Walkthrough of implementing a cohort study using OHDSI tools
Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Rongmei Zhang, PhD; Mary Ross Southworth, PharmD; Mark Levenson, PhD; Ting-Chang Sheu, MPH; Katrina Mott, MHS; Margie R. Goulding, PhD; Monika Houstan, PharmD, MPH; Thomas E. Macurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMSc

Background—The comparative safety of dabigatran versus warfarin for treatment of nonvalvular atrial fibrillation in general practice settings has not been established.

Methods and Results—We formed new-user cohorts of propensity score–matched elderly patients enrolled in Medicare who initiated dabigatran or warfarin for treatment of nonvalvular atrial fibrillation between October 2010 and December 2012. Among 134414 patients with 37587 person-years of follow-up, there were 2715 primary outcome events. The hazard ratios (95% confidence intervals) comparing dabigatran with warfarin (reference) were as follows: ischemic stroke, 0.80 (0.67–0.96); intracranial hemorrhage, 0.34 (0.26–0.46); major gastrointestinal bleeding, 1.28 (1.14–1.44); acute myocardial infarction, 0.92 (0.78–1.08); and death, 0.86 (0.77–0.96). In the subgroup treated with dabigatran 75 mg twice daily, there was no difference in risk compared with warfarin for any outcome except intracranial hemorrhage, in which case dabigatran risk was reduced. Most patients treated with dabigatran 75 mg twice daily appeared not to have severe renal impairment, the intended population for this dose. In the dabigatran 150-mg twice daily subgroup, the magnitude of effect for each outcome was greater than in the combined-dose analysis.

Conclusions—In general practice settings, dabigatran was associated with reduced risk of ischemic stroke, intracranial hemorrhage, and death and increased risk of major gastrointestinal hemorrhage compared with warfarin in elderly patients with nonvalvular atrial fibrillation. These associations were most pronounced in patients treated with dabigatran 150 mg twice daily, whereas the association of 75 mg twice daily with study outcomes was indistinguishable from warfarin except for a lower risk of intracranial hemorrhage with dabigatran. (Circulation. 2015;131:157-164. DOI: 10.1161/CIRCULATIONAHA.114.012061.)

Key Words: anticoagulant □ pharmacoepidemiology □ safety □ thrombin inhibitor □ warfarin
What is the design used by Graham et al?

<table>
<thead>
<tr>
<th>Input parameter</th>
<th>Design choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target cohort (T)</td>
<td>dabigatran new users with prior atrial fibrillation</td>
</tr>
<tr>
<td>Comparator cohort (C)</td>
<td>warfarin new users with prior atrial fibrillation</td>
</tr>
<tr>
<td>Outcome cohort (O)</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>Time-at-risk</td>
<td>1 day after cohort start → cohort end</td>
</tr>
<tr>
<td>Model specification</td>
<td>1:1 propensity score-matched univariable conditional Cox proportional hazards</td>
</tr>
</tbody>
</table>
A new-user retrospective cohort design was used to compare patients initiating dabigatran or warfarin for the treatment of nonvalvular AF. We identified all patients with any inpatient or outpatient diagnoses of AF or atrial flutter based on *International Classification of Diseases, Ninth Revision* coding who also filled at least 1 prescription for either drug from October 19, 2010 (US dabigatran approval date) through December 31, 2012, the study end date. Patients were excluded if they had <6 months of enrollment in Medicare before their index dispensing, were aged <65 years, received prior treatment with a study medication or rivaroxaban or apixaban (anticoagulants approved during the study), were in a skilled nursing facility or nursing home, or were receiving hospice care on the date of their cohort-qualifying prescription. Patients were also excluded if they had a hospitalization that extended beyond the index dispensing date. Patients discharged from the hospital on the same day as their index dispensing were included. Patients undergoing dialysis and kidney transplant recipients were also excluded. Additionally, because warfarin is approved for indications other than AF, we excluded patients with diagnoses indicating the presence of mitral valve disease, heart valve repair or replacement, deep vein thrombosis, pulmonary embolism, or joint replacement surgery in the preceding 6 months.
Graham et al. replication: Designing the target cohort in ATLAS
Graham et al. replication: Designing the target cohort in ATLAS

