Methodology and Interpretation of Real World Data for DOACs

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Disclosures

- **Research Funding**
  - BMS
  - Optum Insight
  - Novosys

- **Consulting**
  - BMS
  - Daiichi-Sankyo
  - Janssen Healthcare
  - Portola

- **Board of Directors**
  - Anticoagulation Forum
  - American College of Cardiology Accreditation Management Board
  - AMA House of Delegates in behalf of SHM

- **Speaking Honoraria**
  - Pfizer
  - BMS
  - Janssen
Overview and Objectives

• Align on the relevance and appropriate use of RWD for SPAF and VTE

• Discuss strengths and limitations of real-world studies in supporting treatment decisions in clinical practice

• Determine gaps in real-world evidence for clinicians
RWD Overview
What is Real-World Data?

- “Everything that goes beyond what is normally collected in the Phase III clinical trials program in terms of efficacy”
  - International Society For Pharmacoeconomics And Outcomes Research (ISPOR) Task Force

- “A measure in understanding health care data collected under real life practice circumstances”
  - European Forum “Relative Effectiveness” Working Group

Need for Increased Awareness of Published RWD Studies

- In qualitative study interviewing PCPs and cardiologists involved in AF management, knowledge and experience stated to influence prescribing:
  - PCPs reported they are less familiar with DOACs vs VKA and less likely to prescribe DOACs
  - All cardiologists surveyed were comfortable prescribing DOACs, reflecting their experience with these medications
- Recent results from Medscape educational activity indicated the majority of audiences are unable to demonstrate knowledge of RWD for DOACs:
  - 30-45% correctly answered questions regarding the ORBIT-AF registry and MarketScan REVISIT-US study
  - 18% self reported they felt “very confident” prescribing DOACs for newly diagnosed patients with AF at risk for stroke

Randomized Clinical Trials (RCTs) vs Real-World Data (RWD)

**RCTs**
RCTs are randomized, blinded clinical trials conducted to test the safety and efficacy of healthcare products or services under carefully controlled conditions.

**RWD**
RWD is observational in nature and generally uses data from actual practice settings to perform analyses on comparative effectiveness, comparative costs, quality of life, and signal detection among others.

**RWD Compared to RCT**
- May include a broader patient population
- Generate data within the routine healthcare system
- Can address research questions which require larger patient numbers and long follow-up periods
- Can address research questions which can’t be studied by experiments for ethical reasons

RWD complements and augments RCT data.
Strengths and Limitations of Using Real-World Data in Research

Strengths of RWD

- Effectiveness in actual practice settings
- Databases typically represent large populations
- Diverse population
- Broader set of outcomes
- Low cost and relatively inexpensive to acquire

Limitations of RWD

- Potential coding errors and missing data
- Confounding factors may be present
- RWD not randomized, potential for bias
- Study associations unable to determine causality
- RWD cannot be used as stand-alone data but in combination with RCTs

RCT=randomized controlled trial; RWD=real-world data.
Weighing the Pros and Cons of RCT vs RWD

<table>
<thead>
<tr>
<th>Advantages</th>
<th>RCTs</th>
<th>Real Life Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Rigorous experimental design</td>
<td>• Non-selected populations</td>
</tr>
<tr>
<td></td>
<td>• Randomization</td>
<td>• Realistic therapy adherence</td>
</tr>
<tr>
<td></td>
<td>• Blinding</td>
<td>• Logistical and ethical feasibility</td>
</tr>
<tr>
<td></td>
<td>• Control</td>
<td>• Able to evaluate complex therapies</td>
</tr>
<tr>
<td></td>
<td>• Rigorous analysis methods</td>
<td>• Useful to detect rare or late side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Routine practice setting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Long duration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>RCTs</th>
<th>Real Life Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Selected patients</td>
<td>• Lack of patient selection brings confounding factors</td>
</tr>
<tr>
<td></td>
<td>• Setting and monitoring bias</td>
<td>• Lack of randomization</td>
</tr>
<tr>
<td></td>
<td>• Economical limitations</td>
<td>• Absence of blinding</td>
</tr>
<tr>
<td></td>
<td>• Logistical and ethical restrictions</td>
<td>• Confounding by indication</td>
</tr>
<tr>
<td></td>
<td>• Unsuitable for complex treatment studies</td>
<td>• Economical limitations</td>
</tr>
<tr>
<td></td>
<td>• Inappropriate for thorough evaluation of side effects</td>
<td>• Logistical problems</td>
</tr>
<tr>
<td></td>
<td>• Short duration</td>
<td></td>
</tr>
</tbody>
</table>

