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

Ting-Ying Jane Huang, PhD[1]

Laura Hou, MPH, MS[1], Laura Shockro, BA[1], Ella Pestine, MPH[1]

Michael Nguyen, MD[2], Judith C Maro, PhD[1], Rima Izem, PhD[2]

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

[2] Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD

Disclosure and Disclaimer

- This study was supported by the U.S. Food and Drug Administration (FDA) through the Department of Health and Human Services Contract No. HHSF223201400030I

- Conflicts of interest: none for all authors
- This presentation reflects the views of the authors and not necessarily those of the U.S. FDA
- Publication status: manuscript in preparation

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

Annals of Internal Medicine®

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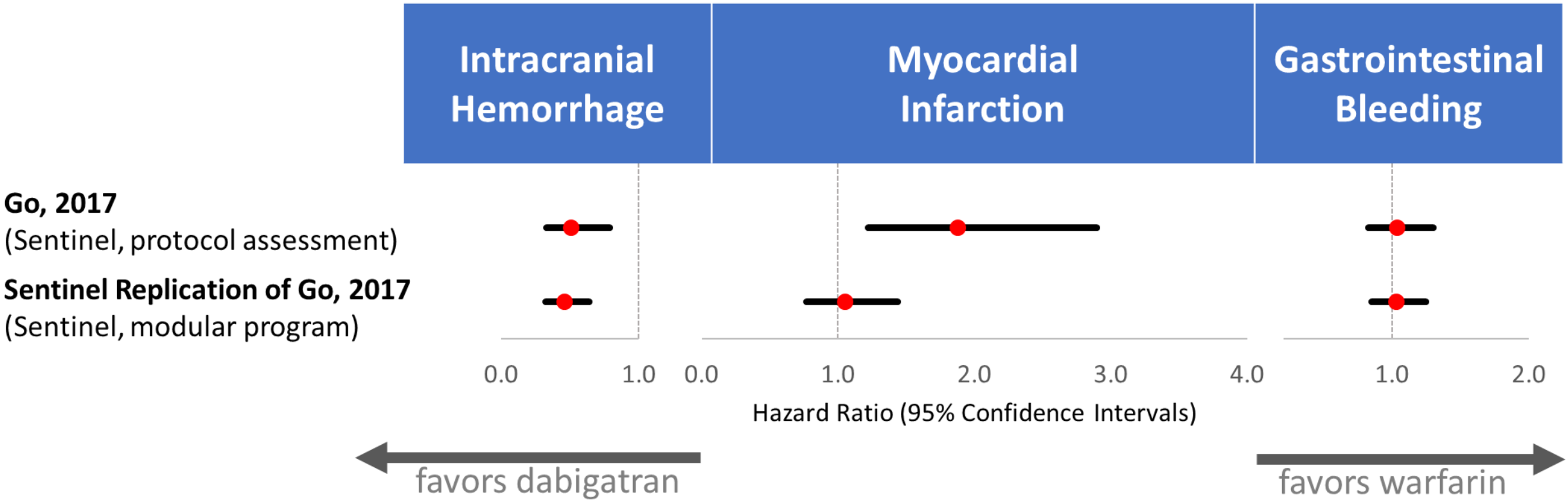
ORIGINAL RESEARCH | 14 NOVEMBER 2017

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

Alan S. Go, MD; Daniel E. Singer, MD; Sengwee Toh, ScD; T. Craig Cheetham, PharmD, MS; Marsha E. Reichman, PhD; David J. Graham, MD, MPH; Mary Ross Southworth, PharmD; Rongmei Zhang, PhD; Rima Izem, PhD; Margie R. Goulding, PhD; Monika Houstoun, PharmD; Katrina Mott, MS; Sue Hee Sung, MPH; Joshua J. Gagne, PharmD, ScD

Article, Author, and Disclosure Information

Background and Motivation



Background and Motivation

- Minor changes in design elements can potentially define different analytic cohorts and subsequently affect causal inference in epidemiological studies
- Understanding the impact of these changes is important for consistency improvement in future investigations

