New Therapeutic Options for Stroke Prevention in Atrial Fibrillation

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February 13, 2013
Atrial Fibrillation: Disclosures

• Dr. Jackson
  – Hoechst-Roussel Pharmaceuticals – 10 years (streptokinase)
  – Dupont-Merck Pharmaceuticals – 2 years (warfarin)
  – Bristol-Myers Squibb – 16 years (clopidogrel, apixaban)
    • Pension and stockholder
  – Thomas Jefferson University – 20 months
  – Health Outcomes Insights – 3 years

• Acknowledgement: Some slides courtesy of
  – Geno J Merli, MD, FACP, FHM, FSVM, Professor of Medicine, Co-Director Jefferson Vascular Center, Senior Vice President and Chief Medical Officer Thomas Jefferson University Hospitals
Stroke Prevention in Atrial Fibrillation: Learning Objectives

1. Describe the characteristics of the population needing stroke prevention in chronic atrial fibrillation

2. Review the comparative effectiveness of oral anticoagulant therapeutic options, benefits and risks

3. Explore issues of effectiveness, safety and value from a population health perspective
Outcomes Research: The Purpose

To determine:

- **Do patients benefit?**
  - Warfarin works, but sub-optimally for many
  - New trials and designs (NOACs...)

- **What treatments work best?**
  - Evaluating opportunities for optimal use
  - Considering implications of RE-LY, ROCKET, ARISTOTLE, and Real World Studies...

- **Are health-care resources well spent?**

Agency for Health Care Policy & Research, 1990
Agency for Healthcare Research and Quality, 2003
Atrial Fibrillation (AF): Morbidity and Mortality

• ~15% of all strokes occur in people with AF

• Risk of stroke in untreated AF patients averages ~ 5% /yr

• Risk of stroke in AF patients by age group
  — 1.5% in 50 to 59 year age group
  — 23.5% in 80 to 89 year age group

• AF is associated with a 50 to 90% increase in risk of death after adjustment for coexisting CV conditions

Projected Number of Persons with AF in the U.S. between 2000 and 2050

Assumes no further increase in age-adjusted AF incidence (yellow curve) and assumes a continued increase in incidence rate as evident in 1980 to 2000 (red curve)

Efficacy and Effectiveness

- Generalizability
- Internal Validity
- Efficacy
- Effectiveness

Source: Fletcher, Fletcher, Wagner 1988
Historical Efficacy of warfarin in Atrial Fibrillation

Five Randomized Trials in Non-Rheumatic AF

<table>
<thead>
<tr>
<th>Study</th>
<th>Warfarin(#)</th>
<th>Cont.(#)</th>
<th>INR</th>
<th>RR</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td>335</td>
<td>336</td>
<td>2.8-4.2</td>
<td>60%</td>
<td>0.027</td>
</tr>
<tr>
<td>SPAF</td>
<td>210</td>
<td>211</td>
<td>2.0-4.5</td>
<td>67%</td>
<td>0.01</td>
</tr>
<tr>
<td>BAATAF</td>
<td>212</td>
<td>208</td>
<td>1.5-2.7</td>
<td>86%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CAFA*</td>
<td>187</td>
<td>191</td>
<td>2.0-3.0</td>
<td>45%</td>
<td>0.25</td>
</tr>
<tr>
<td>SPINAF</td>
<td>260</td>
<td>265</td>
<td>1.4-2.8</td>
<td>79%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Stopped early due to published positive results

68% overall risk reduction for stroke
Relative Effects of Various CV Therapies

Source: Granger S, MacMurray J. JACC 2006;48:434-7; and Michael Hanna, MD.
Trends in Warfarin Use and Therapeutic Outcomes

36% AF patients with no identified contraindications not anticoagulated despite moderate or high risk

40% No-Rx ESC 2012, Garfield Registry


Treatment would prevent 40,000 strokes per year.
Warfarin Liabilities

• Narrow therapeutic range (2.0-3.0).
• Food effect and multiple drug and botanical interactions
• Need for therapeutic monitoring.
• INR of warfarin patients is in the therapeutic range only ~60% of the time, in trials.
• Risk of intracranial hemorrhage, particularly in the elderly.
• Warfarin is a leading cause of adverse drug events and ER visits.

Source: Elaine M. Hylek, MD, MPH, Associate Professor of Medicine, Boston University
Factors Influencing Warfarin Under-Use

1. Lack of consensus on perceived or actual barriers to use: e.g., fall risk, prior bleeding, concurrent medicine use, ETOH...

