Small Changes, Big Differences? Cohort Variation by Parameter Specifications in Claims-Based Drug Use Evaluations

Ting-Ying Huang,[1] Laura Hou,[1] Laura Shockro,[1] Ella Pestine,[1] Michael Nguyen,[2] Judith C Maro,[1] Rima Izem[2]

[1] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA 02215

[2] Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993

BACKGROUND

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

***Figure 1**. Standard Risk Evaluation Steps in a Claims-Based Drug Utilization and Outcome Assessment Using Propensity Score Methods*

- Real-world drug utilization and outcome assessments using health insurance claims or other routinely-collected electronic health data have become a common type of study in pharmacoeconomics and pharmacoepidemiology.
- However, these observational studies may be sensitive to parameter specifications such as outpatient pharmacy dispensing stockpiling algorithm and lead to inconsistent results.
- The earlier the specification variation occurs in the risk evaluation steps (**Figure 1**), the more likely their impact is carried over to risk estimates.

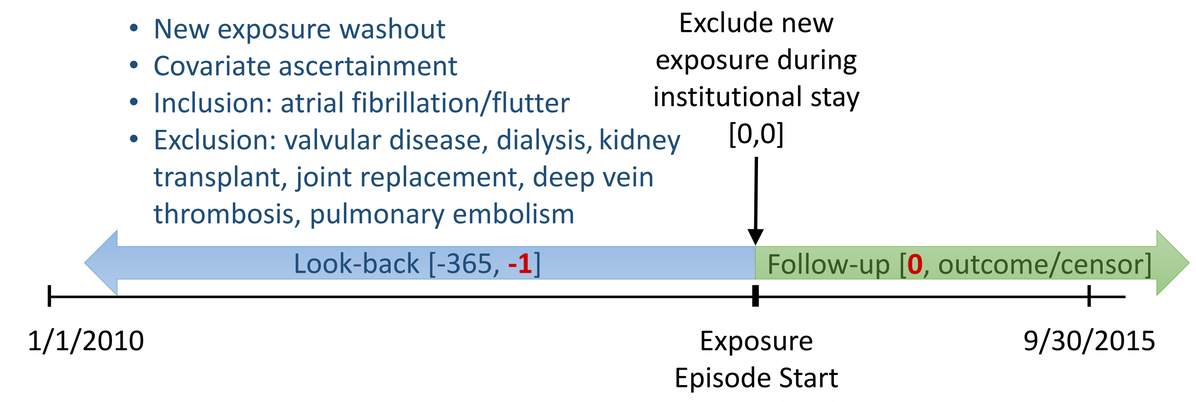
OBJECTIVE

To examine the impact of small specification changes on comparative risk assessments among drug users in a test case

METHODS

We closely replicated the design of a published study[1] and covaried specification factors to evaluate the impact on cohort size, time-at-risk, and effect estimates.

***Figure 2**. Cohort Identification Strategy and Temporal Anchors*



Fixed Specifications

- Study design: new-user, retrospective cohort study
- Data source: 2010-2016 Truven Health MarketScan® Commercial Claims and Medicare Encounters Database
- Exposures
  - Treatment: dabigatran 75 and 150 mg. Comparator: warfarin 1 to 10 mg
  - First outpatient pharmacy dispensing (Day 0) during 1/1/2010-9/30/2015, preceded by a 365-day washout period
  - New use with respect to edoxaban, apixaban, dabigatran, rivaroxaban, warfarin
- Outcome: myocardial infarction, identified as principal discharge diagnosis from an inpatient claim using ICD-9-CM codes 410.x0 and 410.x1
- Follow-up: continuous exposure episode (stockpiled if dispensings overlap; 7-day maximum allowable dispensing gap and extension) until the earliest of episode end, outcome occurrence, initiation of exposure in comparison or non-exposure oral anticoagulant, 9/30/2015, health plan disenrollment, institution admission