ORIGINAL REPORT

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang[1,2] | Sebastian Schneeweiss[1,2] | Marc L. Berger[3] | Jeffrey Brown[4] | Frank de Vries[5] | Ian Douglas[6] | Joshua J. Gagne[1,2] | Rosa Gini[7] | Olaf Klungel[8] | C. Daniel Mullins[9] | Michael D. Nguyen[10] | Jeremy A. Rassen[11] | Liam Smeeth[6] | Miriam Sturkenboom[12] |

on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making

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

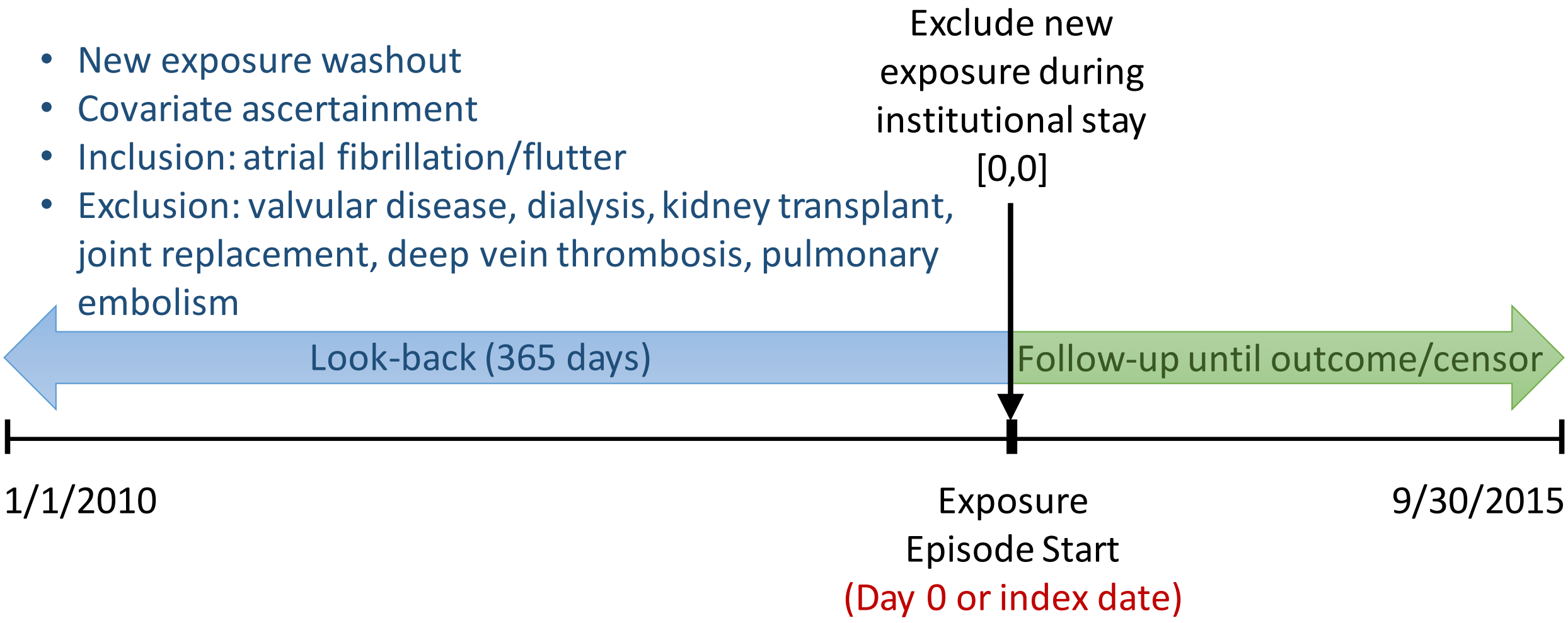
To examine the impact of design element changes in claims-based drug safety evaluations, using the association of oral anticoagulant use with bleeding outcomes as a test case