RWD has Three Main Dimensions

<table>
<thead>
<tr>
<th><strong>TYPE of RWD</strong></th>
<th>Hospital patient-level</th>
<th>Social media</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sources to</td>
<td>▶ Registries</td>
<td>▶ Health plan claims</td>
</tr>
<tr>
<td>access appropriate</td>
<td>▶ Detailed physician/patient</td>
<td>▶ Longitudinal Rx</td>
</tr>
<tr>
<td>variables and settings</td>
<td>panel records for specific populations</td>
<td>▶ EMR</td>
</tr>
<tr>
<td>of care</td>
<td>▶ Hospital charge detail master</td>
<td>▶ Biobanks</td>
</tr>
<tr>
<td></td>
<td>▶ Laboratory results</td>
<td>▶ Any non-interventional study</td>
</tr>
</tbody>
</table>

**GEOGRAPHIC coverage**
Country, region, payer authority, health system, etc

**DISEASE and THERAPY-AREA depth**
General administrative databases, disease-focused registries, etc

EMR=electronic medical records; RWD=real-world data.
### Three Common RWD Types Differ in Their Features and Applications

<table>
<thead>
<tr>
<th></th>
<th>1. CLAIMS DATA</th>
<th>2. MEDICAL RECORDS</th>
<th>3. REGISTRIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical uses</strong></td>
<td>Lack of clinical data but provide useful information to payers</td>
<td>Rich clinical &amp; vital signs data useful for quality of care analyses</td>
<td>Rich clinical &amp; vital signs data, usually collected on longitudinal basis from selected centres in patients with particular condition</td>
</tr>
<tr>
<td><strong>Unique features</strong></td>
<td>Limited data fields relative to EMR</td>
<td>Potential for natural language processing or chart review of unstructured note (eg, smoking status, pain scores, reasons for prescription switch…)</td>
<td>Data usually collected per pre-specified CRF and may include PROs</td>
</tr>
<tr>
<td><strong>Data gaps</strong></td>
<td>Few gaps – data tied to reimbursement</td>
<td>Gaps in data fields due to patient visit frequency variability</td>
<td>Potential for missing data</td>
</tr>
<tr>
<td><strong>Source Limitations</strong></td>
<td>Lack clinical details</td>
<td>Primary care setting only (for some EMR) or hospital setting only</td>
<td>Limited to the data from the participating centres</td>
</tr>
<tr>
<td><strong>Example</strong></td>
<td>MarketScan® databases</td>
<td>Humedica®</td>
<td>PINNACLE-AF</td>
</tr>
</tbody>
</table>

AF=atrial fibrillation; EMR=electronic medical records; CRF=case report form; PRO=patient-reported outcome; RWD=real-world data.
Selected Challenges of RWE

- Association vs causation
- Replicability
- Bias and confounding
  - Statistical Methods to adjust for bias and confounding
- Relevance of studies for other markets

RWE=real-world evidence.
Replicability

- Replicability means consistency
  - Replicate or perish (or validate or perish) rather than publish or perish

- Primary analyses much stronger than secondary or post hoc analyses

- Do not want mere repetitions that repeat biases of original study

- No cause may exist
Compensating for the Lack of Randomization: Regression Modelling vs Propensity-Score Matching (PSM)

**Regression**
- Statistical methodology that helps to estimate the strength and direction of the relationship between two or more variables:
  - **Dependent variable**: Outcome of interest
  - **Independent variables**: Variables that meet the criteria (e.g., baseline characteristics)

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n + \epsilon \]

**PSM**
- The propensity score (PS) is the probability of treatment assignment based on observed baseline covariates
- PSM entails forming matched treatment groups who share a similar PS
- **Positives**:
  - Intuitively appealing
  - Useful tool to check treatment group balance with respect to baseline confounders
- **Negatives**
  - PSM shrinks sample size, possible power issue
  - No clear guidance on variable inclusion, or assessment of model quality

**Caveat**: Neither PSM nor conventional regression methods adjust for unobserved confounders
Varying Research Methodologies of Real-World Studies