Events having any of the following criteria:

- a drug era of **dabigatran**
- for the first time in the person’s history
- era start is: **On or After** 2010-10-19
- with age in years at era start **Greater or Equal To** 65
- with continuous observation of at least **183** days before and **0** days after
- Limit initial events to: **earliest event** per person.
Graham et al. replication: Designing the target cohort in ATLAS

Inclusion Criteria

1. Has prior atrial fibrillation or atrial flutter diagnosis
2. Has no prior treatment with comparator drug (warfarin)
3. Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)
4. Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date
5. Not undergoing dialysis or kidney transplant recipient
6. No mitral valve disease, heart valve repair, or replacement in the prior 6 months
7. No deep vein thrombosis or pulmonary embolism in the prior 6 months
8. No joint replacement surgery in...
Graham et al. replication: Designing the target cohort in ATLAS
Graham et al. replication: Designing the target cohort in ATLAS

Event Persistence:
Event will persist until: end of a continuous drug exposure

Continuous Exposure Persistence:
Specify a concept set that contains one or more drugs. A drug era will be derived from all drug exposure events for any of the drugs within the concept set, using the specified persistence window as a maximum allowable gap in days between successive exposure events and adding a specified surveillance window to the final exposure event. If no exposure event end date is provided, then an exposure event end date is inferred to be event start date + days supply in cases when days supply is available or event start date + 1 day otherwise. This event persistence assures that the cohort end date will be no greater than the drug era end date.

Concept set containing the drug(s) of interest: dabigatran
- Persistence window: allow for a maximum of 3 days between exposure records when inferring the era of persistence exposure
- Surveillance window: add 0 days to the end of the era of persistence exposure as an additional period of surveillance prior to cohort exit.

Censoring Events:
Exit Cohort based on the following criteria:
No censoring events selected.
Every entity referenced the cohort definition needs to a complete definition of concepts and associated source codes.
Graham et al. replication: Designing the target cohort in ATLAS

Cohort Entry Events

Events having any of the following criteria:

- a drug era of warfarin
- for the first time in the person's history
- era start is: On or After 2010-10-19
- with age in years at era start Greater or Equal To 65
- with continuous observation of at least 183 days before and 0 days after event index date

Limit initial events to: earliest event per person.

Restrict initial events
Graham et al. replication: Evaluating the impact of inclusion criteria on the comparator cohort in ATLAS

Inclusion Report for Truven MDCR (v779)

<table>
<thead>
<tr>
<th>Inclusion Rule</th>
<th>Match Rate</th>
<th>Matches</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary Statistics:</td>
<td>31.13%</td>
<td>56,648</td>
<td>182,001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion Rule</th>
<th>N</th>
<th>% Remain</th>
<th>% Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has prior atrial fibrillation or atrial flutter diagnosis</td>
<td>86,995</td>
<td>47.80%</td>
<td>52.20%</td>
</tr>
<tr>
<td>2. Has no prior treatment with comparator drug (dabigatran)</td>
<td>83,161</td>
<td>45.69%</td>
<td>2.11%</td>
</tr>
<tr>
<td>3. Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)</td>
<td>78,222</td>
<td>42.98%</td>
<td>2.71%</td>
</tr>
<tr>
<td>4. Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date</td>
<td>78,161</td>
<td>42.95%</td>
<td>0.03%</td>
</tr>
<tr>
<td>5. Not undergoing dialysis or kidney transplant recipient</td>
<td>76,110</td>
<td>41.82%</td>
<td>1.13%</td>
</tr>
<tr>
<td>6. No mitral valve disease, heart valve repair, or replacement in the prior 6 months</td>
<td>69,645</td>
<td>38.27%</td>
<td>3.55%</td>
</tr>
<tr>
<td>7. No deep vein thrombosis or pulmonary embolism in the prior 6 months</td>
<td>59,195</td>
<td>32.52%</td>
<td>5.74%</td>
</tr>
<tr>
<td>8. No joint replacement surgery in the prior 6 months</td>
<td>56,648</td>
<td>31.13%</td>
<td>1.40%</td>
</tr>
</tbody>
</table>