Varying Specifications

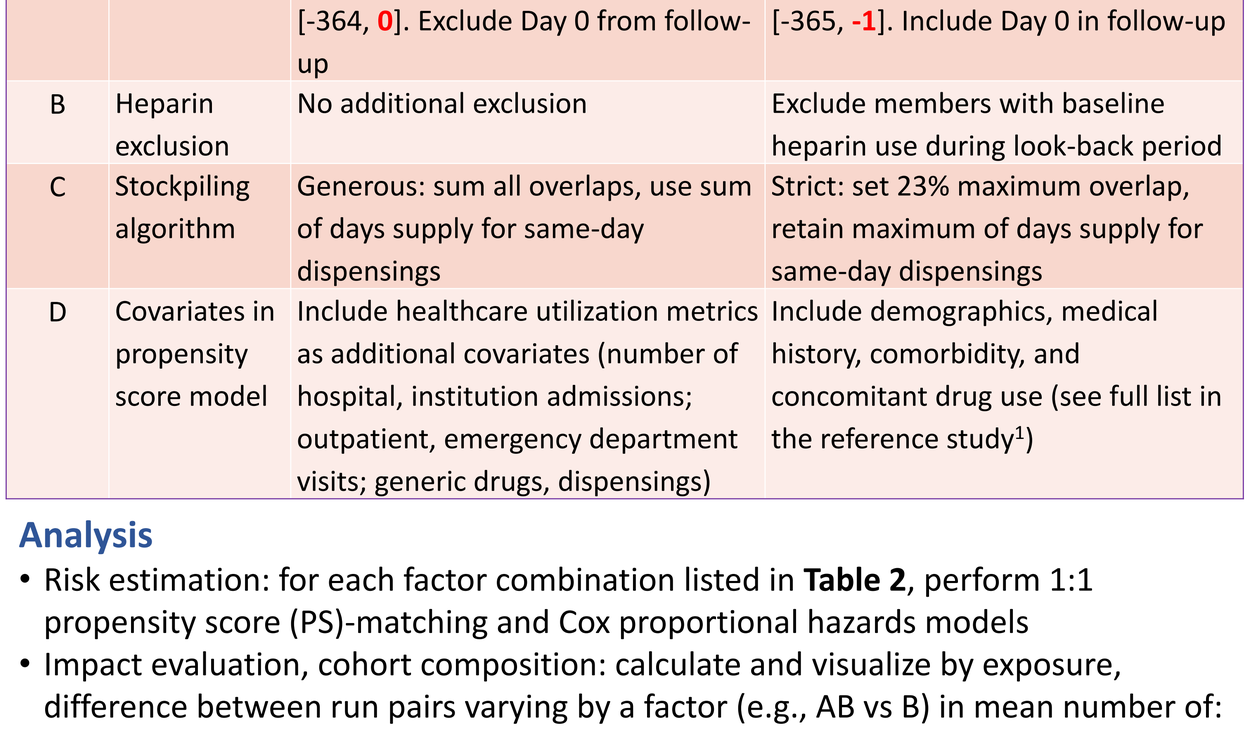
***Table 1.** Varying Specifications and Factor Definitions*

Factor	Specification	Level (+)	Level (-)
A	Day 0	Include Day 0 in look-back period and covariate ascertainment period [-364, **0**]. Exclude Day 0 from follow-up	Exclude Day 0 from look-back period and covariate ascertainment period [-365, **-1**]. Include Day 0 in follow-up
B	Heparin exclusion	No additional exclusion	Exclude members with baseline heparin use during look-back period
C	Stockpiling algorithm	Generous: sum all overlaps, use sum of days supply for same-day dispensings	Strict: set 23% maximum overlap, retain maximum of days supply for same-day dispensings
D	Covariates in propensity score model	Include healthcare utilization metrics as additional covariates (number of hospital, institution admissions; outpatient, emergency department visits; generic drugs, dispensings)	Include demographics, medical history, comorbidity, and concomitant drug use (see full list in the reference study[1])

Analysis

- Risk estimation: for each factor combination listed in **Table 2**, perform 1:1 propensity score (PS)-matching and Cox proportional hazards models
- Impact evaluation, cohort composition: calculate and visualize by exposure, difference between run pairs varying by a factor (e.g., AB vs B) in mean number of: unmatched and matched cohort size, total time-at-risk, and incidence rate
- Impact evaluation, effect estimates: calculate and visualize by factor combination, hazard ratios (HRs) and their 95% confidence intervals (CIs) on the natural logarithm scale