Retrospective
Secondary Data

Hybrid
Studies

Prospective
Primary Data
# National and Worldwide Registries for OACs

<table>
<thead>
<tr>
<th>National registries</th>
<th>International registries sponsored by learned societies</th>
<th>Academic-led registries from one single city/region</th>
<th>Industry sponsored registries</th>
<th>Outpatient only</th>
<th>Inpatient only</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Swedish National Patient Registry</td>
<td>• EORP-AF initiated by ESC and part of the INTER-AF program</td>
<td>• Fushimi AF</td>
<td>• GLORIA-AF</td>
<td>• ORBIT-AF</td>
<td>• GWTG-AFIB</td>
</tr>
<tr>
<td>• Danish National Patient Registry</td>
<td></td>
<td></td>
<td>• GARFIELD-AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• PREFER-AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ORBIT-AF</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tbody>
</table>

Comparing the Registries

**Study Population**
- Patient ethnicities
- Inpatients vs outpatients
- Inclusion criteria
- Exclusion criteria

**Study design**
- Duration
- Time period of data collection
- Calendar year

**Impact of site and setting**
- Medication availability
- Funding
- Regional contribution
- Different HCPs and specialties
- Academic institutions

Objective

To identify and summarize the evidence from real-world studies on the impact of NOACs (apixaban, rivaroxaban, and dabigatran, edoxaban), and vitamin K antagonists (warfarin) on rates of clinical, economic, and health-related quality of life outcomes in patients with NVAF.

Research Question

In adults with NVAF, what is the relative impact on effectiveness, safety, QoL, costs, and resource use of NOACs and warfarin in clinical practice?
### Methodology for Selection of Studies for Literature Review

#### Limits
- Published January 1, 2003–March 17, 2016

#### Data Sources
- Pubmed, Embase, NHS-Economic Evaluation Database, and EconLit databases
- Specific clinical conferences and scientific meetings from 2012 to 2015 (ie, ACC, AHA, EuroStroke, ESC and ISPOR)
- Hand searches of reference lists of identified articles

#### Search Terms
- NVAF
- NOACs
- Real-world observational study designs (eg, cohort, cross-sectional, case-control)

#### Inclusion Criteria
- Patients with NVAF receiving any NOAC dose or warfarin*
  - Clinical outcomes:
    - Bleeding† (eg, major, minor)
    - Systemic emboli
    - Intracranial hemorrhage (ischemic and hemorrhagic)
    - Myocardial infarction
    - Vascular deaths
    - All-cause deaths
    - Non-bleeding adverse events
    - Treatment discontinuation
    - Persistence/adherence
  - Cost of events (medical, non-medical)
  - HCRU (hospitalization, length of stay)
  - Health-related quality of life outcomes or other patient reported outcomes

#### Exclusion Criteria
- Not real-world observation study
- Other patient population
- Other reported outcome

#### Screening and Data Extraction
- Conducted by one reviewer and validated by a 2nd reviewer. Discrepancies were resolved with a 3rd reviewer

#### Risk of Bias Assessment
- Agency for Healthcare Research and Quality (AHRQ) Risk of Bias Assessment tool

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* Studies with mixed population must report NVAF group data separately.
† ISTH or modified ISTH bleeding definition

ACC=American College of Cardiology; AHA=American Heart Association; ESC=European Society of Cardiology; HCRU=healthcare utilization and resource use; ISPOR=International Society for Pharmacoeconomics and Outcomes Research; ISTH=International Society on Thrombosis and Haemostasis; NHS=National Health Service; NOAC=non-vitamin K antagonist oral anticoagulant; NVAF=nonvalvular atrial fibrillation.
**Data Elements Extracted From Studies**

