Janssen Research & Development, LLC*

Observational Study Protocol

Exploring mediation through major bleeding between direct oral anticoagulants and cardiovascular events

MB mediation study

Protocol PCSCVMA0044

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[EU PAS Register Number: [TBD when registered after approvals]

Status:	DRAFT
Date:	16/05/2024
Prepared by:	Janssen Research & Development, LLC
EDMS Number:	RRAMS-PCSCVMA0044, 1.1

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
CDM	Common data model
CV	Cardiovascular
AMI	Acute myocardial infarction
CHADS2	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled)
CHADS2VASc	Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category
DCSI	Diabetes complications severity index
DOAC	Direct oral anticoagulant
EHR	Electronic health record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ER	Emergency room
ER-IP	Emergency room followed by subsequent Inpatient visit
FDA	United States Food and Drug Administration
FOIA	Freedom of Information Act
HAS-BLED	Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly
HIPAA	Health Insurance Portability and Accountability Act
IP	Inpatient
IRB	Institutional review board
LSPS	Large-scale propensity score
MB	Major bleeding
MDCR	Merative™ MarketScan® Medicare Supplemental Database
MDRR	Minimum detectable relative risk
MI	Myocardial infarction
MRS	Mediator risk score
NLP	Natural language processing
NVAF	Non-valvular atrial fibrillation
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PS	Propensity score
PY	person-years
SNOMED	Systemized Nomenclature of Medicine
TAR	Time-at-risk
US	United States

Definition of Term(s)

Study	The term "study" indicates the collection of data for research purposes only. The use of this term in no way implies that any treatments or procedures outside clinical practice, planned or otherwise, have been provided or performed.
Retrospective non-interventional study	An observational study conducted after data has already been collected, often for another purpose, e.g., chart studies, retrospective cohort studies, or case-controlled studies. A non-interventional study is one where no procedures or interventions are assigned to participants by a protocol. In addition, if a medicinal product is involved, it is prescribed in the usual manner in accordance with the terms of the license/marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a protocol but falls within current practice and the treatment decision is clearly separated from the decision to include the patient in the program.

4. RESPONSIBLE PARTIES

Sponsor's Responsible Party	Martijn Schuemie, PhD Zhong Yuan, MD PhD James Weaver MS MPH Elliot Barnathan MD
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5. SYNOPSIS

Protocol Title: Exploring mediation through major bleeding between direct oral anticoagulants and cardiovascular events (1.1, 16/05/2024)

Sponsor's Responsible Party: Elliot Barnathan MD, Janssen Research & Development

NOTE: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

Background and Rationale

It has been reported that MB may have a long-term detrimental effect on CV outcomes, although such an association is often confounded by the underlying diseases and comorbid conditions. Safety evidence precision from a RCT with limited sample size is likely to be insufficient to inform the benefit-risk tradeoff between CV reduced risk and MB increased risk associated with an investigational product. This observational study will estimate the extent to which the effect of DOACs versus warfarin on CV outcomes is mediated through their differential impact on MB rates, particularly extracranial MB that can be managed with supportive care (e.g., blood transfusion).

Research Question and Objectives

To what extent is the effect of DOAC versus warfarin on CV outcomes mediated through their differential impact on extracranial MB rates? The study will quantify the following estimands:

- **Main effect**: The effect of the target on the outcome, relative to the comparator.
- **Direct effect**: The effect of the target on the outcome, relative to the comparator, *not* mediated by the mediator.
- **Indirect effect**: The effect of the target on the outcome, relative to the comparator, mediated by the mediator. The indirect effect is estimated using the difference method, subtracting the (log) direct effect from the (log) main effect.

Exposure-outcome confounding will be minimized by PS matching. Mediator outcome confounding will be minimized using an MRS, which will be included in the PS-matched outcome model.

Study Design

This study will employ a new-user comparative cohort design, comparing a target cohort (rivaroxaban or the entire class of DOACs) to a comparator cohort (warfarin). A single mediator, extracranial MB, will be included in the model.

Setting and Study Population

The study will be conducted in five large observational databases from the US. The data sources include four administrative claims databases and one electronic health record database. The study period is 01-11-2010 to 31-12-2022.

Variables

- Rivaroxaban inferred exposures via pharmacy dispensing and provider prescription records
- DOAC inferred exposures via pharmacy dispensing and provider prescription records

- Warfarin inferred exposures via pharmacy dispensing and provider prescription records
- Extracranial MB mediator events via administrative or clinical records
- AMI events via administrative or clinical records
- Ischemic stroke events via administrative or clinical records
- Potential confounders (drug exposures, condition occurrences, procedure occurrences, measurements, device exposures, risk indices)

Data Sources

Data will be drawn from four administrative claims databases and one electronic health record database. All data sources are from the US. Coding accuracy limitations are inherent to repurposing these data from their original intent for clinical research.

