The Journey to Reliable Evidence - Update

OHDSI Community call - March 2022

Asieh Golozar
Glucagon-Like Peptide 1 Receptor Agonists and Chronic Lower Respiratory Disease Exacerbations Among Patients With Type 2 Diabetes

Diabetes Care 2021;44:1-9 | https://doi.org/10.2337/dc20-1754
Fully Reproduced Study

Same data + same analysis

Plus

• Diagnostics
• Sensitivity analyses
• Different data
• Different population
• Different geography
• Different methods
• Meta-analysis
OHDSI Reproducibility Service

A team of experts available on-demand to provide consults to execute this systematic process

David Madigan
Christian Reich
Kristin Kostka
Andrew Williams
Asieh Golozar
Justin Manjourides
Brianne Olivieri-Mui
What is a good candidate for reproducibility?

• Any observational research with impact on human lives
• The question is not easily amenable to clinical trials
• Many patients involved
Our approach

Identification of the reproducibility candidate

Initial assessment
- Data
- Methodology
- Details

1. Call for collaboration
2. Protocol and phenotype development
3. Analytic package
4. Execution

Other permutations
- Diagnostics
- Sensitivity analyses
- Different data
- Different population
- Different geography
- Different methods
- Meta-analysis

Dissemination
Original Investigation
December 21, 2021

Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation

Wayne A. Ray, PhD; Cecilia P. Chung, MD, MPH; C. Michael Stein, MB, ChB; et al

Author Affiliations
Direct Oral Anticoagulant Therapy in Patients with Atrial Fibrillation

- Widespread use
- Increasing rate of DOACs use since approval

• What about the choice of DOACs for patients with atrial fibrillation?
• DOACs have not been compared directly in randomized trials
• Evidence on the comparative benefit and/or risk of DOACs comes from
  - indirect comparison of trial data
  - observational data using US claims
• Choice of DOACs is driven by clinical preference, local practices and insurance coverage
• A randomized trial with head-to-head comparison of all DOACs would be lengthy and expensive
  - ~85,000 patients should be followed up for at least 5 years to observe a 10% difference in major bleeding events
Another approach could reexamine the observational data using more sophisticated methods for causal inference that are less susceptible to bias from residual confounding or immortal time (like the target trial emulation approach, which uses observational data to emulate pragmatic comparative effectiveness trials). ¹⁷
Ray et al. JAMA 2021

**Design:** Active comparator, new-user cohort design

**Data source:** Medicare beneficiaries

**Study population (T& C):** atrial fibrillation/flutter patients who initiated treatment between 2013 & 2018

**Outcomes (O):** Major ischemic and hemorrhagic events

**Analysis:**
- Inverse probability of treatment weighting using propensity scores to balance the characteristics between the groups
- Cox-Proportional hazard & Poisson models

**Finding:** treatment with rivaroxaban compared with apixaban was associated with a significantly increased risk of major ischemic or hemorrhagic events
Ray et al. JAMA 2021

• A single measure for clinical impact
  • benefits and harms of anticoagulation for patients with atrial fibrillation assessed together
• Evaluation of multiple doses
  • Standard and reduced
• Large sample size
• One data
• One method
• One anticoagulant pair
**Target Cohort**

**Start of the observation period**

1a. age ≥ 65
1b. Known sex
1c. Prior observation of 365.25 days

2. 1 OP visit [-365:1] + 1 drug exposure [-365:1]
3. No hospice [-364:0] + no terminal illness [-364:0]
4. No nursing home [-364:0] except IP + NS [-364:0] after and length of visit <30d
   No IP with length of visit >30d [-364:0]
5. Rivaroxaban 15 or 20 mg [0:0]
6. No other oral anticoagulants [-364:0] + no rivaroxaban [-364:1] + no 2 occurrences of any of 3 ICD/CPT codes 7 days apart [-364;30] + no subcutaneous anticoagulant with ICD/CPT code within 30d prior [-364:30]
7. Afib/Aflutter [-89:0]
8. No mitral valve stenosis [-364:0]
9. No hyperthyroidism, open coronary artery bypass graft/open cardiac valve surgery [-29:0]
10. No DVT/PE, hip or knee replacement, femur/tibia/patella fracture, thrombectomy, chronic hypercoagulable state [-29:0]
11. No stage 4 or 5 CKD [-364:0]
12. No stroke/systemic embolism [-29:0]
13. No anticoagulant-related bleeding hospitalization [-29:0]

**Cohort Exit**

- rivaroxaban discontinuation +30d
- Any other oral anticoagulant
- Decreased/increased dose
- Stage 4/5 CKD
- Outcome, death, end of obs period, 11/30/2018

**End of the observation period**
So far

- ~800k patients on Apixaban or Rivaroxaban in Open Claims
- Similar demographics and baseline characteristics to Ray’s cohorts

- Full protocol development and execution
- Call for collaboration

<table>
<thead>
<tr>
<th>Count</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8,599,490</td>
<td>Patients with rivaroxaban or apixaban prescription between Jan 1, 2011 and Nov 30, 2018</td>
</tr>
<tr>
<td>5,135,106</td>
<td>at least 365d prior and alive on next day, age &gt;= 65, and known sex</td>
</tr>
<tr>
<td>4,334,745</td>
<td>prescription filled &amp; outpatient visit in the past year</td>
</tr>
<tr>
<td>4,104,899</td>
<td>No terminal illness or long-term care</td>
</tr>
<tr>
<td>3,711,064</td>
<td>Medication dose approved for Atrial fibrillation/flutter</td>
</tr>
<tr>
<td>2,405,590</td>
<td>No oral anticoagulant in the past year</td>
</tr>
<tr>
<td>873,892</td>
<td>Atrial fibrillation diagnosis, no other indication</td>
</tr>
<tr>
<td>852,413</td>
<td>No study outcome in the past month</td>
</tr>
<tr>
<td>333,954</td>
<td>Rivaroxaban users</td>
</tr>
<tr>
<td>518,459</td>
<td>Apixaban users</td>
</tr>
</tbody>
</table>

3,464,384 excluded
800,361 excluded
229,846 excluded
393,835 excluded
1,305,474 excluded
1,531,698 excluded
21,479 excluded

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The Roux Institute at Northeastern University