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Patient Characteristics</th>
<th>Treatment Characteristics</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• First author</td>
<td>• Number of patients, type of NVAF</td>
<td>• Treatment name</td>
<td>• Evaluation timepoint</td>
</tr>
<tr>
<td>• Publication year</td>
<td>• Age, Race, Gender</td>
<td>• Dose &amp; schedule</td>
<td>• Outcome definition</td>
</tr>
<tr>
<td>• Study design</td>
<td>• Treatment status (naive or pretreated)</td>
<td>• Route of administration</td>
<td>• Number of patients assessed (n/N)</td>
</tr>
<tr>
<td>• Study (registry/database) name or lead institution</td>
<td>• Prior treatment(s)</td>
<td>• Duration of use</td>
<td>• Event rates (including how they were derived)</td>
</tr>
<tr>
<td>• Data source</td>
<td>• Current treatment(s)</td>
<td>• Other medications prescribed or allowed</td>
<td>• Cost of events (year, currency, source, duration for cost calculations)</td>
</tr>
<tr>
<td>• Related publications (kinship)</td>
<td>• Comorbidities—HF, DM, HTN (if &gt; 160), history and type of bleeding, history of GERD, renal dysfunction</td>
<td>• Information will be captured for all relevant treatment arms as reported in each study</td>
<td>• HCRU (eg, hospitalizations)</td>
</tr>
<tr>
<td>• Geographic location (country and continent)</td>
<td>• Baseline CHADS\textsubscript{2} score</td>
<td></td>
<td>• QoL outcomes (instruments, values)</td>
</tr>
<tr>
<td>• Study duration</td>
<td>• Baseline CHA\textsubscript{2}DS\textsubscript{2}-Vasc score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Study period</td>
<td>• Baseline HAS-BLED score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Statistical test between groups were captured as applicable</td>
<td>• Comorbidities—HF, DM, HTN, and treatments</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Selection of Studies for RWD Literature Review

Records meeting initial eligibility criteria (n=4152)

Unique records (n=3468 unique)

Abstracts for full-text review (n=974)

Full-text articles (n=288)

Comparative studies (n=149)

Reported evaluation of ≥1 NOAC and reported outcomes (n=91)

Apixaban* (n=26)  Dabigatran* (n=68)  Rivaroxaban* (n=41)  Edoxaban* (n=0)

* Numbers do not add up to 91 due to overlap between studies.
Geographic Distribution of DOAC-Related Comparative Studies

Europe=27
UK: 4; Denmark: 4; Sweden: 6; Spain: 3; Turkey: 3; Germany/France: 2 each; Belgium/Italy/Poland: 1 each

N America=52
USA: 49; Canada: 3

Asia=10
China: 2; Japan: 4; Taiwan: 2; Malaysia/UAE: 1 each

Multi-continent=1
Canada & Sweden: 1

Oceania=1
New Zealand: 1
Data Sources and Sponsorship of Literature Review Studies

**Data Sources**

- Pharmacy/claims database: 50
- Medical Records: 26
- Others: 13
- NR: 2

**Funding**

- Non-industry: 42
- Industry: 39
- None: 10
Study Designs, Models, and Publication Format of Literature Review Studies

**Study Design**

- **Observational Model**
  - Total: 105
  - Retrospective OS: 75
  - Prospective OS: 16
  - CC/Nested CC: 86
  - Cohort: 4
  - Cross-sectional: 1

**Publication Format**

- **Full manuscript**
- **Congress presentations**

CC=case control; GI=gastrointestinal; OS=observational studies.
Comparison of Major Bleeding Risk

Number of Evaluations* and Risk of Major Bleeding†

<table>
<thead>
<tr>
<th>Reference</th>
<th>Comparator</th>
<th>Total #</th>
<th>Risk of Major Bleeding Compared to Reference, #</th>
<th>US</th>
<th>Ex-US</th>
<th>CP</th>
<th>FM</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA</td>
<td>Apixaban</td>
<td>8</td>
<td>↓ 8</td>
<td>8</td>
<td>-</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dabigatran</td>
<td>21</td>
<td>↓ 7  ↑ 1</td>
<td>9</td>
<td>12</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>6</td>
<td>↑ 1  ↓ 5</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Dabigatran</td>
<td>6</td>
<td>↓ 6</td>
<td>6</td>
<td>-</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>7</td>
<td>↑ 7</td>
<td>7</td>
<td>-</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Comparator statistically significant decrease vs reference
- Comparator statistically significant increase vs reference
- Not statistically significant

* Some studies contributed to more than one evaluation related to major bleeding. Some analyses included stratification by dose, age, or bleeding in different settings (eg, inpatient, outpatient).

† The definition for major bleeding varied between studies.