Study Size

Retrospective analysis of secondary data does not allow for traditional sample size calculations used in prospective studies. The exposure drugs have been on the US market for over a decade wo we do not expect the minimum detectable relative risk to be large.

Data Analysis

PS-matched Cox proportional hazards model estimating the risk of CV outcomes for 1) rivaroxaban vs warfarin and 2) DOACs vs warfarin, with the extracranial MB mediator as time-varying covariate.

6. AMENDMENTS AND UPDATES

Version	Date	Rationale
1.0	29-04-2024	Initial protocol.
1.1	16-05-2024	Validity diagnostics supplement added.

7. MILESTONES

The planned dates for key milestones in this study are outlined in Table 2.

Table 1: Study Milestones

Milestone:	Planned Date:
Start of data collection	Not applicable to retrospective analysis of secondary sue data
End of data collection	Not applicable to retrospective analysis of secondary sue data
ENCePP registry submission	Pending sponsor protocol approval, approximately May 14, 2024
Start of data analysis	Pending sponsor protocol approval, approximately May 14, 2024
Final report of study results	Approximately May 21, 2024

8. RATIONALE AND BACKGROUND

8.1. Background

Anticoagulant therapies have undergone significant evolution with the development of DOACs, which have been increasingly favored over traditional warfarin due to their promising safety profiles, fewer dietary restrictions, and reduced need for monitoring (Patel 2011). While DOACs may have greatly advanced patients care in this setting, MB remains a critical concern in anticoagulant therapy (~3-4 events/100 PY [Patel 2011]) due to the pharmacological mechanism, which could influence patient outcomes and treatment efficacy, and even befit-risk tradeoff. However, a potential adverse effect on CV outcomes from MB remains unclear (Serebruany 2022, Spyropoulos 2022). In the FDA's position paper (Unger 2009, Beasley 2011), it has been suggested that bleeding that can be managed via supportive care (e.g., blood transfusion) may not cause irreversible harm, but a research question remains whether these bleeding events may have a long-term detrimental effect on CV outcomes, although such an association could also be confound by other factors, because patients experiencing bleeding events tend to be older and have multiple comorbidities (e.g., hypertension and diabetes), and differential analytical methods may further complicate such investigation.

This real-world study aims to dissect the complex interplay between anticoagulant type, extracranial MB events, and CV outcomes. This protocol outlines the methodology for an observational study that will estimate the extent to which the effect of DOACs versus warfarin on CV outcomes is mediated through their differential impact on extracranial MB rates. By leveraging real-world data, the study will contribute valuable insights into the comparative effectiveness and safety of these anticoagulants, guiding clinical decision-making and potentially informing future guidelines.

This study will utilize novel advanced statistical techniques to model the mediation effects, controlling for a range of confounding factors that could influence both bleeding risk and cardiovascular outcomes.

8.2. Overall Rationale for the Study

As expected, clinical investigation of antithrombotic therapy continually entails tradeoffs between thrombotic event protection and potential adverse bleeding events from pharmacological mechanism of action. MB is often considered a key safety outcome. Because of relatively limited sample size, follow-up time, and MB event counts, the data will likely be insufficient to estimate and quantify the potential causal effect of major bleeding on CV outcomes. This study intends to use real-world data to assess the subsequent, detrimental CV effects of extracranial MB. The evidence generated will be used as an external source of information for further evaluating clinical importance of extracranial MB to assist the structured benefit-risk assessments.

9. RESEARCH QUESTION AND OBJECTIVES

Research Question

To what extent is the effect of direct oral anticoagulants (DOAC) versus warfarin on subsequent CV outcomes mediated through their differential impact on extracranial MB rates among adult patients with NVAF?

Objective(s) and Outcome(s)/Measure(s) of Interest

New-user comparative cohort studies will compare the following target vs comparator cohorts to answer the research question:

Target	Comparator	Mediator	Outcome
Rivaroxaban	Warfarin	IP extracranial MB	AMI
Rivaroxaban	Warfarin	IP extracranial MB	Ischemic stroke
Rivaroxaban	Warfarin	IP Extracranial MB	AMI or Ischemic stroke
DOACs	Warfarin	IP extracranial MB	AMI
DOACs	Warfarin	IP extracranial MB	Ischemic stroke
DOACs	Warfarin	IP Extracranial MB	AMI or Ischemic stroke
Rivaroxaban	Warfarin	ER-IP extracranial MB	AMI
Rivaroxaban	Warfarin	ER-IP extracranial MB	Ischemic stroke
Rivaroxaban	Warfarin	ER-IP Extracranial MB	AMI or Ischemic stroke
DOACs	Warfarin	ER-IPIP extracranial MB	AMI
DOACs	Warfarin	ER-IP extracranial MB	Ischemic stroke
DOACs	Warfarin	ER-IP Extracranial MB	AMI or Ischemic stroke

The measures of interest are the following:

- **Main effect**: The effect of the target on the outcome, relative to the comparator.
- **Direct effect**: The effect of the target on the outcome, relative to the comparator, *not* mediated by the mediator.
- **Indirect effect**: The effect of the target on the outcome, relative to the comparator, mediated by the mediator. The indirect effect is estimated using the difference method, subtracting the (log) direct effect from the (log) main effect.