2. Suboptimal candidacy for anticoagulant therapy e.g., comorbidities, polypharmacy, non-adherence...

3. Barriers to INR monitoring-dependence on caregivers, logistical constraints, cost, hassle

4. Inability to tolerate therapy long-term

Source: Elaine M. Hylek, MD, MPH, Associate Professor of Medicine, Boston University
## Adherence to Quality Indicators: Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>76</td>
</tr>
<tr>
<td>Prenatal care</td>
<td>73</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65</td>
</tr>
<tr>
<td>CHF</td>
<td>64</td>
</tr>
<tr>
<td>Depression</td>
<td>58</td>
</tr>
<tr>
<td>Asthma</td>
<td>53</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>45</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>25</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>23</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>11</td>
</tr>
</tbody>
</table>

Perceived or Actual Barriers to Warfarin Use in Atrial Fibrillation Based on Electronic Medical Records

M. Rosenman,¹,² T. Simon,³ E. Teal,¹ P. McGuire,¹ D. Nisi,¹ J. Jackson⁴

¹ Regenstrief Institute, Inc., Indianapolis, Indiana, USA
² Indiana University School of Medicine, Indianapolis, Indiana, USA
³ Bristol-Myers Squibb, Lawrenceville, NJ, USA
⁴ Thomas Jefferson University, Philadelphia, PA, USA

Presented: European Society of Cardiology, 2009
American Heart Association, 2009

This study was funded by Bristol-Myers Squibb and Pfizer Inc.
Methods: Study Population

• Inclusion criteria
  – New-onset NVAF between 1998 and 2007
    • Defined as first encounter (hospital or office visit) with AF stored in the RMRS

• Exposure: Warfarin (vitamin K antagonist [VKA])
  – Hospital/Clinic pharmacy transaction records
  or
  – Physician Order Entry System (Gopher)¹
    • An electronic version of a prescription


Source: Rosenman, ESC and AHA 2009
Methods: Identification of Barriers

• Perceived or actual barriers to warfarin use:
  – Alcohol abuse (ETOH)
  – Cirrhosis/Hepatitis
  – Intracranial hemorrhage
  – Gastrointestinal or genitourinary hemorrhage
  – Other hemorrhage
  – Predisposition to falls (Falls)
  – Renal insufficiency (RI)

any time before or on the AF index date

• ICD9 codes

• RMRS dictionary terms (Gopher system has drop-down menus with diagnoses, etc)

Source: Rosenman, ESC and AHA 2009
Methods: Risk Adjustments

<table>
<thead>
<tr>
<th>Risk Score / Factor (points)</th>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt;</th>
<th>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt; – VASc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prior Stroke or TIA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (Previous MI, PAD, aortic plaque)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Age (65-74)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Results: Perceived or Actual Barriers by Exposure to Warfarin by CHADS$_2$ Score

Source: Rosenman, ESC and AHA 2009
Results: How long before the AF index date was the most recent record of the barrier? (N=599 exposed to warfarin, and with CHADS2 > 0)

- **ETOH**: 45% Within the past 60 days, 44% 61-364 days, 10% A year or more ago
- **GI/GU Hemorrhage**: 50% Within the past 60 days, 39% 61-364 days, 11% A year or more ago
- **Renal Insufficiency**: 74% Within the past 60 days, 19% 61-364 days, 7% A year or more ago
- **Predisposition to Falls**: 26% Within the past 60 days, 16% 61-364 days, 58% A year or more ago
- **Cirrhosis/Hepatitis**: 63% Within the past 60 days, 31% 61-364 days, 6% A year or more ago

Source: Rosenman, ESC and AHA 2009
Outcomes Research: The Purpose

To determine:

- Do patients benefit?
  - Warfarin works – RCTs = 68% Relative Risk Reduction (RRR) of Strokes
  - But in the REAL WORLD
    - ~40% UNTREATED
    - ~27% GOOD QUALITY OF CARE
    - Many BARRIERS to effective care
      - REAL or IMAGINED

Agency for Health Care Policy & Research, 1990
Agency for Healthcare Research and Quality, 2003
Current Trials of Antithrombotic Therapy for Stroke Prevention in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Blind</th>
<th>CHADS</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran</td>
<td>OL</td>
<td>≥ 1</td>
<td>18,000</td>
</tr>
<tr>
<td>ROCKET</td>
<td>Rivaroxaban</td>
<td>DB</td>
<td>≥ 2-3</td>
<td>14,000</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban</td>
<td>DB</td>
<td>≥ 1</td>
<td>15,000</td>
</tr>
<tr>
<td>ENGAGE</td>
<td>Endoxaban</td>
<td>DB</td>
<td>≥ 2</td>
<td>20,000</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>66,000</td>
</tr>
</tbody>
</table>

