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 Houstoun, 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

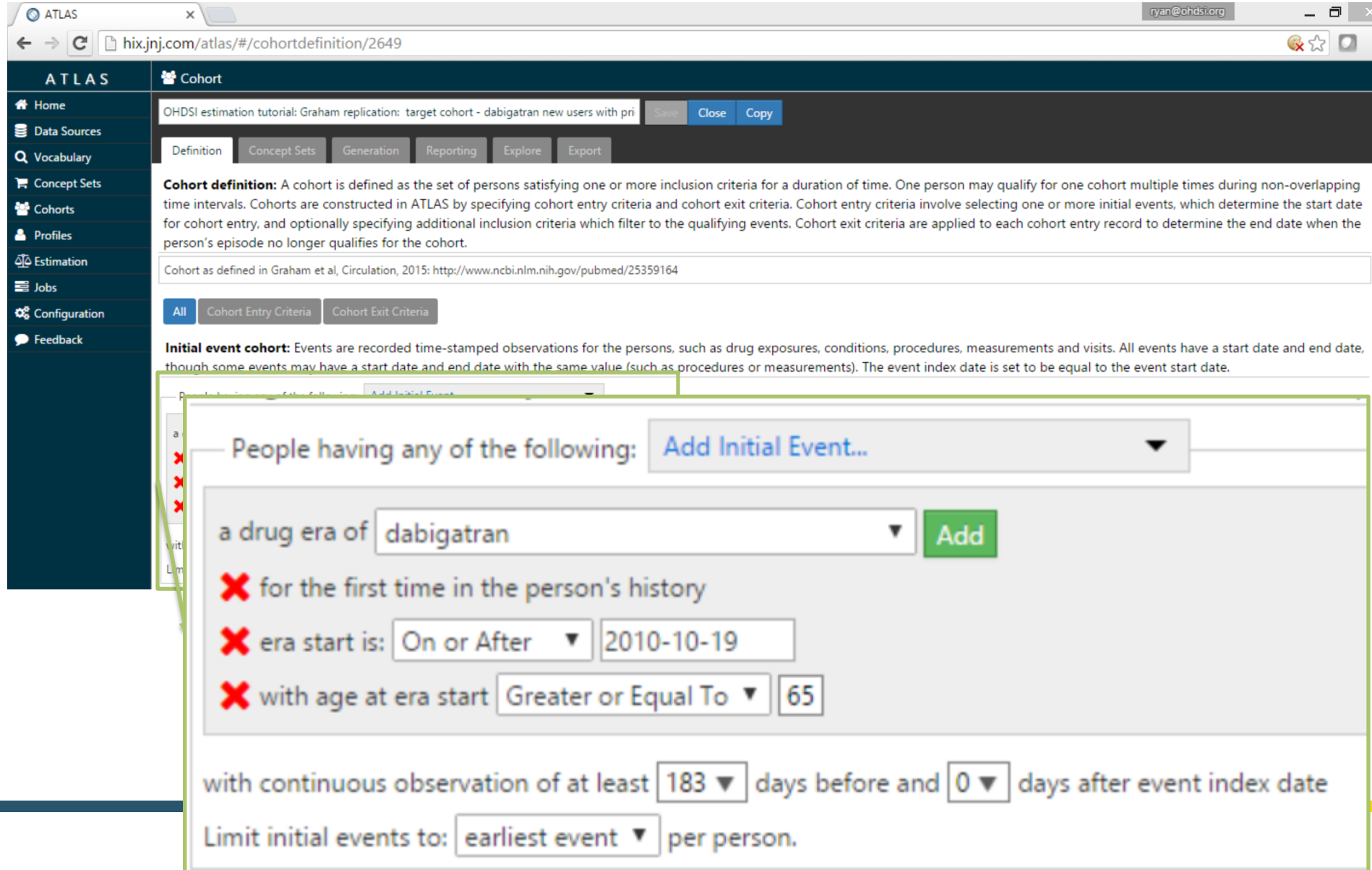
What is the design used by Graham et al?