***Figure 3.** Stockpiling Algorithm Options*



[1] Go AS, Singer DE, Toh S, Cheetham TC, Reichman ME, et al. 2017. Outcomes of Dabigatran and Warfarin for Atrial Fibrillation in Contemporary Practice: A Retrospective Cohort Study. *Ann Intern Med* 167:845-54

RESULTS

***Figure 4**. Impact of Factors A and B on Cohort Size*

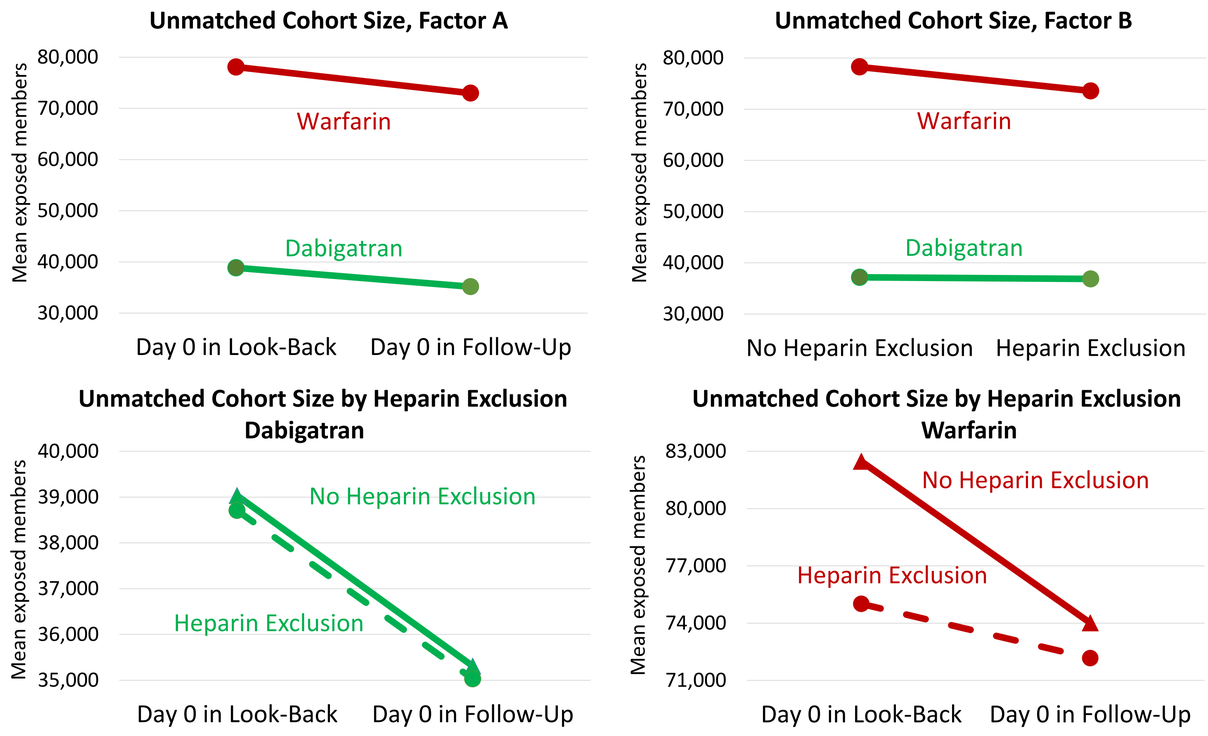
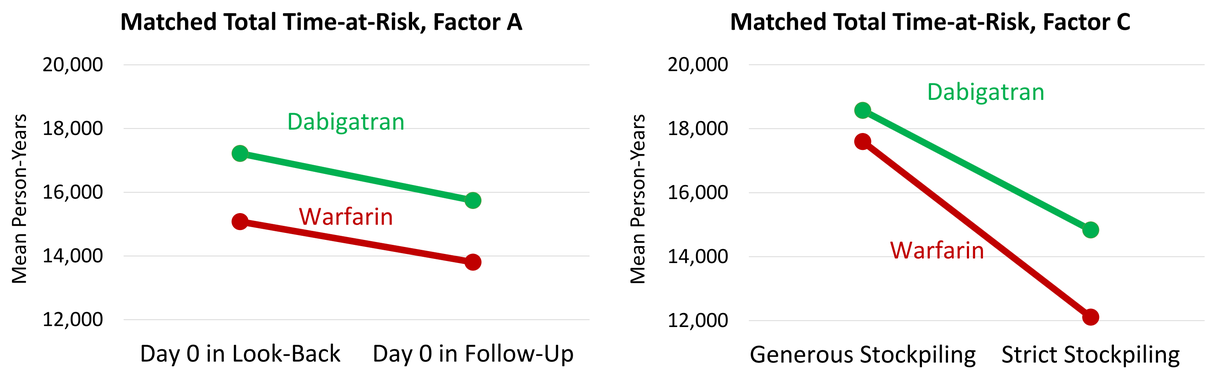