OAC=oral anticoagulant.
Safety/Efficacy of DOACs in Real-World Setting
Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban vs Warfarin in NVAF

- US insurance database study of patients with NVAF who were users of apixaban, dabigatran, rivaroxaban, or warfarin between October 1, 2010, and June 30, 2015
- Matched cohorts using 1:1 propensity score matching and Cox proportional hazards regression

<table>
<thead>
<tr>
<th></th>
<th>Stroke/SE HR (95% CI)</th>
<th>P-value vs warfarin</th>
<th>Major Bleeding HR (95% CI)</th>
<th>P-value vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban vs warfarin (n=15 390)</td>
<td>0.67 (0.46–0.98)</td>
<td>0.04</td>
<td>0.45 (0.34–0.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dabigatran vs warfarin (n=28 614)</td>
<td>0.98 (0.76–1.26)</td>
<td>0.98</td>
<td>0.79 (0.67–0.94)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rivaroxaban vs warfarin (n=32 350)</td>
<td>0.93 (0.72–1.19)</td>
<td>0.56</td>
<td>1.04 (0.90–1.20)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Apixaban and Dabigatran Initiation Associated With Lower Major Bleeding Risk vs VKA Initiation in Claims Study

- US MarketScan claims Database study from January 2012 – Dec 2014 comparing major bleeding risk among newly anticoagulated patients with NVAF within a ≥1 year baseline period (N=45,361)

- Cox proportional hazard models used to estimate PSM HR of major bleeding

**Major bleeding incidence rates and HR (VKA-NOAC PSM Cohort)**

REVISIT-US: ICH Reductions for Apixaban and Rivaroxaban vs VKA Were Consistent With ARISTOTLE and ROCKET AF

- MarketScan claims analysis study from 2012-2014 of patients with NVAF newly initiated on apixaban, rivaroxaban, or VKA with baseline CHAD$_2$S$_2$-VASc score $\geq$2

- Eligible rivaroxaban and apixaban users were 1:1 PSM to VKA users

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Apixaban (n=4083) vs VKA (n=4083)</th>
<th>Rivaroxaban (n=11,411) vs VKA (n=11,411)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.13 (0.49-2.63)</td>
<td>0.71 (0.47-1.07)</td>
</tr>
<tr>
<td>ICH</td>
<td>0.38 (0.17-0.88)</td>
<td>0.53 (0.35-0.79)</td>
</tr>
<tr>
<td>Ischemic stroke or ICH</td>
<td>0.63 (0.35-1.12)</td>
<td>0.61 (0.45-0.82)</td>
</tr>
</tbody>
</table>

PSM=propensity-score matched.
Net Clinical Outcome* of NOACs in SPAF

- Data from RCTs and a real-world sample of patients with NVAF selected from Medco healthplans (2007-2010) were combined to estimate the absolute effect of each NOAC vs warfarin in real-world clinical practice.

- All NOACs reduced stroke events vs warfarin in a real-world setting; apixaban was the only NOAC to reduce major bleeding excluding ICH vs warfarin.

### Net clinical outcomes for NOACs vs warfarin in real-world setting

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Apixaban (ARISTOTLE)</th>
<th>Dabigatran (RE-LY)</th>
<th>Rivaroxaban (ROCKET-AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net clinical outcome (stroke + major bleeding excluding ICH) difference in real world for NOAC vs warfarin per 100 P-Y</td>
<td>-3.2%</td>
<td>-1.2%</td>
<td>+0.6%</td>
</tr>
<tr>
<td>NNT in real world to avoid one net clinical outcome for NOAC vs warfarin, per year</td>
<td>32</td>
<td>84</td>
<td>---</td>
</tr>
<tr>
<td>NNH in real world to cause one net clinical outcome for NOAC vs warfarin, per year</td>
<td>---</td>
<td>---</td>
<td>166</td>
</tr>
</tbody>
</table>

* Reduction in net clinical outcome was calculated by summing the absolute risk reductions for stroke and major bleeding excluding ICH for each NOAC vs warfarin.

ICH=intracranial hemorrhage; NNH=number needed to harm: stroke prevention in AF; NNT=number needed to treat.

US Retrospective Database Study Design: The Million Study

**Study Details**
- Retrospective propensity score matching analysis of 4 US nationwide databases:
  - Databases: MarketScan, PharMetrics, Optum, Humana
  - Dates: Jan 2013-Sept 2015
  - Propensity score matching conducted between groups followed by patient matching 1:1 within each dataset. Cox proportional hazard models with robust sandwich estimates were performed to evaluate risk of outcomes between groups.