Population Visualization

Attrition Visualization

Switch to attrition view

Switch to intersect view
Graham et al. description of the outcomes

Study Outcomes
The primary outcomes were ischemic stroke, major bleeding with specific focus on intracranial and gastrointestinal bleeding, and AMI. Secondary outcomes were all hospitalized bleeding events and mortality. The *International Classification of Diseases, Ninth Revision, Clinical Modification* codes used to define these outcomes are listed in Table II in the online-only Data Supplement. The codes defining ischemic stroke have a positive predictive value (PPV) of 88% to 95%.\textsuperscript{18–20} Major bleeding was defined as

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<th>Outcome</th>
<th>ICD-9 Codes</th>
<th>Position</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>410 (all)</td>
<td>1st or 2nd</td>
<td>IP only</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>433.x1, 434.x (except subcode: x0), 436</td>
<td>1st</td>
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Graham et al. description of the outcomes

**Study Outcomes**

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Major bleeding was defined as ... and look, ischemic stroke is a ‘validated’ outcome!

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Sidebar: just how good was that validation?

Ref 18 from Graham et al.:

Validating Administrative Data in Stroke Research

David L. Tirschwell, MD; W.T. Longstreth, Jr, MD

Background and Purpose—Research based on administrative data has advantages, including large numbers, consistent data, and low cost. This study was designed to compare different methods of stroke classification using administrative data.

Methods—Administrative hospital discharge data and medical record review of 206 patients were used to evaluate 3 algorithms for classifying stroke patients. These algorithms were based on all (algorithm 1), the first 2 (algorithm 2), or the primary (algorithm 3) administrative discharge diagnosis code(s). The diagnoses after review of medical record data were considered the gold standard. Then, using a large administrative data set, we compared patients with a primary discharge diagnosis of stroke with patients with their stroke discharge diagnosis code in a nonprimary position.

Results—Compared with the gold standard, algorithm 1 had the highest $\kappa$ for classifying ischemic stroke, with a sensitivity of 86%, specificity of 95%, positive predictive value of 90%, and $\kappa=0.82$. Algorithm 3 had the highest $\kappa$ values for intracerebral hemorrhage and subarachnoid hemorrhage. For intracerebral hemorrhage, the sensitivity was 85%, specificity was 96%, positive predictive value was 89%, and $\kappa=0.82$. For subarachnoid hemorrhage, those values were 90%, 97%, 94%, and 0.88, respectively. Nonprimary position ischemic stroke patients had significantly greater comorbidity and 30-day mortality (odds ratio, 3.2) than primary position ischemic stroke patients.

Conclusions—Stroke classification in these administrative data were optimal using all discharge diagnoses for ischemic stroke and primary discharge diagnosis only for intracerebral and subarachnoid hemorrhage. Selecting ischemic stroke patients on the basis of primary discharge diagnosis may bias administrative samples toward more benign, unrepresentative outcomes and should be avoided. (Stroke. 2002;33:2465-2470.)