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

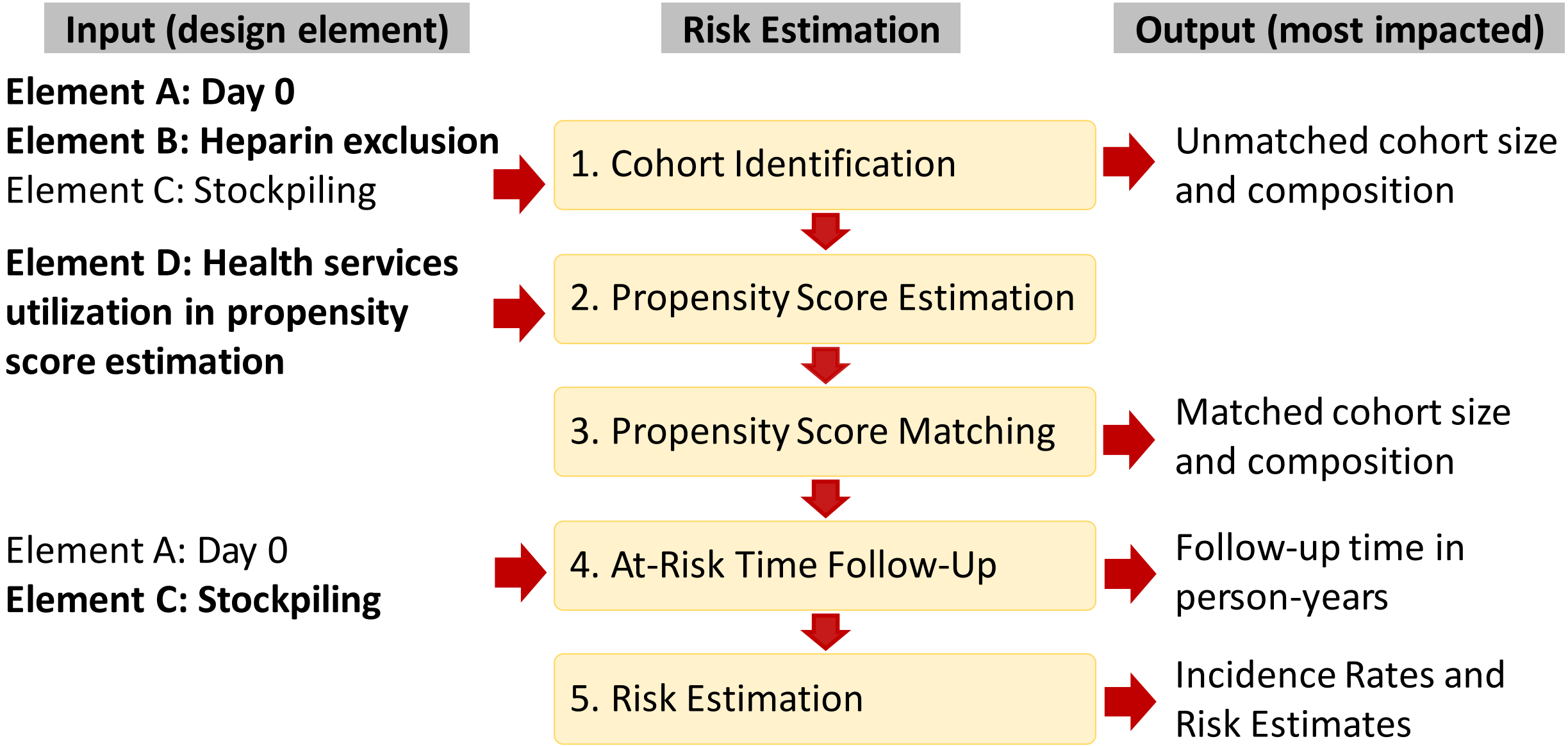


Covariates

- 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)
Risk Estimation
Output (most impacted)
Element A: Day 0
Element B: Heparin exclusion
Element C: Stockpiling
Element D: Health services utilization in propensity score estimation
Element A: Day 0
Element C: Stockpiling
1. Cohort Identification
2. Propensity Score Estimation
3. Propensity Score Matching
4. At-Risk Time Follow-Up
5. Risk Estimation
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+

