64.5</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>66.8</td>
</tr>
<tr>
<td>Italy</td>
<td>67.2</td>
</tr>
<tr>
<td>Canada</td>
<td>68.5</td>
</tr>
<tr>
<td>Germany</td>
<td>69.3</td>
</tr>
<tr>
<td>Australia</td>
<td>74.5</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>74.8</td>
</tr>
<tr>
<td>Sweden</td>
<td>77.8</td>
</tr>
</tbody>
</table>

“In medicine, geography is destiny.”
Dabigatran: FDA Approval (1st NOAC)

FDA approval Oct 19, 2010

Ethnic group reported in results: 12,679 European/Arab; 5,433 Other (trended NS better at both doses vs. warfarin than “white”). Ethnicity not reported for other 2 NOAC in main paper. Apixaban 1.2 %/Rivaroxaban 1.3 %/Dabigatran 1.2 % Black (FDA).
FDA Report: Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database October 2010-December 2011

October 2010 - August 2012: ~3.7 million Pradaxa prescriptions 
~ 725,000 patients from U.S. outpatient pharmacies.

| Analysis                     | Dabigatran | | Warfarin | | |
|------------------------------|------------|-----------------|------------|-----------------|
|                              | No. of      | No. of          | Incidence  | No. of          | Incidence  |
|                              | Patients    | Events          | (no. of    | Patients        | (no. of    |
|                              |             |                 | events/100,000 days at risk) |                 | events/100,000 days at risk) |
| Gastrointestinal hemorrhage  | 10,599      | 16              | 1.6        | 43,541          | 160        | 3.5       |
| Intracranial hemorrhage      | 10,587      | 8               | 0.8        | 43,594          | 109        | 2.4       |

Racial Disparities in Anticoagulation of AF

• Anticoagulation Challenges
  – Racial differences in warfarin anticoagulation: dosing, TTR, genotyping for warfarin
  – Underdiagnosis?
  – Less guideline based prescribing in ethnic groups
  – Less than 2% of study pts in 3 approved NOACs were black
  – The CV Outcomes Paradox
Potential Solutions

• Racial differences in healthcare access, quality of care, and cardiovascular outcomes must be addressed to achieve more meaningful population health benefits, especially as the non-white population becomes less prevalent in the coming decades.

• Patient education, public education, and scientific data will be helpful in this regard.

• Inclusion of racial diversity in all types of studies will reduce the burden of potential gaps in diagnosis and therapy related to CV disease and AF.

• Use of Real-World Data to address gaps in clinical trials.