Input parameter	Design choice
Target cohort (T)	dabigatran new users with prior atrial fibrillation
Comparator cohort (C)	warfarin new users with prior atrial fibrillation
Outcome cohort (O)	Ischemic stroke
Time-at-risk	1 day after cohort start → cohort end
Model specification	1:1 propensity score-matched univariable conditional Cox proportional hazards

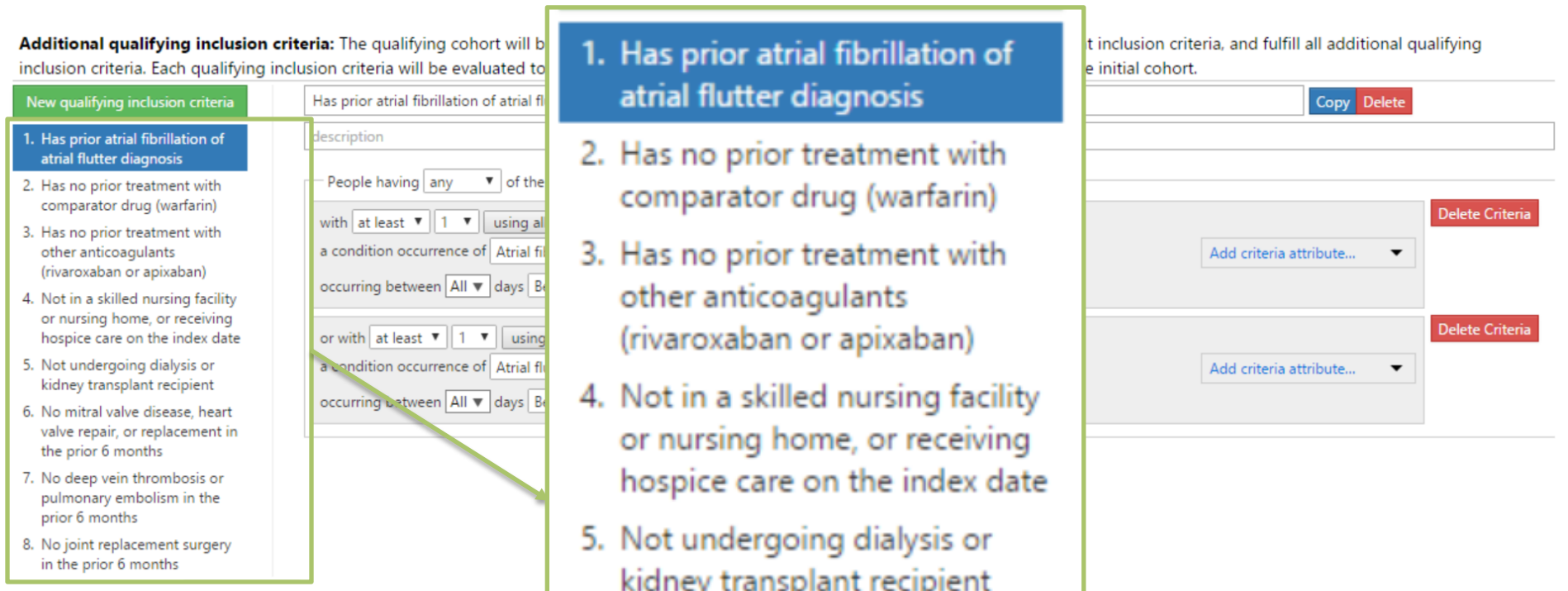
Graham et al. description of the cohort(s)

A new-user retrospective cohort design was used to compare patients initiating dabigatran or warfarin for the treatment of nonvalvular AF.[10] 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