Ref 18 from Graham et al.:

**Conclusions** - Stroke classification in these administrative data were **optimal using all discharge diagnoses** for ischemic stroke....Selecting ischemic stroke patients on the basis of **primary discharge diagnosis may bias** administrative samples toward more benign, unrepresentative outcomes and should be avoided.
Graham et al. replication: Designing the outcome cohort in ATLAS
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Events having any of the following criteria:
- a condition occurrence of Ischemic stroke
- Condition Type is any of Inpatient detail - primary, Inpatient header - primary, Primary Condition
- Inpatient detail - 1st position, Inpatient header - 1st position
- with a Visit occurrence of: Emergency Room Visit, Inpatient Visit
- with continuous observation of at least 0 days before and 0 days after event index date
- Limit initial events to: earliest event per person.
Graham et al. replication: Cohort exports

mschemi graham dabigatran

Initial Event Cohort
People having any of the following:
  • a drug era of dabigatran\(^4\)
    ◦ for the first time in the person's history
    ◦ era start is on or after 2010-10-19
    ◦ with age in years at era start \(\geq 65\)

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to earliest event per person.

Inclusion Rules
Inclusion Criteria #1: Has prior atrial fibrillation or atrial flutter diagnosis
Having any of the following criteria:
  • at least 1 occurrences of a condition occurrence of Atrial fibrillation\(^2\)
    where event starts between all days Before and 0 days After index start date
  • or at least 1 occurrences of a condition occurrence of Atrial flutter\(^3\)
    where event starts between all days Before and 0 days After index start date

Inclusion Criteria #2: Has no prior treatment with comparator drug (warfarin)
Having all of the following criteria:
  • exactly 0 occurrences of a drug exposure of warfarin\(^1\)
    where event starts between all days Before and 0 days Before index start date

Inclusion Criteria #3: Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)
Having all of the following criteria:
  • exactly 0 occurrences of a drug exposure of rivaroxaban\(^2\)
    where event starts between all days Before and 0 days After index start date
  • and exactly 0 occurrences of a drug exposure of apixaban\(^1\)
    where event starts between all days Before and 0 days After index start date

Inclusion Criteria #4: Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date
Having all of the following criteria:
  • exactly 0 occurrences of a visit occurrence of long term care visit\(^1\)
    where event starts between 0 days Before and 0 days After index start date
  • and exactly 0 occurrences of a procedure of Hospice observations\(^2\)
    where event starts between all days Before and 0 days After index start date
  • and exactly 0 occurrences of an observation of Hospice observations\(^3\)
    where event starts between all days Before and 0 days After index start date
Graham et al. replication: Designing the study in ATLAS
Graham et al. replication: Designing the full study in ATLAS
Graham et al. replication: Specifying the comparison
Graham et al. replication: Specifying the comparison
Graham et al. replication: Specifying the comparison

### Population Level Effect Estimation - Comparative Cohort Analysis

**Add or update the target, comparator, outcome(s) cohorts and negative control outcomes**

**Comparison**

- **Choose your target cohort:**
  - mshuemie graham dabigatran

- **Choose your comparator cohort(s):**
  - mshuemie graham warfarin

- **Choose your outcome cohort(s):**
  - mshuemie graham gabled
  - mshuemie graham ischemic stroke

**Covariate selection**

*Please note:* If you would like to include/exclude covariates based on descendant concepts, it is most efficient to specify this as part of the analysis settings. If you plan to include/exclude descendants, define your concept sets utilizing the ancestor concepts only.

**What concepts do you want to include in baseline covariates in the propensity score model? (Leave blank if you want to include everything)**

- mshuemie graham gabled

**What concepts do you want to exclude from baseline covariates in the propensity score model? (Leave blank if you want to include everything)**

- mshuemie graham concepts to exclude from covariates
Graham et al. replication: Specifying the analysis settings
Graham et al. replication: Specifying the analysis settings

Analysis Settings
Add or update the analysis settings

- Analysis name: Primary

Study start date - a calendar date specifying the minimum date that a cohort index can appear (leave blank to use all time):
YYYY-MM-DD

Study end date - a calendar date specifying the maximum date that a cohort index can appear (leave blank to use all time). Important: the study end date is also used to truncate risk windows, meaning no outcomes beyond the study end date will be considered.
YYYY-MM-DD