AF Historical trials: 3,763
AF Trials: Key Design Issues

• Superiority vs. non-inferiority?
  • Non-inferiority margin
• Open-label (PROBE) vs. double-blind (DB)?
• Dosing issues for benefit, for risk (e.g. renal)
• Benefit-risk tolerances
• Extrapolations for populations at risk

See: Jessica Mega’s NEJM (28 Aug 11) editorial and Kevin Jackson’s AHJ (2008) article!
1. Dabigatran 150 mg, BID  
2. Dabigatran 110 mg, BID  
3. Warfarin INR 2 to 3 range  

*Courtesy: Dr. G Merli* 

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Rivaroxaban 20 mg, Qday
Warfarin INR 2-3 Range

Courtesy: Dr. G Merli

Patel M et al, NEJM 2011;365:883-891
Apixaban versus Warfarin in Patients with Atrial Fibrillation

Apixaban 5 mg, BID
Warfarin INR 2 - 3

Courtesy: Dr. G Merli

# Comparison of Oral Anticoagulants*

<table>
<thead>
<tr>
<th>Generic name</th>
<th>warfarin</th>
<th>dabigatran</th>
<th>rivaroxiban</th>
<th>apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>Coumadin</td>
<td>Pradaxa</td>
<td>Xarelto</td>
<td>Eliquis</td>
</tr>
<tr>
<td>Half-Life (hours)</td>
<td>40</td>
<td>12-14</td>
<td>7-10</td>
<td>12</td>
</tr>
<tr>
<td>Renal Clearance %</td>
<td>0</td>
<td>80</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>Dose</td>
<td>Once a day</td>
<td>Twice a day</td>
<td>Once a day</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Approx $/pill</td>
<td>$0.64</td>
<td>$4.37 bid</td>
<td>$8.75</td>
<td>&gt;$4.50 bid</td>
</tr>
</tbody>
</table>

## Comparison of oral anticoagulants – baseline*

<table>
<thead>
<tr>
<th>Baseline Data</th>
<th>warfarin</th>
<th>dabigatran</th>
<th>rivaroxiban</th>
<th>apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71</td>
<td>73</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>CHADS₂ (mean)</td>
<td>2.2</td>
<td>3.5</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>CHADS₂ 3-6 (%)</td>
<td>32</td>
<td>87</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Prior stroke (%)</td>
<td>20</td>
<td>55</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Prior warfarin (%)</td>
<td>50</td>
<td>62</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

* Lip GYH, et.al. *JACC* 2012;60:738-46
## Comparison of oral anticoagulants – outcomes*

### Annual Incidence – rate per 100 person-years

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran (150 mg)</th>
<th>Rivaroxiban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Results (P †)</strong></td>
<td>Versus placebo-asa</td>
<td>Versus warfarin</td>
<td>Versus warfarin</td>
<td>Versus warfarin</td>
</tr>
<tr>
<td><strong>Stroke or systemic emb</strong></td>
<td>1.4 v. 4.7 †</td>
<td>1.11 v. 1.71 †</td>
<td>2.12 v. 2.42</td>
<td>1.27 v. 1.60 †</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>0.1 v. 0.38 †</td>
<td>0.5 v. 0.7 †</td>
<td>0.24 v. 0.47 †</td>
<td></td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td>0.92 v. 1.20 †</td>
<td>NR</td>
<td>0.97 v. 1.05</td>
<td></td>
</tr>
<tr>
<td><strong>Major bleeding (on treatment)</strong></td>
<td>1.6 v. 1.0 †</td>
<td>3.11 v. 3.36</td>
<td>3.6 v. 3.45</td>
<td>2.13 v. 3.09 †</td>
</tr>
<tr>
<td><strong>All cause death</strong></td>
<td>3.64 v. 4.13</td>
<td>4.5 v. 4.9</td>
<td>3.52 v. 3.94 †</td>
<td></td>
</tr>
</tbody>
</table>

NR – not reported

*Granger and Armaganijan, *Circ* 2012;125:159-64.