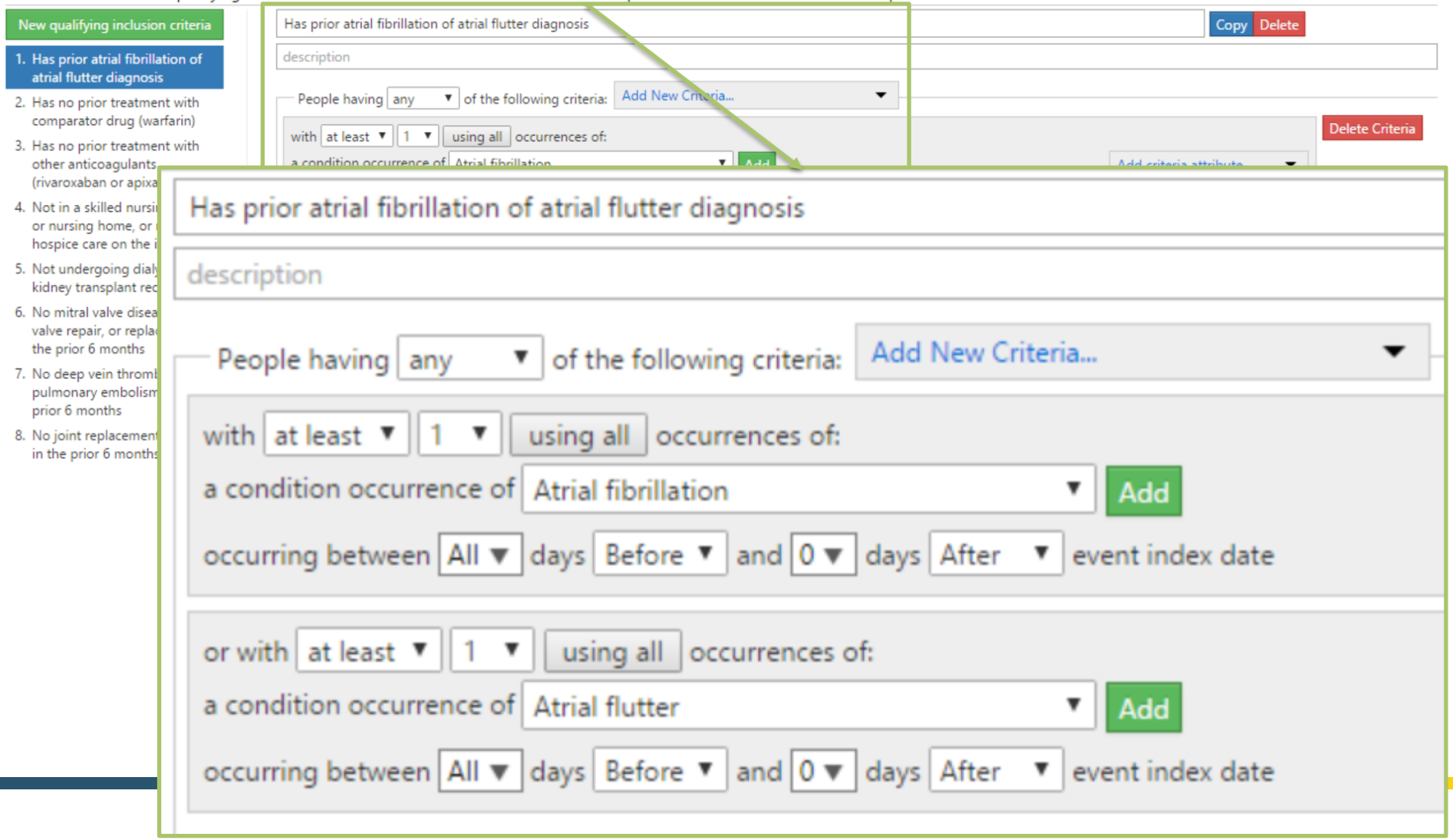


Graham et al. replication: Designing the target cohort in ATLAS



Graham et al. replication: Designing the target cohort in ATLAS

Additional qualifying inclusion criteria: The qualifying cohort will be defined as all persons who have an initial event, satisfy the initial event inclusion criteria, and fulfill all additional qualifying inclusion criteria. Each qualifying inclusion criteria will be evaluated to determine the impact of the criteria on the attrition of persons from the initial cohort.



Graham et al. replication: Designing the target cohort in ATLAS

Cohort Exit Criteria

Cohort exit criteria based on the end of an era of persistent exposure to any drug within a defined concept set:

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 cohort exit criteria assures that the cohort end date will be no greater than the drug era end date.