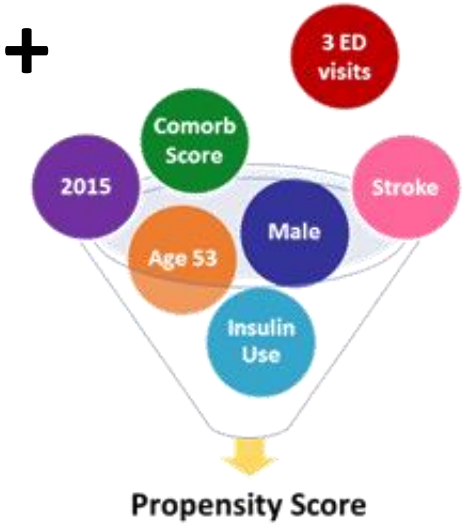
Look-back [-364, **0**] Follow-up [**1**, outcome]

A-

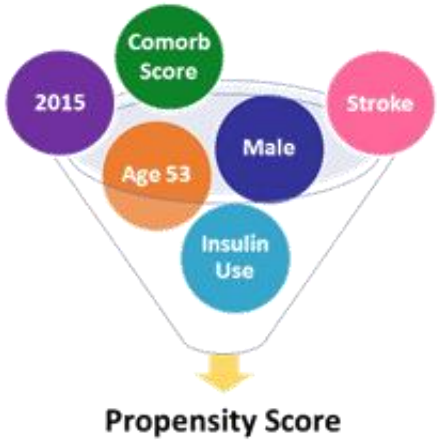
Look-back [-365, **-1**] Follow-up [**0**, outcome]