Should only the first exposure per subject be included?
- No

Remove subjects that are in both the target and comparator cohort?
- Keep All

Restrict the analysis to the period when both exposures are observed?
- No

The minimum required continuous observation time prior to index date for a person to be included in the cohort.
- 0

If either the target or the comparator cohort is larger than this number it will be sampled to this size. 0 for this value indicates no maximum size.
- 0

Remove subjects that have the outcome prior to the risk window start?
- Yes

How many days should we look back when identifying prior outcomes?
- 99999

If a subject is in multiple cohorts, should time-at-risk be censored when the new time-at-risk start to prevent overlap?
- No
Claims data on chronic medical conditions, cardiovascular risk factors, risk factors for bleeding events, and healthcare utilization were collected for each patient during the 6 months preceding their cohort-qualifying prescription fill. We also collected data on prescriptions for medications used for treatment of cardiovascular disease and other chronic medical conditions, as well as potentially interacting medications that might alter warfarin or dabigatran pharmacokinetics. Finally, to the extent possible using claims data, we calculated the CHADS<sub>2</sub> score, which predicts the risk of stroke in patients with AF, and the HAS-BLED score, which predicts the risk of bleeding in patients with AF treated with warfarin.

To reduce confounding due to imbalance in study covariates, propensity score matching was used. Unconditional logistic regression was used to estimate the predicted probability of patients initiating dabigatran therapy given their sociodemographic characteristics, baseline medical comorbidities, medications used during the preceding 6 months, prescriber characteristics, and other potentially relevant variables (Table 1 and
Graham et al. replication: covariates for confounding adjustment
Graham et al. replication: covariates for confounding adjustment
Leverages FeatureExtraction package

Default settings create covariates for all drug and condition group concepts, and procedure, measurement, observation, and device exposure concepts during 2 lookback window

Defaults also include demographics and 4 risk indexes

Graham et al. replication: covariates for confounding adjustment
Follow-up began on the day after the first qualifying anticoagulant prescription fill and continued until disenrollment from Medicare, occurrence of a study outcome, a gap in anticoagulant days of supply >3 days.
Graham et al. replication: specifying the propensity score model

Dabigatran users were propensity score matched to warfarin users in a 1:1 ratio with the use of a greedy matching algorithm. The balance of measured covariates between the matched cohorts was assessed with the standardized mean difference, a measure not influenced by sample size and thus useful for comparing cohorts in large observational studies. A standardized mean difference of ≤0.1 indicates a negligible difference in the measured variables between groups.
Graham et al. replication: specifying the propensity score model
Analyses were performed on the propensity score–matched cohorts, thereby accounting for the potential confounding factors shown in Table 1 and in the online-only Data Supplement. Incidence rates were estimated with the use of event counts and exposure follow-up time. Kaplan–Meier plots were generated to characterize the contour of risk over time for each outcome. Cox proportional hazards regression was used to compare time to event in dabigatran compared with warfarin (reference) cohorts.
Graham et al. replication: specifying the outcome model
Graham et al. replication: specifying the evaluation settings

Evaluation Settings

Negative Control Outcome Cohort Definition

This expression will define the criteria for inclusion and duration of time for cohorts intended for use as negative control outcomes. The type of occurrence of the event when selecting from the domain.

First occurrence

When true, descendant concepts for the negative control outcome concept IDs will be used to detect the outcome and roll up the occurrence to the concept ID.

Yes

What domains should be considered to detect negative control outcomes? (Hold control to select multiple domains)

Condition
Drug
Device
Measurement
Observation
Procedure
Visit

Positive Control Synthesis

Should we perform positive control synthesis to calibrate confidence intervals?

Yes

Model Types:

Survival

Using OHDSI covariates for model. (Click to view details)

Define the time-at-risk window start, relative to target/comparator cohort entry:

0

end
Graham et al. replication: exporting the study package for execution