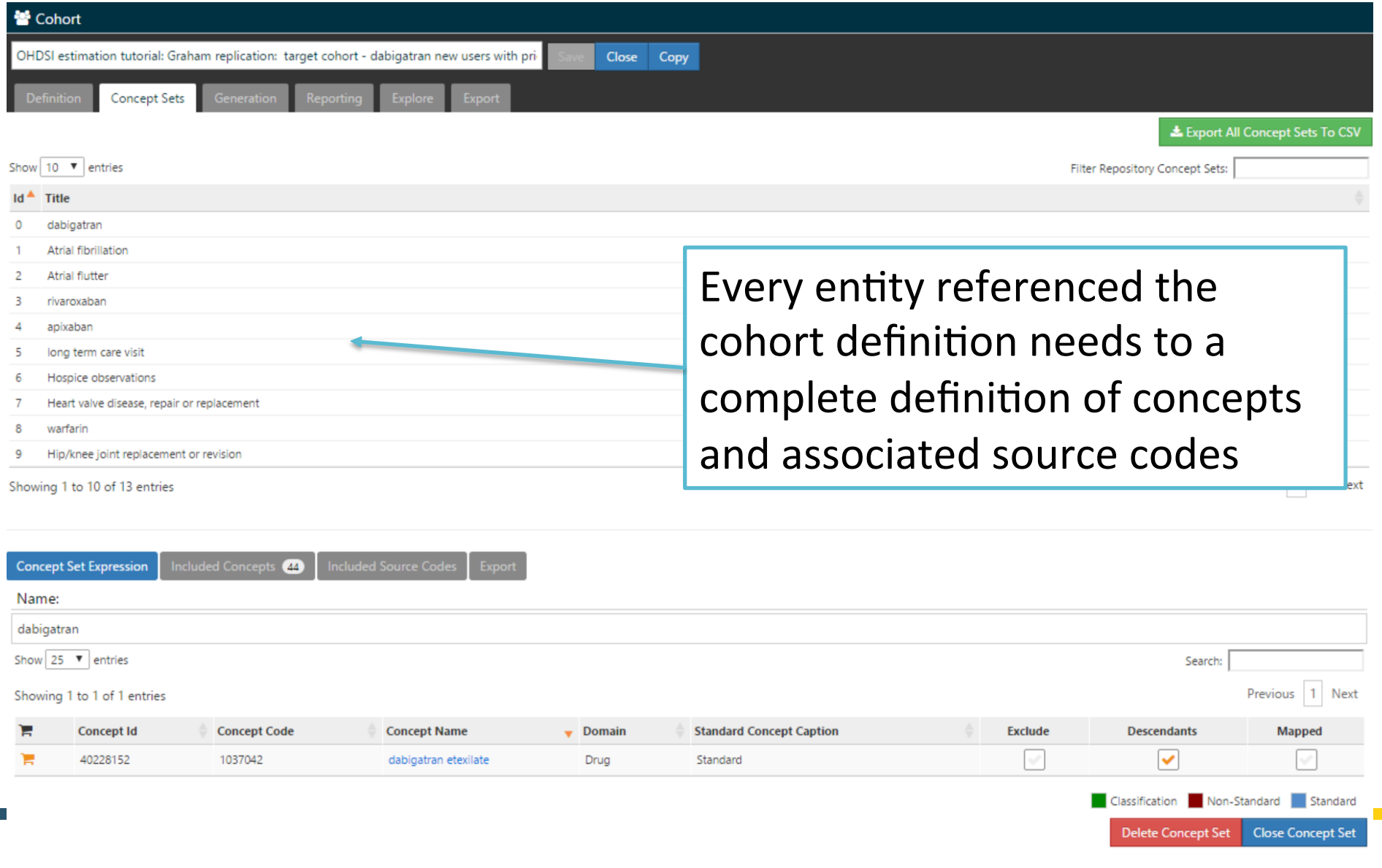
Concept set containing the drug(s) of interest: dabigatran ▼ Add

- 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.