Element D: Covariates in PS model

D+



D-



Element B: Heparin exclusion

B+

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

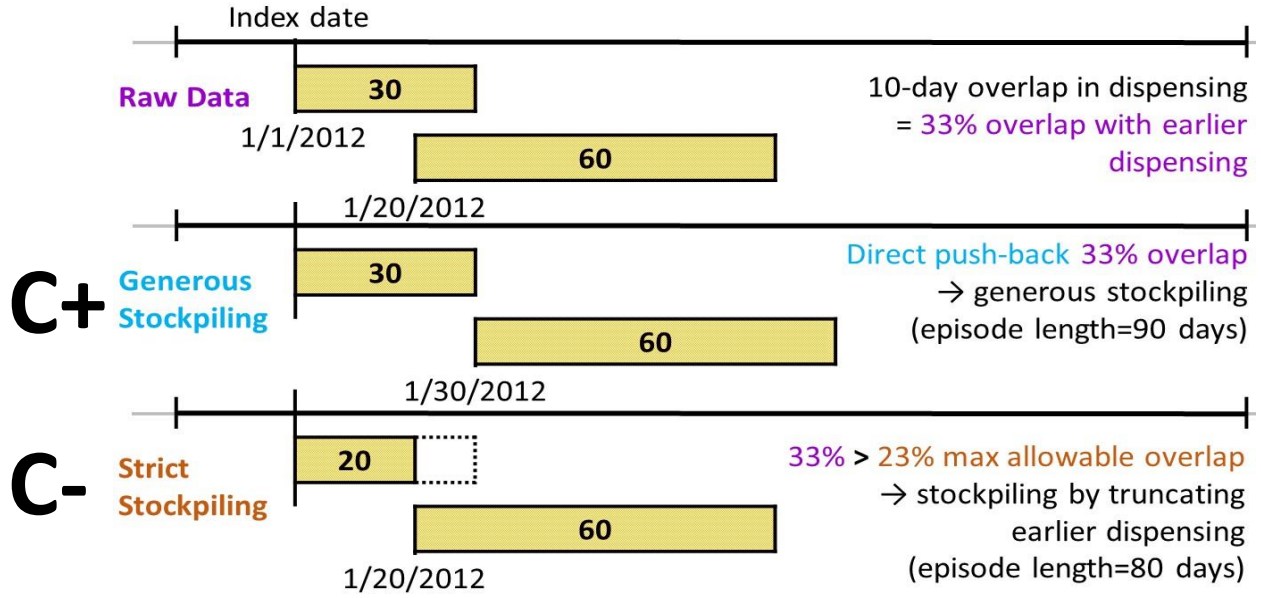
Look-back

B-

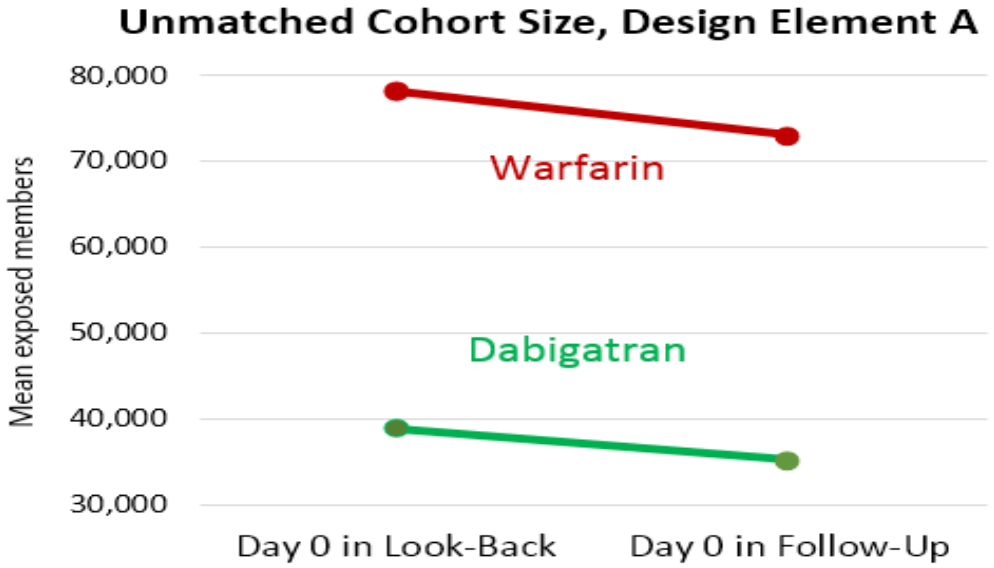
Exclusion: valvular disease, dialysis, kidney transplant, joint replacement, deep vein thrombosis, pulmonary embolism, **heparin use**