***Figure 5**. Impact of Factors A and C on Total Time-at-Risk*



- Among tested combination of factors, co-presence of the *baseline inclusion of the index date (A+)* and *no exclusion of heparin use (B+)* impacted cohort sizes most substantially, where the unmatched dabigatran and warfarin new users respectively increased by 11% and 14%, compared to analyses without these factors (**Figure 4**). The disproportional increase was later attenuated by matching.
- *Generous stockpiling (C+)* extended total time-at-risk by 26% and 47% for dabigatran and warfarin new users respectively, compared to analyses with strict stockpiling, regardless of matching status (**Figure 5**).
- Crude HRs were consistently estimated within 0.62 to 0.67 range (**Table 2**).
- After PS-matching, all adjusted HRs crossed the null, with the most extreme estimates ranged from HR_D 0.75 (0.54-1.04) to HR_{AC} 0.98 (0.74-1.31).

***Table 2**. Factor Combinations and Effect Estimates*

Run	Combination A	B	C	D	Risk Estimates: Analysis	LN (HRs and 95% CIs)
Null	-	-	-	-	Unmatched	-0.73 -0.46 -0.20
					PS-matched	**-0.53 -0.21 0.12**
A	+	-	-	-	Unmatched	-0.69 -0.43 -0.17
					PS-matched	**-0.56 -0.24 0.08**
B	-	+	-	-	Unmatched	-0.73 -0.48 -0.21
					PS-matched	**-0.53 -0.20 0.12**
C	-	-	+	-	Unmatched	-0.65 -0.42 -0.17
					PS-matched	**-0.51 -0.22 0.06**
D	-	-	-	+	Unmatched	-0.73 -0.46 -0.20
					PS-matched	**-0.62 -0.29 0.04**
AB	+	+	-	-	Unmatched	-0.71 -0.46 -0.21
					PS-matched	**-0.39 -0.06 0.26**
AC	+	-	+	-	Unmatched	-0.63 -0.40 -0.17
					PS-matched	**-0.30 -0.02 0.27**
AD	+	-	-	+	Unmatched	-0.69 -0.43 -0.17
					PS-matched	**-0.54 -0.22 0.09**
BC	-	+	+	-	Unmatched	-0.65 -0.42 -0.17
					PS-matched	**-0.42 -0.13 0.16**
CD	-	-	+	+	Unmatched	-0.65 -0.42 -0.17
					PS-matched	**-0.39 -0.09 0.21**
ABC	+	+	+	-	Unmatched	-0.63 -0.42 -0.19
					PS-matched	**-0.34 -0.06 0.22**
ABCD	+	+	+	+	Unmatched	-0.63 -0.42 -0.19
					PS-matched	**-0.45 -0.17 0.10**

-0.8 -0.6 -0.4 -0.2 0.0 0.2

CONCLUSIONS

- Small specification changes can lead to differences in analytic cohorts.
- Among the tested factors, *Day 0 disposition (Factor A)* and *outpatient pharmacy dispensing stockpiling algorithm (Factor C)* impacted cohort size and total time-at-risk the most.
- Robust confounding adjustment methods such as PS matching may attenuate the differences caused by varying specifications.
- Our findings are most relevant to drug use evaluations in which the outcome is rare and effect size is small. Study conclusions may not be generalizable to alternative specification changes or exposure-outcome pairs.
- Further investigation is warranted for details of the cohort composition change.

DISCLOSURES

- This study was supported by the U.S. Food and Drug Administration (FDA) through the Department of Health and Human Services Contract # HHSF223201400030I
- This poster presents views of the authors' and not necessarily those of the U.S. FDA
- Conflicts of interest to disclose: none for all authors