## Comparison of oral anticoagulants – % RRR*

**Relative Risk Reduction (RRR)**

<table>
<thead>
<tr>
<th></th>
<th>warfarin</th>
<th>dabigatran (150 mg)</th>
<th>rivaroxiban</th>
<th>apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Results</strong></td>
<td>Versus placebo-asa</td>
<td>Versus warfarin</td>
<td>Versus warfarin</td>
<td>Versus warfarin</td>
</tr>
<tr>
<td>(RRR; P *)</td>
<td>68 % ♦</td>
<td>34 % ♦</td>
<td>12 %</td>
<td>21 % ♦</td>
</tr>
<tr>
<td><strong>Stroke or systemic emb</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74 % ♦</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 % ♦</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 %</td>
<td></td>
<td></td>
<td>31 % ♦</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 %</td>
<td></td>
<td>104 %</td>
<td>31 % ♦</td>
</tr>
<tr>
<td><strong>All cause death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 %</td>
<td></td>
<td>8 %</td>
<td>11 % ♦</td>
</tr>
</tbody>
</table>

* Granger and Armaganijan, *Circ* 2012;125:159-64.
Caveats Relating to Published Trials Concerning Hemorrhage

Randomized trials
- Enrolled few patients ≥ 80 years
- Highly selected, closely monitored
- Vitamin K antagonist at entry

Prospective cohort studies
- Predominantly non-inception cohort studies of prevalent warfarin use (survivor bias)
- Enrolled few patients ≥ 80 years
- Varying definitions of bleeding
Danger Ahead:
Watch Out for Indirect Comparisons!*

• Use Extreme Caution – e.g. Fibrinolytics misleading
• Potential Mitigating Issues with Anticoagulants:
  • Trial designs
  • Event rates (e.g. MI and Bleeding)
  • CHADS\textsubscript{2} Risk Cohorts
  • INR – TTR (Time in Therapeutic Range)
• Regulatory Considerations, for example:
  • Dabigatran - 110 mg not approved
    • bleeding vs. warfarin - similar
  • Rivaroxiban - Stroke and bleeding vs. warfarin - similar
  • Apixaban - Mortality vs. warfarin - superior

* Cannon and Kohi, JACC 2012;60:747-8
Pooled Indirect Comparisons:
DABI, RIVA and APIX versus Warfarin*

Stroke or Systemic Embolism  ↓ 21% (p<0.001)
Stroke  ↓ 23% (p<0.001)
Hemorrhagic Stroke  ↓ 53% (p<0.001)
All Cause Mortality  ↓ 12% (p<0.001)
Major Bleeding  ↓ 13% (p<0.001)

* Lip GYH et.al, JACC 2012;60:738-46
Indirect Comparisons: CAUTION

◆ Lip GYH, et al. *JACC* 2012;60:738-746
  - Stroke / sys emb: DABI better RIVA (by 26%)
  - Ischemic stroke, no significant differences
  - Major bleeding: APIX < DABI_{150} 26%; < RIVA 34%; = DABI_{110}
  - No profound significant differences in efficacy
    - safety – better for APIX or DABI_{110}

  - CHADS\_2 \geq 3 – ADJUSTMENT: DABI 150 vs. APIX vs. RIVA
  - For efficacy, no significant differences
    - although DABI & APIX numerically better RIVA
  - For major hemorrhage, APIX less than DABI or RIVA
  - Until head-to-head trials, adjusted indirect comparisons are one tool to guide initial therapeutic choices
Outcomes Research: The Purpose

To determine:

- What treatments work best?
  - RCT EVIDENCE: RE-LY, ROCKET-AF, ARISTOTLE
    - NOACs superior to warfarin
    - First viable alternatives in 50 years
  - Real World Studies ????
    - Usual Care: Safety and Effectiveness
    - Monitoring
    - Cost

Agency for Health Care Policy & Research, 1990
Agency for Healthcare Research and Quality, 2003
Recent Literature: Commentaries

◆ Ansell J, *Circ* 2012;125:165-170
  • Time in Therapeutic Range is important to effectiveness
  • Short $T_{1/2}$, has implications for adherence and stroke risk
  • No monitoring has implications for safety
  • No antidote for emergent situations
  • Cost

◆ Spinler SA and Shafir V, *Circ* 2012;126:133-137
  • Pharmacy perspective; case study approach; easy read
  • P-450 system and CYP3A4 metabolic implications
    • Drug-drug interactions, renal disease adjustments
  • Switching therapies
  • Combined use of other anticoagulants (UFH, LMWH...)

Jefferson.
School of Population Health
# Novel Anticoagulant Comparison

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialyzable</td>
<td>Yes</td>
<td>Probably Not</td>
<td>Probably Not</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>35%</td>
<td>&gt;90%</td>
<td>87%</td>
</tr>
<tr>
<td>Reversing Agent</td>
<td>No</td>
<td>Possibly</td>
<td>Possibly</td>
</tr>
</tbody>
</table>

**Courtesy: Dr. G Merli**

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate: A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

Courtesy: Dr. G Merli

Package Insert Recommendations

• Dabigatran
  – FFP, Prothrombin Complex Concentrate
  – Activated Factor VII
  – Dialysis

• Rivaroxaban and Apixaban
  – Prothrombin Complex Concentrate
  – FFP

*Courtesy: Dr. G Merli*
AF Evidence: Key Practice Issues

• Well controlled vs. usual care?
• Controlling barriers to effective care:
  • Patient medical characteristics (elderly...)
  • Patient capabilities (logistics...) and comprehension (instructions, risk...)
  • Systems (MD/office logistics, testing, $, legal...)  
  • Therapeutic motivations (Pt/Carer/MD/RN/PharmD)
• Net clinical benefit - tradeoffs?
  • For the patient..., For the family...
  • For the providers..., For the system...
  – Value assessments, for whom...

