Minor Differences, Major Consequences? Lessons Learned from Replication of a Claims-Based Drug Safety Assessment

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Background and Motivation

• Dabigatran vs warfarin
  • Oral direct thrombin inhibitor vs vitamin K antagonist
  • Anticoagulants indicated for atrial fibrillation
  • Comparative thromboembolic and safety risks: conflicting evidence from observational studies

• Discrepancy in risk estimates for myocardial infarction observed between two Sentinel studies
  1. Protocol-based assessment: conducted in Mini-Sentinel era
  2. Modular programs: replication of the above using Sentinel tools
Background and Motivation

Outcomes of Dabigatran and Warfarin for Atrial Fibrillation in Contemporary Practice: A Retrospective Cohort Study

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Article, Author, and Disclosure Information
Background and Motivation

- RF-Wave (Connolly, 2010; Frataza label)
- Graham, 2014 (Medicare)
- Go, 2017 (Sentinel, protocol assessment)
- Sentinel Replication of Go, 2017 (Sentinel, modular program)

![Diagram showing hazard ratios for intracranial hemorrhage, myocardial infarction, and gastrointestinal bleeding, favoring dabigatran or warfarin.]

Hazard Ratio (95% Confidence Intervals)

- Intracranial Hemorrhage
- Myocardial Infarction
- Gastrointestinal Bleeding

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34th ICPE, Prague, Czech Republic
Background and Motivation

• Minor changes in design elements can potentially define different analytic cohorts and subsequently affect causal inference in epidemiological studies

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Study Objective
To examine the impact of design element changes in claims-based drug safety evaluations, using the association of oral anticoagulant use with bleeding outcomes as a test case
Test Case (fixed design elements)

• Data: 2010-2015 Truven Health MarketScan® Research Databases (formatted to Sentinel Common Data Model)
• Study design: retrospective new-user cohort
• Exposure: dabigatran vs warfarin
• Outcome: myocardial infarction (MI), gastrointestinal bleeding (GIB), and intracranial hemorrhage (ICH)
• Censoring: treatment episode end, initiation of exposure in comparison or non-exposure oral anticoagulant, 9/30/2015, health plan disenrollment, or institutional admission

• Risk estimation
  • Sentinel tools: Cohort Identification and Descriptive Analysis and Propensity Score Analysis Tools (version 5.0.3)
  • 1:1 propensity score-matching and Cox proportional hazards models
Study Cohort

- New exposure washout
- Covariate ascertainment
- Inclusion: atrial fibrillation/flutter
- Exclusion: valvular disease, dialysis, kidney transplant, joint replacement, deep vein thrombosis, pulmonary embolism

Exclude new exposure during institutional stay [0,0]

Look-back (365 days)

Follow-up until outcome/censor

Exposure Episode Start
(Day 0 or index date)

1/1/2010

9/30/2015
Covariates

- Demographics: age, sex, calendar year of index exposure day
- Medical history: advanced kidney dysfunction, advanced liver disease, alcoholism, anemia, chronic heart failure, coagulation defects; metastatic cancer, osteoporotic fracture, major surgery, coronary artery bypass surgery, hospitalized GIB, hospitalized ICH, hyperlipidemia, ischemic stroke, MI, non-specific cerebrovascular disease, arterial embolism, gastrointestinal ulcer, hospitalized bleed, venous thromboembolism risk, peripheral vascular disease, percutaneous coronary intervention, prior central venous thrombosis, transient ischemic attack, comorbidity score; diabetes, hypertension, smoking
- Mobility: cane use, commode chair use, falls, wheelchair use, walker use, use of home oxygen, trauma with likely immobilization;
- Drug use history: antihypertensive, aldosterone antagonist, antianginal agents, antiarrhythmic, aspirin, calcium channel, Cox-2 inhibitor, diuretics, estrogen, H-2 antagonist, H pylori combination, heparin and related, CYP3A4 inducer, CYP3A4 inhibitor, insulin, non-statin lipid lowering drugs, nonsteroidal anti-inflammatory drug (NSAIDs), oral antidiabetic, platelet inhibitors, proton pump inhibitors, progestin, selective serotonin reuptake inhibitor and serotonin–norepinephrine reuptake inhibitor, statin
Methods (covarying design elements)

• MI: covary pre-identified design elements and examine changes in cohort size, time-at-risk, and effect estimates
  A. Day 0 disposition (look-back vs follow-up)
  B. Excluding heparin use at baseline
  C. Stockpiling algorithms for outpatient dispensing records
  D. Health services utilization matrices as additional covariates in the propensity score (PS) estimation model