Concept set containing the drug(s) of interest: dabigatran ▼ Add

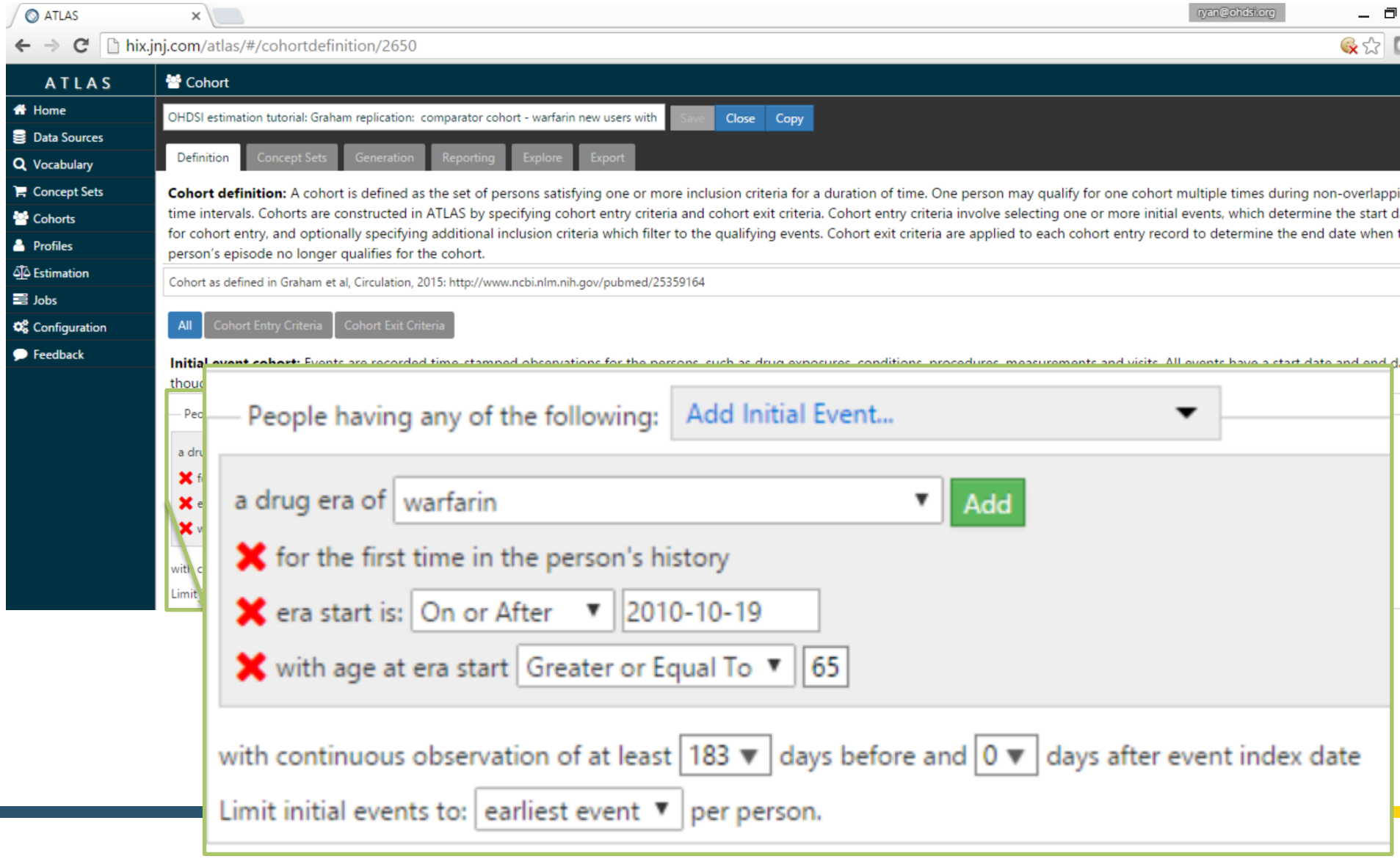
- Persistence window: allow for a maximum of 3 ▼ days between exposure records when inferring the era of persistence exposure
- Surveillance window: add 0 ▼ days to the end of the era of persistence exposure as an additional period of surveillance prior to cohort exit.

Graham et al. replication: Designing the target cohort in ATLAS



Every entity referenced the cohort definition needs to a complete definition of concepts and associated source codes