The primary objective is to estimate the indirect effect as defined above.

The secondary objectives are to estimate the main and direct effects as defined above.

See Section 10.7 for statistical aspects of outcomes or measures of interest.

Hypothesis

Test whether the main, direct, and indirect effect differ from the null hypothesis of no effect.

10. RESEARCH METHODS

10.1. Study Design

This study will employ a new-user comparative cohort design, comparing a target cohort (rivaroxaban or the entire class of DOACs) to a comparator cohort (warfarin). Both target and cohort are defined as first exposure to drug of interest, requiring 365 days of prior observation. TAR for outcome starts on the day of treatment initiation and ends at end of continuous exposure (allowing for 30-day gaps) plus a 30-day surveillance window or occurrence of the outcome, whichever comes first. Target and comparator TAR will be right-censored at switch to the other drug. A single mediator – extracranial MB - is defined and included in the model. This table lists all the comparisons that will be made:

Table 2. Target-comparator-mediator-outcome comparisons

Target	Comparator	Mediator	Outcome
Rivaroxaban	Warfarin	IP extracranial MB	AMI
Rivaroxaban	Warfarin	IP extracranial MB	Ischemic stroke
Rivaroxaban	Warfarin	IP Extracranial MB	AMI or Ischemic stroke
DOACs	Warfarin	IP extracranial MB	AMI
DOACs	Warfarin	IP extracranial MB	Ischemic stroke
DOACs	Warfarin	IP Extracranial MB	AMI or Ischemic stroke
Rivaroxaban	Warfarin	ER-IP extracranial MB	AMI
Rivaroxaban	Warfarin	ER-IP extracranial MB	Ischemic stroke
Rivaroxaban	Warfarin	ER-IP Extracranial MB	AMI or Ischemic stroke
DOACs	Warfarin	ER-IP extracranial MB	AMI
DOACs	Warfarin	ER-IP extracranial MB	Ischemic stroke
DOACs	Warfarin	ER-IP Extracranial MB	AMI or Ischemic stroke

The model is a Cox proportional hazards model, with the mediator as time-varying covariate. Cohort definitions of the targets, comparator, mediator, and outcomes are provided in Sections 15.1, 15.2, and 15.3.

In this study, data collected will be de-identified data drawn from the Merative™ MarketScan® Commercial Database (CCAE), Merative™ MarketScan® Medicare Supplemental Database (MDCR), Optum de-identified Electronic Health Record data set (Optum® EHR), Optum's de-identified Clinformatics® Data Mart Database (Clinformatics®), and IQVIA PharMetrics Plus Database (PharMetrics). Further details of data sources are provided in Section 9.4.

The study period covers 01-11-2010 to 31-12-2022 (inclusive). The study period start date was selected because dabigatran was the first DOAC approved in the US on 19-10-2010. The study period end date was selected because 2022 is the last year for which the study databases have complete data capture. Note that, in each database, target vs comparator comparisons will only be made during calendar time when both exposures are observed in that database. This is to ensure provider choice between alternative therapies for NVAF was available.

10.1.1. Rationale for Study Design Elements

The causal mediation analysis required to estimate the extent to which extracranial MB mediates the effect of anticoagulation therapy on CV outcomes requires the following design elements: Longitudinal observational healthcare databases with drug exposure records for rivaroxaban, DOACs, and warfarin and condition occurrence records for extracranial MB and CV outcomes. Longitudinal observational healthcare databases must include demographic information, drug exposure, condition occurrence, procedure occurrence, and laboratory measurement records for observed and unobserved confounding control. There is no intent to extrapolate the DOAC within-class benefit-risk profile. The 30-day surveillance window was appended to the end of continuous exposure to attribute CV events to exposure if they occurred within a liberal period of inferred persistent drug effect from biological half-life or stockpiling. TAR beyond treatment discontinuation was not included because doing so may measure the effect of treatment discontinuation or other mediators/time-varying confounders rather than the effect of treatment itself.