• ICH and GIB: based on findings above, evaluate changes contributed by individual design element or select element combinations of the highest and lowest impact
**Input (design element)**

- **Element A:** Day 0
- **Element B:** Heparin exclusion
- **Element C:** Stockpiling
- **Element D:** Health services utilization in propensity score estimation

**Risk Estimation**

1. Cohort Identification
2. Propensity Score Estimation
3. Propensity Score Matching
4. At-Risk Time Follow-Up
5. Risk Estimation

**Output (most impacted)**

- Unmatched cohort size and composition
- Matched cohort size and composition
- Follow-up time in person-years
- Incidence Rates and Risk Estimates
Element A: Day 0

- **A+** Look-back [-364, 0] Follow-up [1, outcome]
- **A-** Look-back [-365, -1] Follow-up [0, outcome]

Element B: Heparin exclusion

Exclusion: valvular disease, dialysis, kidney transplant, joint replacement, deep vein thrombosis, pulmonary embolism

- **B+** Look-back
- **B-** Look-back

Element C: Stockpiling algorithm

Exclusion: valvular disease, dialysis, kidney transplant, joint replacement, deep vein thrombosis, pulmonary embolism, **heparin use**

Element D: Covariates in PS model

- **D+** Covariates in PS model
- **D-** Covariates in PS model
Results: MI, cohort size

Unmatched Cohort Size, Design Element A

- Warfarin
- Dabigatran

Day 0 in Look-Back vs. Day 0 in Follow-Up

Mean exposed members:
- 80,000
- 70,000
- 60,000
- 50,000
- 40,000
- 30,000

Unmatched Cohort Size by Heparin Exclusion

- Dabigatran
- Warfarin

Day 0 in Look-Back vs. Day 0 in Follow-Up

Mean exposed members:
- 40,000
- 39,000
- 38,000
- 37,000
- 36,000
- 35,000

No Heparin Exclusion vs. Heparin Exclusion

Unmatched Cohort Size, Design Element B

- Warfarin
- Dabigatran

Day 0 in Look-Back vs. Day 0 in Follow-Up

Mean exposed members:
- 80,000
- 70,000
- 60,000
- 50,000
- 40,000
- 30,000

Unmatched Cohort Size by Heparin Exclusion

- Warfarin

Day 0 in Look-Back vs. Day 0 in Follow-Up

Mean exposed members:
- 83,000
- 80,000
- 77,000
- 74,000
- 71,000

No Heparin Exclusion vs. Heparin Exclusion
Results: MI, follow-up time, risk estimates
## Results: Propensity Score-Matched Risk Estimates

<table>
<thead>
<tr>
<th>Element combination</th>
<th>Intracranial Hemorrhage</th>
<th>Myocardial Infarction</th>
<th>Gastrointestinal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>B</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>C</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>D</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

- **Intracranial Hemorrhage** favors dabigatran
- **Myocardial Infarction**
- **Gastrointestinal Bleeding** favors warfarin
Discussion

• Among the tested design elements, Day 0 disposition (Element A) and outpatient pharmacy dispensing stockpiling algorithm (Element C) demonstrated the most impact on cohort size and total time-at-risk.

• Robust confounding adjustment methods such as propensity score matching may attenuate the differences caused by varying specifications, but final results need to be generalized with caution.

• Further investigation is needed for details of the cohort composition (i.e., characteristics) change.
Limitations

• No two analyses in this study reproduced the motivating discrepancy observed from the prior Sentinel analyses

• Impact of design element changes was examined in one test case, and study conclusions may not be generalizable to alternative design element changes, exposure-outcome pairs, or population subgroups
  • Stockpiling impact: titrated drug (warfarin) > fixed-dose drug (dabigatran)
    • Differential impact may not exist if comparing two fixed-dose drugs
  • Variation in risk estimates resulted from design element changes may be smaller for other more prevalent outcomes
Conclusions

• Minor changes in design elements can lead to major differences in analytic cohorts
  • Impact of individual design element or design element combinations on cohort composition and follow-up time varies

• We recommend clear definitions of design elements in claims-based drug safety assessments
  • Particularly for potentially impactful design elements such as Day 0 disposition and outpatient pharmacy dispensing stockpiling algorithm
  • A practice to facilitate consistency of future or follow-up investigations
References

- Sentinel System and Routine Querying Tools: https://www.sentinelinitiative.org
- Pradaxa (dabigatran etexilate mesylate) [package insert]. Ridgefield: Boehringer Ingelheim Pharmaceuticals, Inc., CT; 2015.