Comparative effectiveness and safety of direct ORal Anticoagulants in patients with atrial fibrillation: a standardiZed Observational data Network study (CORAZON)

Wallis Lau, PhD (wallis.lau@ucl.ac.uk)
Kenneth Man, PhD (kenneth.man@ucl.ac.uk)
University College London School of Pharmacy
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• Study background and objective
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British Medical Association (BMA) House, London
Cluster of Pharmacoepidemiology And Medication Safety, UCL School of Pharmacy

- Observational studies using population databases in the UK (IMRD/CPRD)
- Asia Pharmacoepidemiology Network (AsPEN) (Hong Kong, Taiwan, Korea, Australia …)
Research on direct oral anticoagulants

Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation

Wallis C. Y. Lau, BSc; Esther W. Chan, PhD; Ching-Lung Cheung, PhD; Chor Wing Sing, BSc; Kenneth K. C. Man, MPH; Gregory Y. H. Lip, MD; Chung Wah Siu, MD; Joanne K. Y. Lam, FHKAM; Alan C. H. Lee, FHKAM; Ian C. K. Wong, PhD

Sex-Based Differences in Outcomes of Oral Anticoagulation in Patients With Atrial Fibrillation

Sharon W.Y. Law, MPWAM,⁎ Wallis C.Y. Lau, PhD,⁎ Ian C.K. Wong, PhD,⁎ Gregory Y.H. Lip, MD,⁎⁎ Michael T. Mok, MBBS,⁎⁎ Chung-Wah Siu, MD,⁎ Esther W. Chan, PhD

Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study

Esther W. Chan,⁎ Wallis C. Y. Lau,⁎ Wai K. Leung,² Michael T. C. Mok,³ Ying He,¹ Teresa S. M. Tong,² and Ian C. K. Wong¹
Comparative effectiveness and safety of direct ORal Anticoagulants in patients with atrial fibrillation: a standardized Observational data Network study (CORAZON)
Study background

• Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting 33 million people worldwide and is a leading cause of stroke

• Current guidelines\(^1,2\) recommend direct oral anticoagulants (DOACs) over warfarin for stroke prevention in AF

• No further guidance on how to choose between the DOACs, due to the absence of randomized controlled trials directly comparing the DOACs
Study background

- Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting 33 million people worldwide and is a leading cause of stroke.
- Current guidelines\(^1,2\) recommend direct oral anticoagulants (DOACs) over warfarin for stroke prevention in AF.
- No further guidance on how to choose between the DOACs, due to the absence of randomized controlled trials directly comparing the DOACs.

<table>
<thead>
<tr>
<th>Clinical trials of DOACs vs Warfarin in AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke or systemic embolism</strong></td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
</tr>
<tr>
<td>Edoxaban (Savaysa)</td>
</tr>
</tbody>
</table>

\(\downarrow\): reduced in comparison to warfarin; \(\leftrightarrow\): comparable to warfarin

Adapted from Wadhera RK et al. 2014
Study objective

• To compare the effectiveness and safety outcomes between the four DOACs in patients with AF (dabigatran vs rivaroxaban vs apixaban vs edoxaban)

• Outcomes of interest:
  – Ischemic stroke/systemic embolism
  – Intracranial bleeding
  – Gastrointestinal bleeding
  – All-cause mortality
Method

- A new user cohort
- Population-Level Estimation (PLE) study
- Propensity score matching
- Pair-wise hazard ratios

**Inclusion criteria**

- INDEX date (First DOAC prescription) Day 0
- At least 365 days of observational period Day [-365, 0]
- Assessment window for previous anticoagulant exposure Days [-180, -1]
- Assessment window for diagnosis for Atrial Fibrillation Day [-90, 90]
- Assessment window for diagnosis for mitral stenosis Day [-365, 90]
- Assessment window for procedure for mechanical heart valve Day [-365, 90]
- Assessment window for transient AF Day [-90, 90]
- Assessment window for previous outcomes Day [-365, 0]
- Assessment window for outcomes Days [1, study end*]

**Exclusion criteria**

- Assessment window for age (18 years or older) Days [0, 0]
- Assessment window for another anticoagulant Days [0, 0]

*The earliest of 31-Dec-2019 (study end), date of death, discontinuation of index DOAC (90 days gap), prescription of another anticoagulant
Method

- Subgroup analyses for clinically important patient groups who are unlikely to be included in future RCTs:
  - Renal impairment
  - Older age (aged $\geq 80$ years)
OHDSI Comparative effectiveness and safety of direct ORal Anticoagulants in patients with atrial fibrillation: a standardized Observational data Network study (CORAZON)

Version: 1.2

Wallis CY Lau, PhD, UCL School of Pharmacy, United Kingdom
Kenneth KC Man, PhD, UCL School of Pharmacy, United Kingdom
Ian CK Wong, PhD, University of Hong Kong, Hong Kong; UCL School of Pharmacy, United Kingdom
Current progress – ATLAS

• We are working with IQVIA OHDSI team for the data analyses

• Exposure cohorts:
  – Dabigatran
  – Rivaroxaban
  – Apixaban
  – Edoxaban

• Outcome cohorts:
  – Ischemic stroke/systemic embolism
  – Intracranial bleeding
  – Gastrointestinal bleeding
  – All-cause mortality
## Preliminary counts

<table>
<thead>
<tr>
<th>Data Sources (IQVIA)</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>France. LPD 2019/04</td>
<td>3,300</td>
<td>1,932</td>
<td>0</td>
<td>4,767</td>
</tr>
<tr>
<td>Germany. DA 2019Q3</td>
<td>13,302</td>
<td>3,721</td>
<td>5,788</td>
<td>14,807</td>
</tr>
<tr>
<td>UK. IMRD 2019/03</td>
<td>15,092</td>
<td>2,564</td>
<td>1,554</td>
<td>12,883</td>
</tr>
<tr>
<td>US AmbEMR. 2019/11</td>
<td>121,904</td>
<td>32,863</td>
<td>1,043</td>
<td>78,935</td>
</tr>
<tr>
<td>US Hospital. Full 2020/01</td>
<td>65,045</td>
<td>18,178</td>
<td>70</td>
<td>44,585</td>
</tr>
<tr>
<td>US Open Claims. Full 2019/07</td>
<td>951,389</td>
<td>269,867</td>
<td>6,438</td>
<td>706,820</td>
</tr>
</tbody>
</table>
More preliminary results…
Summary

• There has been no RCTs directly comparing DOACs to guide the choice of DOACs.

• The objective of this study is to generate comprehensive evidence on the comparative outcomes of dabigatran, rivaroxaban, apixaban, and edoxaban in patients with AF, using data from a range of data sources.
Join us!