**Study Population**
- 76,940 patients were evaluated (38,740 patients per treatment): 4-times the RCT ARISTOTLE enrollment
- Patients were required to have ≥1 pharmacy claim for apixaban or warfarin and to be identified as AF patients
- Continuous medical/pharmacy health plan enrollment for ≥12 years prior to index data
- Patients treated with any OACs within 12 months before the index date or with >1 OAC on the index date were excluded

Li, Deitelzweig et al., *Thromb Haemost.* 2017 march 16 [Epub ahead of print]
Results in 1st MILLION manuscript: DRR results in overall population

Stroke/SE

Cumulative Incidence of Stroke/Systemic Embolism

<table>
<thead>
<tr>
<th>Time from Anticoagulation Initiation (in days)</th>
<th>% of Patients with Stroke/Systemic Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Apixaban: 0.2, Warfarin: 0.3</td>
</tr>
<tr>
<td>60</td>
<td>Apixaban: 0.4, Warfarin: 0.5</td>
</tr>
<tr>
<td>120</td>
<td>Apixaban: 0.6, Warfarin: 0.8</td>
</tr>
<tr>
<td>180</td>
<td>Apixaban: 0.8, Warfarin: 1.0</td>
</tr>
<tr>
<td>240</td>
<td>Apixaban: 1.0, Warfarin: 1.2</td>
</tr>
<tr>
<td>300</td>
<td>Apixaban: 1.2, Warfarin: 1.4</td>
</tr>
<tr>
<td>360</td>
<td>Apixaban: 1.4, Warfarin: 1.6</td>
</tr>
</tbody>
</table>

Number of people at risk:
- Apixaban 38470: 26948, 19075, 13738, 9764, 7122, 5192
- Warfarin 38470: 28196, 19327, 14288, 10542, 8113, 6177

Hazard ratio (95% CI): 0.67 (0.59-0.76, p-value<0.001)

Major bleeding

Cumulative Incidence of Major Bleeding

<table>
<thead>
<tr>
<th>Time from Anticoagulation Initiation (in days)</th>
<th>% of Patients with Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Apixaban: 0.2, Warfarin: 0.3</td>
</tr>
<tr>
<td>60</td>
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<tr>
<td>360</td>
<td>Apixaban: 1.4, Warfarin: 1.6</td>
</tr>
</tbody>
</table>

Number of people at risk:
- Apixaban 38470: 26910, 18997, 13670, 9728, 7103, 5176
- Warfarin 38470: 28031, 19203, 14188, 10461, 8076, 6138

Hazard ratio (95% CI): 0.60 (0.54-0.65, p-value<0.001)
Pharmacoeconomic and Health Impact of DOACs in Patients With AF
Real-World Assessment of Bleeding-Related Hospital Readmissions With NOACs

- Premier database (N=74,730; January 1, 2012-March 31, 2014) and Cerner database (N=14,201; January 1, 2012- August 31, 2014) study of US hospitalized patients with NVAF
- Patients receiving apixaban were older, had more comorbidities, and were higher risk

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Database</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age mean</td>
<td>Cerner</td>
<td>74.9</td>
<td>72.4</td>
<td>72.1</td>
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<tr>
<td></td>
<td>Premier</td>
<td>73.6</td>
<td>71.9</td>
<td>72.3</td>
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<tr>
<td>CCI mean</td>
<td>Cerner</td>
<td>2.71</td>
<td>2.47</td>
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<tr>
<td></td>
<td>Premier</td>
<td>2.35</td>
<td>2.12</td>
<td>2.09</td>
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</tr>
<tr>
<td>CHADS$_2$ score mean</td>
<td>Cerner</td>
<td>2.35</td>
<td>2.15</td>
<td>2.06</td>
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<tr>
<td></td>
<td>Premier</td>
<td>2.19</td>
<td>2.09</td>
<td>2.04</td>
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<tr>
<td>CHA$_2$DS$_2$-VASc score mean</td>
<td>Cerner</td>
<td>4.14</td>
<td>3.80</td>
<td>3.68</td>
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<tr>
<td></td>
<td>Premier</td>
<td>3.93</td>
<td>3.73</td>
<td>3.71</td>
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<tr>
<td>HAS-BLED score mean</td>
<td>Cerner</td>
<td>2.50</td>
<td>2.37</td>
<td>2.31</td>
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</tr>
<tr>
<td></td>
<td>Premier</td>
<td>2.56</td>
<td>2.33</td>
<td>2.35</td>
<td></td>
</tr>
</tbody>
</table>

