NOACs – Update 2016

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Conflict of Interest Statement

- Consulting: Amgen, Astra Zeneca, AtriCure, Bayer, Biosense Webster, Biotronik, BMS, Boehringer Ingelheim, Boston Scientific, Daiichi-Sankyo, Medtronic, Pfizer, Sanofi-Aventis, SJM
- Speaker honoraria: Astra Zeneca, Bayer, Biosense Webster, Biotronik, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Novartis, Pfizer, Roche, Sanofi-Aventis, SJM, Sorin, Zoll
- Grants (through institution): Bayer, Biotronik, Boston Scientific, Daiichi-Sankyo, Medtronic, St. Jude Medical
- Co-president CorXL
- Collaboration with TIMI study group (ENGAGE AF-TIMI 48)
Phase III AF trials: All-cause mortality

For illustrative purpose only! No head-to-head comparisons!

‘Real Life’ Data aims to complement Clinical Trial Data

**Clinical trial**
- Patients are selected by stringent protocol criteria
- Treatment / observation is defined in the protocol
- Methodology aims for reducing bias when a randomized design is used

**RLE study**
- Patients are selected by the treating physician
- Over- and under-reporting of events possible
- Observation of real-life subgroups possible
Table 1. Incidence rates and adjusted hazard ratios comparing matched new user cohorts treated with Pradaxa 75 mg or 150 mg* or warfarin for non-valvular atrial fibrillation based on 2010-2012 Medicare data. Warfarin is the reference group.

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence rate per 1,000 person-years</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa (dabigatran)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>11.3</td>
<td>0.80 (0.67-0.96)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>3.3</td>
<td>0.34 (0.26-0.46)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>34.2</td>
<td>1.28 (1.14-1.44)</td>
</tr>
<tr>
<td>Acute MI</td>
<td>15.7</td>
<td>0.92 (0.78-1.08)</td>
</tr>
<tr>
<td>Mortality</td>
<td>32.6</td>
<td>0.86 (0.77-0.96)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>26.5</td>
<td></td>
</tr>
<tr>
<td>Acute MI</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>37.8</td>
<td></td>
</tr>
</tbody>
</table>

* Primary findings for Pradaxa are based on analysis of both 75 and 150 mg together without stratification by dose.
XANTUS: Study Objective and Design

**Objective:** Prospective Real world study on the safety profile of rivaroxaban in patients with NVAF

*Population:*
Consecutively enrolled adult patients with NVAF receiving rivaroxaban for stroke/non-CNS SE prevention

*Rivaroxaban:*
treatment duration and dose at physician’s discretion

N=6,784

Data collection at initial visit, hospital discharge (if applicable) and quarterly*

1 year

Prospective, single-arm, observational, non-interventional phase IV study
Statistical analyses were descriptive and exploratory in nature

**Primary outcomes:** major bleeding (ISTH definition), all-cause mortality, any other adverse events

**Secondary outcomes:** symptomatic thromboembolic events (stroke, SE, TIA) and MI, non-major bleeding events (all adjudicated centrally by an independent committee (CAC) blinded to individual patient data)

* Exact referral dates for follow-up visits not defined (every 3 months recommended)
# For rivaroxaban discontinuation ≤1 year, observation period ends 30 days after last dose. Observational design means no interference with clinical practice was allowed

Rivaroxaban was associated with a

- Significant 47% reduction in ICH vs. VKA
- Comparable rate of ischemic stroke vs. VKA
- Significant 39% reduction in the combined endpoint of ICH and ischemic stroke vs. VKA

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>VKA</th>
<th>HR (95% CI) Rivaroxaban vs. VKA</th>
<th>HR (95% CI) Rivaroxaban vs. VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (%/year)</td>
<td>Rate (%/year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>0.49</td>
<td>0.96</td>
<td>0.53 (0.35–0.79)*</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.54</td>
<td>0.83</td>
<td>0.71 (0.47–1.07)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>0.95</td>
<td>1.6</td>
<td>0.61 (0.45–0.82)*</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05 vs. VKA
Unadjusted incidence rates of major bleeding (in-patient bleeding per 100 person-year) and adjusted HR\(^1\) for apixaban vs warfarin

Unadjusted major bleeding incidence (% / year)

Adjusted HR=0.52 (95% CI: 0.30-0.89)

Warfarin (n=12,713)

Apixaban (n=2,402)

Adjusted major bleeding incidence (% / year)

4.66 %

2.35 %

Adapted from Lip et al. 2015

Data from retrospective real-world research, not a randomised controlled trial

* Cox-proportional hazards model was used to assess the risk of first major bleed across index OAC prescription categories, adjusted for age, gender, region, embolic or primary ischaemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of stroke or transient ischaemic attack, history of bleeding, Charlson comorbidity index, and co-medications at baseline.