Graham et al. replication: Designing the comparator cohort in ATLAS

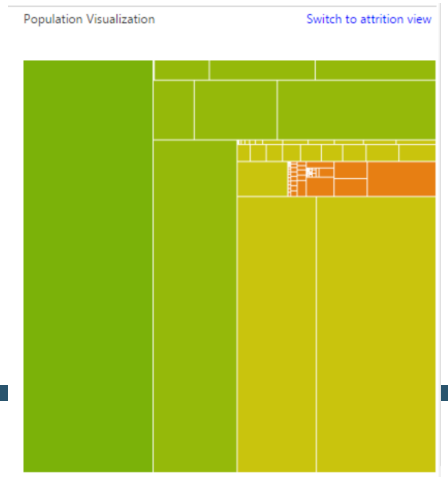


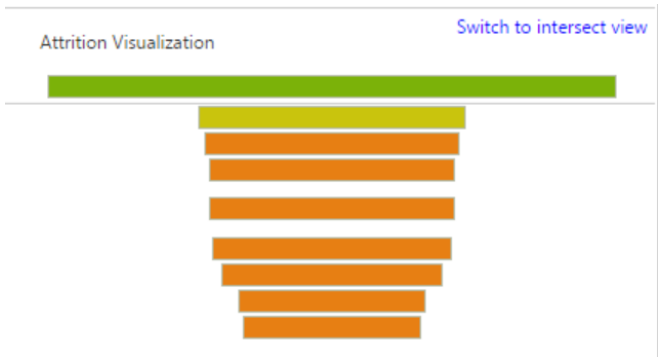
Graham et al. replication: Evaluating the impact of inclusion criteria on the comparator cohort in ATLAS

Inclusion Report for Truven MDCR

	Match Rate	Matches	Total
Summary Statistics:	31.52%	52,400	166,243

	Inclusion Rule	N	% Satisfied	% To-Gain
1.	Has prior atrial fibrillation of atrial flutter diagnosis	78,371	47.14%	16.40%
2.	Has no prior treatment with comparator drug (dabigatran)	162,601	97.81%	1.44%
3.	Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)	161,768	97.31%	1.26%
4.	Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date	166,149	99.94%	0.01%
5.	Not undergoing dialysis or kidney transplant recipient	163,463	98.33%	0.65%
6.	No mitral valve disease, heart valve repair, or replacement in the prior 6 months	157,221	94.57%	2.91%
7.	No deep vein thrombosis or pulmonary embolism in the prior 6 months	118,058	71.02%	5.56%
8.	No joint replacement surgery in the prior 6 months	138,630	83.39%	1.44%