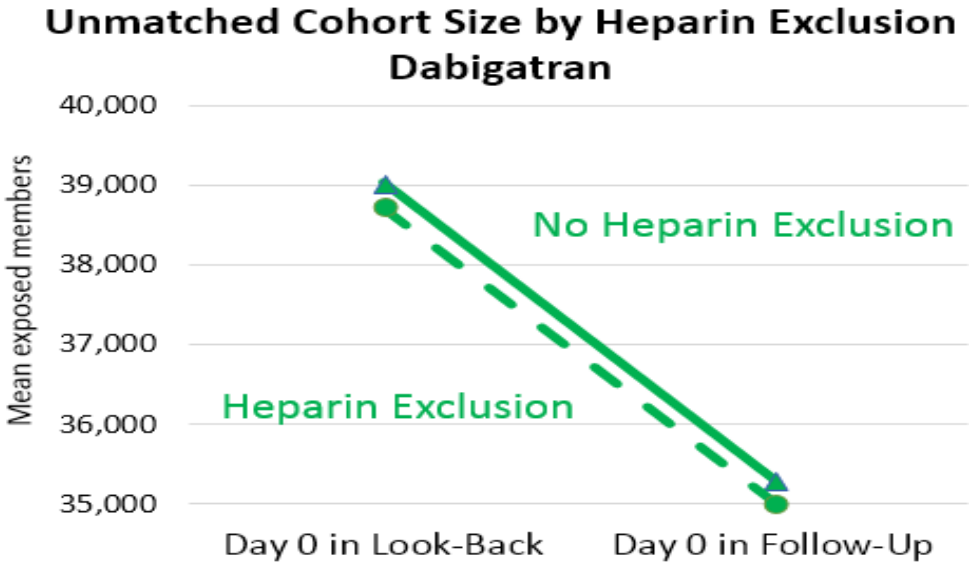
Look-back

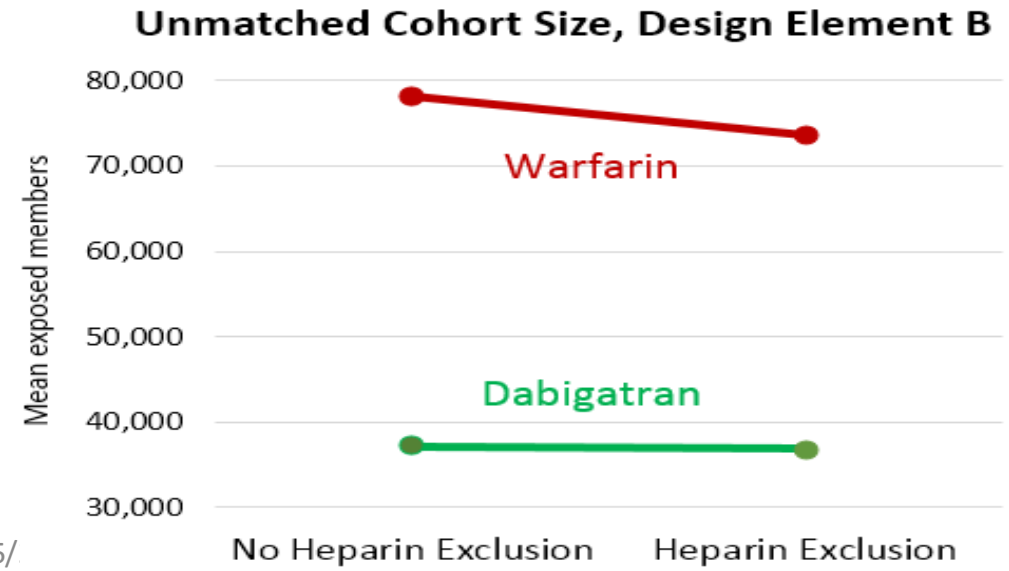
Element C: Stockpiling algorithm

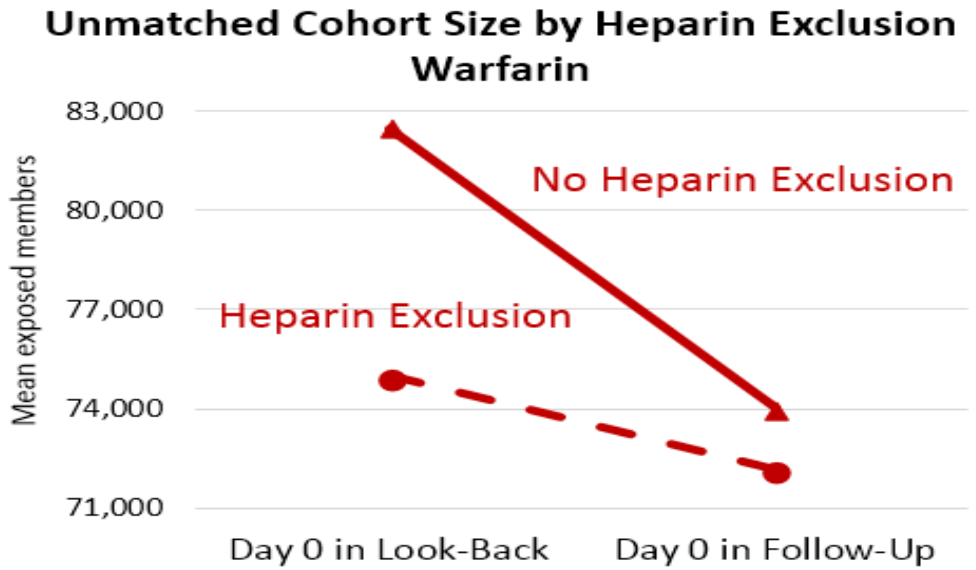


Results: MI, cohort size



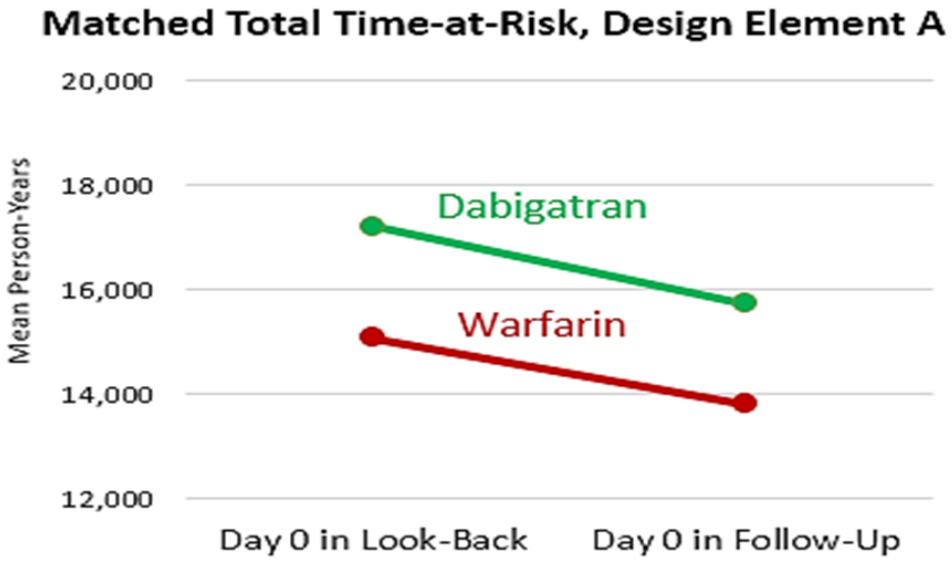


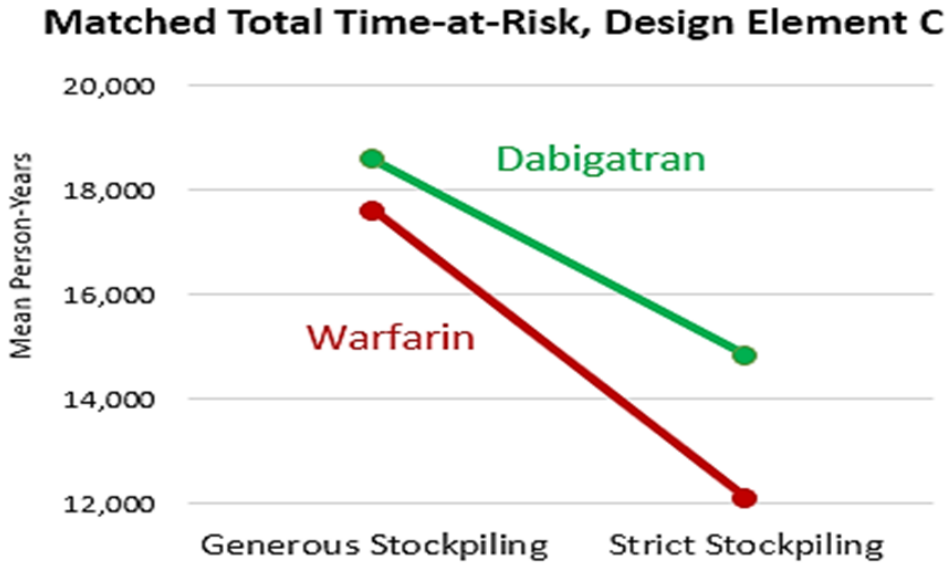




Results: MI, follow-up time, risk estimates