Lip GYH et al. Real world comparison of major bleeding risk among non-valvular atrial fibrillation patients newly initiated on apixaban, dabigatran, rivaroxaban or warfarin.

Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a ‘real world’ atrial fibrillation population: A modelling analysis based on a nationwide cohort study

Amitava Banerjee¹; Deirdre A. Lane¹; Christian Torp-Pedersen²; Gregory Y. H. Lip¹
¹University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; ²Department of Cardiology, Copenhagen University Hospital Gentofte, Denmark

• Event rates / 100 pys for ischemic stroke and intracranial hemorrhage were calculated using data from the Danish study population for patients on no treatment and on warfarin

• Using data from recent trials of the new OACs, the event rates for ischemic stroke and intracranial hemorrhage were estimated for the Danish population
Net clinical benefit: CHADS-VASC vs. HAS-BLED

CHADS-VASC and HAS-BLED ≤ 2

Banerjee et al., Thromb & Hemost 2012
Net clinical benefit: CHADS-VASC vs. HAS-BLED

Banerjee et al., Thromb & Hemost 2012
Idarucizumab

A

Dab

PT

IIa

a-Xa

Xa

Va

B

C

Dab

PT

IIa

Idarucizumab

Xa

Va

Enriquez et al., Europace 2014
REVERSE-AD

A Dilute Thrombin Time in Group A

B Dilute Thrombin Time in Group B

Pollack et al., NEJM 2015
A Concentration of Unbound Dabigatran in Group A

B Concentration of Unbound Dabigatran in Group B

Pollack et al., NEJM 2015
Andexanet Alfa
Reversal of anticoagulation by factor Xa inhibitors

Recombinant engineered version of human factor Xa
• Acts as a factor Xa decoy
• High affinity for all direct factor Xa inhibitors
• Changed in a way that catalytic activity is eliminated (serine → alanine) and prothrombin cleavage is prevented
• GLA domain removed to prevent anticoagulation effect

PROTECT-AF long-term data

Freedom from Primary Efficacy Event* (%)

Time (Years)

<table>
<thead>
<tr>
<th></th>
<th>Watchman</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>463</td>
<td>244</td>
</tr>
<tr>
<td>1</td>
<td>382</td>
<td>218</td>
</tr>
<tr>
<td>2</td>
<td>360</td>
<td>200</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>173</td>
</tr>
<tr>
<td>4</td>
<td>317</td>
<td>147</td>
</tr>
<tr>
<td>5</td>
<td>196</td>
<td>87</td>
</tr>
</tbody>
</table>

*Primary efficacy event – stroke, cardiovascular death, or systemic thromboembolism
### PROTECT-AF long-term data

**Table 2. Intention-to-Treat Primary Efficacy and Safety Outcomes According to Treatment Group by Bayesian Model**

<table>
<thead>
<tr>
<th>Event</th>
<th>Device Group (n = 463)</th>
<th>Warfarin Group (n = 244)</th>
<th>Device/Warfarin Rate Ratio (95% Credible Interval)</th>
<th>Posterior Probabilities, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/Patient-Years</td>
<td>Observed Rate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Events/Patient-Years</td>
<td>Observed Rate&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Primary efficacy end point&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39/1720.2</td>
<td>2.3 (1.7-3.2)</td>
<td>34/900.8</td>
<td>3.8 (2.5-4.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>26/1720.7</td>
<td>1.5 (1.0-2.2)</td>
<td>20/900.9</td>
<td>2.2 (1.3-3.1)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>24/1720.8</td>
<td>1.4 (0.9-2.1)</td>
<td>10/904.2</td>
<td>1.1 (0.5-1.7)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>3/1774.2</td>
<td>0.2 (0.0-0.4)</td>
<td>10/916.2</td>
<td>1.1 (0.5-1.8)</td>
</tr>
<tr>
<td>Disabling&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8/1771.3</td>
<td>0.5 (0.2-0.8)</td>
<td>11/912.7</td>
<td>1.2 (0.6-1.9)</td>
</tr>
<tr>
<td>Nondisabling&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18/1723.7</td>
<td>1.0 (0.7-1.7)</td>
<td>9/907.7</td>
<td>1.0 (0.4-1.7)</td>
</tr>
</tbody>
</table>