Outcomes Research: The Purpose

To determine:

- Are health-care resources well spent?
  - Cost Offsets
  - REAL WORLD Scenarios
- Concluding thoughts

Agency for Health Care Policy & Research, 1990
Agency for Healthcare Research and Quality, 2003
## Comparison of Oral Anticoagulants – continued*

### Average medical costs in $/patient/year

<table>
<thead>
<tr>
<th></th>
<th>warfarin</th>
<th>dabigatran</th>
<th>rivaroxiban</th>
<th>apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke</td>
<td>490</td>
<td>373</td>
<td>461</td>
<td>451</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>225</td>
<td>59</td>
<td>133</td>
<td>115</td>
</tr>
<tr>
<td>Systemic emb</td>
<td>40</td>
<td>38</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>MI</td>
<td>292</td>
<td>371</td>
<td>237</td>
<td>257</td>
</tr>
<tr>
<td>Major bleed</td>
<td>998</td>
<td>1030</td>
<td>1106</td>
<td>715</td>
</tr>
<tr>
<td>CRN-M bleed</td>
<td>38</td>
<td>35</td>
<td>41</td>
<td>26</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2084</td>
<td>1905</td>
<td>1995</td>
<td>1599</td>
</tr>
</tbody>
</table>

Savings vs warfarin

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-----</td>
<td>179</td>
<td>89</td>
<td>485</td>
</tr>
</tbody>
</table>

**CRN-M Bleed** – Clinically relevant non-major bleed

---

* Deitelzweig, S, et.al. Ochsner Clinic, New Orleans, LA, American College of Cardiology, April, 2012, Chicago, IL
## Intervention Scenarios Representing Actual Practice Management / Outcomes

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Stroke Rate</th>
<th>Bleeding Rate</th>
<th>INR compliance</th>
<th>Discontinuation rates</th>
<th>CEA v. warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin Poor</td>
<td>higher</td>
<td>higher</td>
<td>poor</td>
<td>poor</td>
<td>+++</td>
</tr>
<tr>
<td>Warfarin Fair</td>
<td>high</td>
<td>high</td>
<td>fair</td>
<td>fair</td>
<td>++</td>
</tr>
<tr>
<td>Warfarin Good</td>
<td>Low</td>
<td>low</td>
<td>good</td>
<td>minimal</td>
<td>– / +</td>
</tr>
<tr>
<td>ASA</td>
<td>Higher</td>
<td>low</td>
<td>NA</td>
<td>minimal</td>
<td>+++</td>
</tr>
<tr>
<td>No Therapy</td>
<td>highest</td>
<td>some</td>
<td>NA</td>
<td>NA</td>
<td>+++</td>
</tr>
<tr>
<td>No Therapy post DC</td>
<td>highest</td>
<td>some</td>
<td>NA</td>
<td>100%</td>
<td>+++++</td>
</tr>
</tbody>
</table>

* Estimated from literature, see notes

CEA v. warfarin, plus: + Potential for positive findings
FDA approval of the latest NOAC for stroke prevention in AF: The "tipping point" for novel oral anticoagulants

January 11, 2013

Samuel Z. Goldhaber, MD
Professor of Medicine, Harvard Medical School
Director, Venous Thromboembolism Research Group
Co-Director, Anticoagulation Management Service
Cardiovascular Division, Brigham and Women's Hospital, Boston, MA
Concluding Thoughts

• Effective drugs are usually cost-effective
• Well-controlled trials suggest superiority of NOACs, BUT...
• Real world experience is needed! Issues to watch:
  – Non-trial subjects (elderly, renal, falls...)
  – Emergent situations (bleeding and risk)
  – Usual Care: Adherence, DDIs, dosing, switching...
  – Afib and ACS (WOEST at ESC 2012)
    • clopidogrel + warfarin > aspirin + clopi + warf
      — yielded better efficacy and less bleeding
• Other uses: Surgery-medical VTEp, DVT, PE, ACS and valves?
Please fill out your evaluation
Thank You!

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