Sentinel





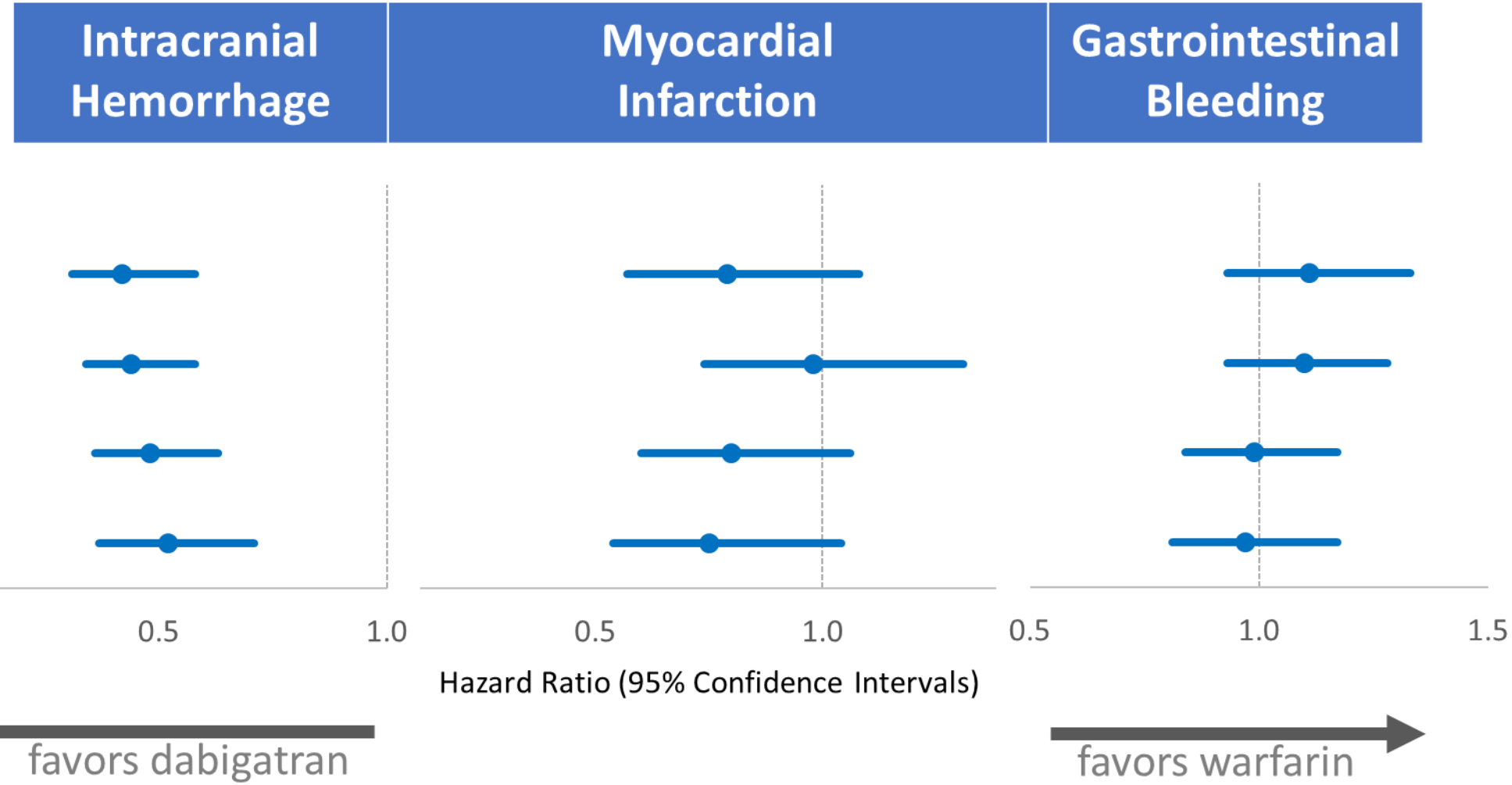
Run	Combination A	B	C	D	Risk Estimates: Analysis	LN (HRs and 95% CIs)
Null	-	-	-	-	Unmatched	-0.73 -0.46 -0.20
					PS-matched	-0.53 -0.21 0.12
A	+	-	-	-	Unmatched	-0.69 -0.43 -0.17
					PS-matched	-0.56 -0.24 0.08
B	-	+	-	-	Unmatched	-0.73 -0.48 -0.21
					PS-matched	-0.53 -0.20 0.12
C	-	-	+	-	Unmatched	-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

Results: Propensity Score-Matched Risk Estimates

Element combination

A	B	C	D
+	-	-	-
+	-	+	-
-	-	+	-
-	-	-	+



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

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