Graham et al. description of the outcomes

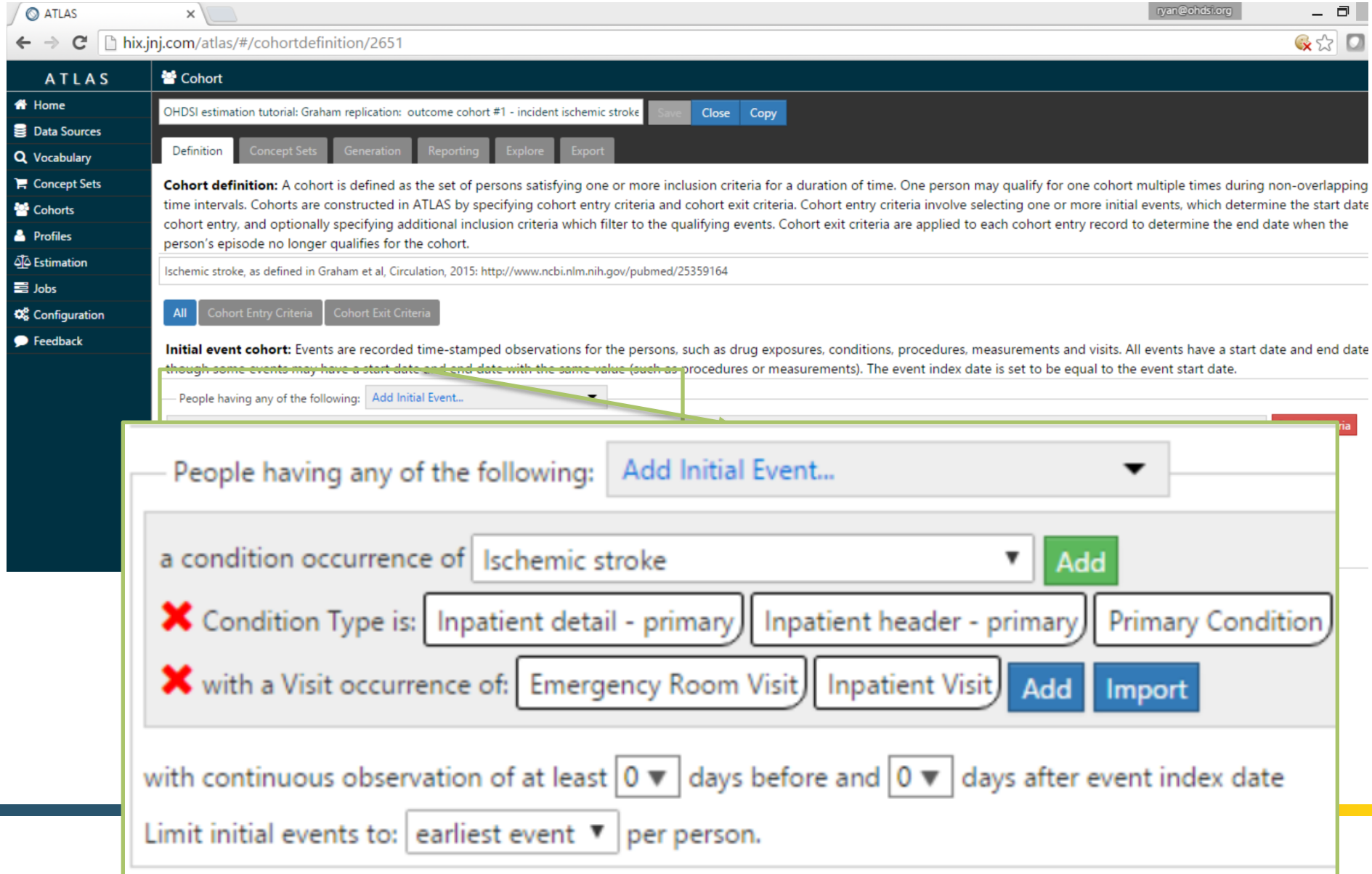
Study Outcomes

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%.[18–20] Major bleeding was defined as

Table 2. International Classification of Disease, 9th edition, Clinical Modification (ICD 9-CM) codes used to define study outcomes.

Outcome	ICD-9 Codes	Position	Setting
AMI	410 (all)	1st or 2nd	IP only
Ischemic stroke	433.x1, 434.x (except subcode: x0), 436	1st	IP only