**Table 3. Causes of Mortality by Treatment Group**

<table>
<thead>
<tr>
<th>Event</th>
<th>Device Group, No. (%) (n = 463)</th>
<th>Warfarin Group, No. (%) (n = 244)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>17 (3.7)</td>
<td>22 (9.0)</td>
<td>.005</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3 (0.6)</td>
<td>2 (0.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>2 (0.4)</td>
<td>8 (3.3)</td>
<td>.004</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1 (0.2)</td>
<td>1 (0.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.4)</td>
<td>2 (0.8)</td>
<td>.61</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>4 (0.9)</td>
<td>4 (1.6)</td>
<td>.46</td>
</tr>
<tr>
<td>Unexplained/other</td>
<td>5 (1.0)</td>
<td>5 (2.0)</td>
<td>.33</td>
</tr>
</tbody>
</table>

Reddy et al., JAMA 2014
### PREVAIL over time

PREVAIL-only endpoint events and event rates (sponsor and FDA analyses)\(^4\)

<table>
<thead>
<tr>
<th>Dataset Date</th>
<th>Endpoint Event</th>
<th>WATCHMAN</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N Events/Total Pt-ys</td>
<td>Rate (95% CI(^8))</td>
</tr>
<tr>
<td>January 2013</td>
<td>Stroke-Ischemic</td>
<td>5/257.1</td>
<td>1.94 (0.63, 4.54)</td>
</tr>
<tr>
<td></td>
<td>Stroke-Hemorrhagic</td>
<td>1/259.0</td>
<td>0.39 (0.01, 2.15)</td>
</tr>
<tr>
<td></td>
<td>Systemic Embolism</td>
<td>1/259.6</td>
<td>0.39 (0.01, 2.15)</td>
</tr>
<tr>
<td></td>
<td>Death (Cardiovascular or Unexplained)</td>
<td>7/259.7</td>
<td>2.70 (1.08, 5.55)</td>
</tr>
</tbody>
</table>
NOACs are standard therapy for stroke prevention in AF
Real World data very consistent
Net Clinical Benefit matters for patients!
Direct antagonists are available (idarucizumab) or just around the corner (for Xa inhibitors)
LAA occluder: Good option for special patient populations (esp contraindicated for anticoagulation)
NOACs – Update 2016

PD Dr. Jan Steffel
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LAAOs vs. NOACs

- NOACs in real world vs. LAAO in real world (efficacy and safety)
- Not all AF is created equal
  - Valvular vs. non-valvular
  - "Paroxysmal" vs. "Persistent" → many shortcomings!
- Careful in extrapolating "off-label" use of NOACs and LAAOs
  - No data for patients with contraindication for anticoagulation (PROTECT-AF vs. ASAP)
- Careful in extrapolating (rather) small scale trials to the entire AF population, and combining trial results


**LAAOs vs. NOACs**

- NOACs in real world vs. LAAO in real world (efficacy and safety)
- Not all AF is created equal
  - Valvular vs. non-valvular
  - "Paroxysmal" vs. "Persistent" → many shortcomings!
- Careful in extrapolating "off-label" use of NOACs and LAAOs
  - No data for patients with contraindication for anticoagulation (PROTECT-AF vs. ASAP)
- Careful in extrapolating (rather) small scale trials to the entire AF population, and combining trial results
- All strokes from LAA...?
- How does LAAO compare with NOACs?
  - Beware of cross-trial comparisons...

→ Only a well-designed RCT will answer this question!
In ENGAGE-AF, investigators prospectively categorized patients as having an increased risk of falling particularly if they had any of the following 8 criteria at randomization:

- A prior history of falls
- Lower extremity weakness
- Poor balance
- Cognitive impairment
- Orthostatic hypotension
- Use of psychotropic drugs
- Severe arthritis
- Dizziness
<table>
<thead>
<tr>
<th></th>
<th>Fall Risk (n = 900, 4%)</th>
<th>No Fall Risk (n = 20205, 96%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>51%</td>
<td>62%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>77</td>
<td>72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHADS$_2$ score (mean)</td>
<td>3.3</td>
<td>2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$VASc score (mean)</td>
<td>5.1</td>
<td>4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHADS$_2$ score &gt;3</td>
<td>39%</td>
<td>22%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of Stroke (incl. TIA)</td>
<td>41%</td>
<td>28%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CrCl (ml/min, median)</td>
<td>58</td>
<td>71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TTR (warfarin arm, median)</td>
<td>67</td>
<td>69</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Steffel et al., submitted (presented at AHA 2015)
Edoxaban versus Warfarin in Patients with an Increased Risk of Falls

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Edoxaban versus Warfarin in Patients with an Increased Risk of Falls

- ICH: -39
- Life-threatening bleed: -33
- All-cause mortality: -66

At increased risk of falling
Not at increased risk of falling

Steffel et al., submitted (presented at AHA 2015)