CCI=Charlson Comorbidity Index.
Rivaroxaban Associated With Greater Risk of Bleeding-Related Readmissions vs Apixaban Across Two Database Claims Analyses

- Regression adjusted results for NVAF study population treated with DOACs

Application of RWD in VTE on use of DOACs for SPAF
Dresden DOAC Registry of Bleeding Outcomes on Rivaroxaban in Patients With NVAF and VTE

- Dresden DOAC registry study of patients receiving rivaroxaban for SPAF (n=1200) and VTE (n=575) to analyze rivaroxaban-related bleeding

Kaplan-Meier estimation for major bleeding in SPAF and VTE patients

Hospitalizations and Other Healthcare Resource Utilization among Patients with Deep Vein Thrombosis Treated with Rivaroxaban versus Low-Molecular Weight Heparin and Warfarin in the Outpatient Setting

Study Results

∆Hosp. [95% CI] = \(-0.020\) \([-0.039; -0.002]\); \(P = 0.044\)

∆Hosp. [95% CI] = \(-0.026\) \([-0.050; -0.002]\); \(P = 0.040\)

∆Hosp. [95% CI] = \(-0.023\) \([-0.051; 0.008]\); \(P = 0.112\)

∆Hosp. [95% CI] = \(-0.033\) \([-0.066; 0.001]\); \(P = 0.058\)

Figure 1. All-Cause Hospitalization – Matched Rivaroxaban and LMWH/Warfarin Users
Study Results

Associated Healthcare Costs:

- All-cause total healthcare costs were significantly lower for rivaroxaban users compared to LMWH/warfarin users over 1 week ($2,332 vs $3,428; P <0.001) and 2 weeks ($3,108 vs $4,524; P <0.001) and were numerically (but not statistically significantly) lower over 3 and 4 weeks.

- All-cause hospitalization costs were significantly lower for rivaroxaban users compared to LMWH/warfarin users over 1 week ($171 vs $873; P = 0.014) and 2 weeks ($466 vs $1,342; P = 0.036) and were numerically (but not statistically significantly) lower over 3 and 4 weeks.

- The pharmacy costs were significantly lower for patients treated with rivaroxaban over 1, 2, 3, and 4 weeks (P <0.001), with rivaroxaban users incurring about half the cost of the LMWH/warfarin users over the first 2 weeks.
Apixaban Associated With Largest Reduction in Medical Costs Compared With Other NOACs for VTE in the US

Objective
Real-world medical cost avoidances from a US payer perspective were estimated when DOACs are used instead of warfarin for the treatment of patients with VTE

Dabigatran: -$572
Edoxaban: -$1957
Rivaroxaban: -$2971
Apixaban: -$4440

Substantial reductions in both VTE and major bleeding event rates

- Annual total medical cost avoidances vs warfarin were greatest for patients with VTE treated with apixaban
- Validity of the estimates of differences in medical costs between NOACs and warfarin may need further assessment when applying these findings to other locations

Data Gaps
Addressing RCT Gaps With RWD: Which studies are available to address these gaps?

<table>
<thead>
<tr>
<th>GAP</th>
<th>Study</th>
<th>Author. Journal. Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHD</td>
<td>Safety and efficacy of NOACs vs VKA in patients with AF and VHD</td>
<td>Noseworthy et al. <em>Int J Cardiol.</em> 2016</td>
</tr>
<tr>
<td>Mechanical Heart Valves</td>
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</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Risks in NOAC (dabi, apix, riva)- and VKA-treated patients with hypertrophic cardiomyopathy and AF</td>
<td>Noseworthy et al. <em>J Am Coll Cardiol.</em> 2016</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioversion</td>
<td>Apixaban vs heparin and/or VKA in patients with NVAF undergoing cardioversion: Rationale and design of EMANATE</td>
<td>Ezekowitz et al. <em>Am Heart J.</em> 2016</td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>Efficacy and safety of NOACs (dabi, apix, riva) in secondary stroke prevention in patients with AF: single center experience</td>
<td>Lasek-Bal et al. <em>Int Angiol.</em> 2015</td>
</tr>
<tr>
<td>Others?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY

- Defined RWD or RWE in 2017 with alignment on the relevance and appropriate use for SPAF and VTE
- Discussed strengths and limitations of real-world studies in supporting treatment decisions in clinical practice
- Determine gaps in real-world evidence for clinicians
Questions ?