Graham et al. replication: Designing the outcome cohort in ATLAS

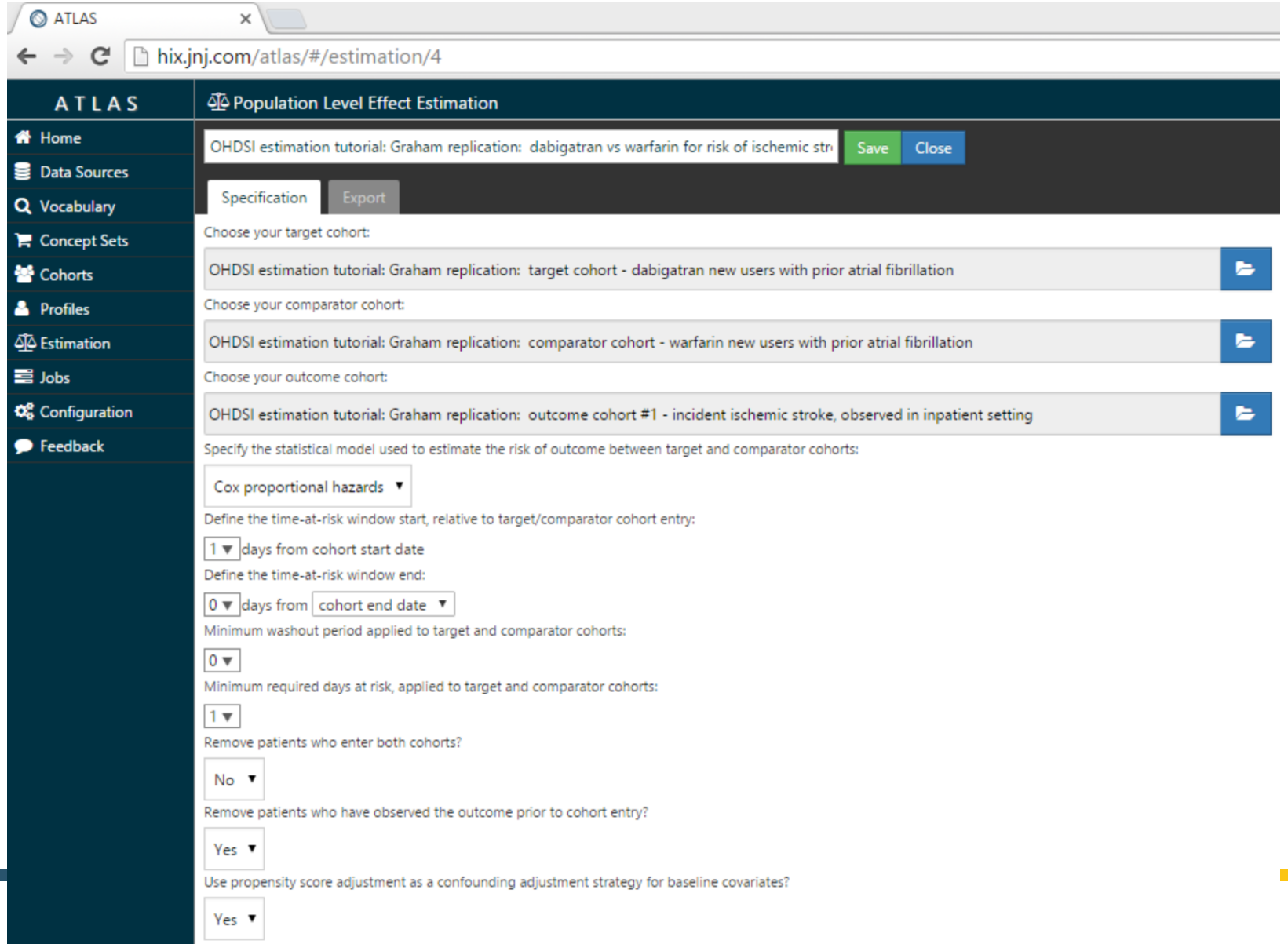


Graham et al. description of the outcome model

Statistical Analysis

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: Designing the outcome model in ATLAS



Graham et al. replication: Designing a protocol in ATLAS

Population Level Effect Estimation

OHDSI estimation tutorial: Graham replication: dabigatran vs warfarin for risk of ischemic str | Save | Close

Specification | Export

Print Friendly | R Code

Research question

To compare the risk of **OHDSI estimation tutorial: Graham replication: outcome cohort #1 - incident ischemic stroke, observed in inpatient setting** between **OHDSI estimation tutorial: Graham replication: target cohort - dabigatran new users with prior atrial fibrillation** and **OHDSI estimation tutorial: Graham replication: comparator cohort - warfarin new users with prior atrial fibrillation**, we will estimate the population-level effect of exposure on the hazards of the outcome during the period from 1 days from cohort start date to 0 days from cohort end date.

Study Design:

This study will follow a retrospective, observational, comparative cohort design. We define 'retrospective' to mean the study will be conducted using data already collected prior to the start of the study. We define 'observational' to mean there is no intervention or treatment assignment imposed by the study. We define 'cohort' to mean a set of patients satisfying a one or more inclusion criteria for a duration of time. We define 'comparative cohort design' to mean the formal comparison between two cohorts, a target cohort and comparator cohort, for the risk of an outcome during a defined time period after cohort entry.

In this study, we compare **OHDSI estimation tutorial: Graham replication: target cohort - dabigatran new users with prior atrial fibrillation** with **OHDSI estimation tutorial: Graham replication: comparator cohort - warfarin new users with prior atrial fibrillation** for the hazards of **OHDSI estimation tutorial: Graham replication: outcome cohort #1 - incident ischemic stroke, observed in inpatient setting** from 1 days from cohort start date to 0 days from cohort end date.

For both cohorts, we impose a requirement that patients must have at least 1 days of continuous observation after the time-at-risk start, 1 days from cohort start date.

The overall study population could be considered to be patients who entered either the target cohort or comparator cohort.

The time-to-event of outcome among patients in the target and comparator cohorts is determined by calculating the number of days from the start of the time-at-risk window, 1 days from cohort start date until the earliest event among 1) the first occurrence of the outcome, **OHDSI estimation tutorial: Graham replication: outcome cohort #1 - incident ischemic stroke, observed in inpatient setting** before 0 days from cohort end date, 2) the end of the time-at-risk window, 0 days from cohort end date, and 3) the end of the observation period that spans the time-at-risk start.

Patients with **OHDSI estimation tutorial: Graham replication: outcome cohort #1 - incident ischemic stroke, observed in inpatient setting** prior to target or comparator cohort entry were excluded from consideration.

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates. In this study, the propensity score is estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation, using a starting variance of 0.01 and a tolerance of 2e-7.

The types of baseline covariates used to fit the propensity score model will be:

- Demographics
  - Gender
  - Age group (5-year bands)
  - Race
  - Ethnicity