10.2. Setting and Study Population

10.2.1. Study Setting

Data will be drawn from CCAE, MDCR, Optum® EHR, Clinformatics®, and PharMetrics databases. All data sources are from the United States. These data sources met data element requirements per empirical evaluation (See Section 9.4).

10.2.2. Patient Selection Criteria

The study will include patients who meet criteria for inclusion in the target cohorts and comparator cohort. Both target and comparator cohorts are defined as first exposure to drug of interest (index date), requiring 365 days of prior observation. Patients are required to have ≥1 condition occurrence record of NVAF observed between 365 days before until and including the index date. Full details of the target, comparator, mediator, and outcome definitions are reported in Sections 15.1-15.4.

10.2.2.1. Inclusion Criteria

Three exposure cohorts will be used in the mediation analysis; two target cohorts and one comparator cohort. All are defined by the first exposure (index date) to the drug of interest (target cohorts: rivaroxaban, DOACs; comparator cohort: warfarin). The following inclusion criteria are applied to the target and comparator cohorts;

- ≥ 18 years of age at index date
- ≥1 condition occurrence record of NVAF observed between 365 days before until and including the index date

10.2.2.2. Exclusion Criteria

- <365 days database observation before index date
- Patients who initiate target and comparator therapy on the same day.

10.2.2.3. Patient Selection: Matching and Other Sampling Techniques

Patients in exposure cohorts will be matched on PS to minimize observed confounding. Variable ratio matching will be used at a ratio of 1:100 (maximum). See Section 9.7.2 for details.

10.2.2.4. Patient Stratification

Not applicable.

10.2.2.5. Calculation of Time-at-Risk

TAR will be defined as inferred continuous exposure to the study drugs of interest: allowing 30 days between exposures, adding 30 days after continuous exposure ends, and using days' supply and exposure end date for exposure duration. The estimands of interest are described in Section 9.7.1. Target cohort TAR will be right-censored if a comparator exposure is observed before target TAR end. Comparator cohort TAR will be right-censored if a target exposure is observed before comparator TAR end. Target and comparator TAR will also be right-censored at event occurrence or database observation end.

10.2.3. Duration of Study Period(s) and Follow-Up

The study period is 01-11-2010 to 31-12-2022, the time during which exposure index dates can occur. A patient's baseline data will be extracted, where available, up to the index date of the target and comparator cohorts, respectively. The exposure date is defined as the date of treatment initiation provided ≥365 days of prior database observation time. Full target and comparator cohort definitions are available in Sections 15.1 and 15.2.

10.3. Variables

10.3.1. Baseline Information

The following consistently extracted set of baseline patient characteristics will be constructed for input in the PS and MRS model. From this large set of typically tens of thousands of covariates, key predictors of exposure classification will be selected for inclusion in the PS model. Note that not all data sources necessarily include data for all covariates.

- Demographics (age in 5-year bands, sex, race, ethnicity, index year, index month)
- All conditions occurrence records aggregated to SNOMED clinical finding level during the following lookback windows:
    - in 365 days prior to and including index date

    - in 30 days prior to and including index date
- All drug exposure records aggregated to RxNorm ingredient level and ATC classes during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
    - persistent exposure that overlaps index date
- All procedure occurrence records during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- Measurements (including laboratories) within, above, and below normal range during the following lookback window:
    - in 365 days prior to and including index date
- Device exposure records during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- Comorbidity or risk scores including:
    - Charlson comorbidity index
    - DCSI
    - CHADS2
    - CHADS2VASc
    - HAS-BLED

10.3.2. Exposures

- Rivaroxaban initiators with prior NVAF observed during 365 days before and including index date provided 365 days of prior database observation.

- DOAC initiators with prior NVAF observed during 365 days before and including index date provided 365 days of prior database observation.

- Warfarin initiators with prior NVAF observed during 365 days before and including index date provided 365 days of prior database observation.

See Sections 15.1.1, 15.1.2, and 15.2.1 for detailed exposure cohort definitions.

10.3.3. Outcomes

- All occurrences of an AMI or MI complication records observed during an ER-IP visit with prior events observed during a 365-day washout period.

- All occurrences of an ischemic stroke records observed during an ER-IP visit with no prior events observed during a 365-day washout period.

- All occurrences of [AMI or MI complication] or [ischemic stroke] records observed during an ER-IP visit with no prior events observed during a 365-day washout period.

See Sections 15.4.1 and 15.4.2 for detailed outcome cohort definitions.

10.3.4. Potential Confounders

See Section 9.3.1 for potential confounders used in the PS analysis and in the MRS analysis.

10.3.5. Other Variables (mediator)

- All occurrences of [primary position bleeding] or [bleeding related disorders with bleeding] records observed during an IP visit with no prior events observed during a 30-day washout period. Patients with traumatic and non-traumatic intracranial bleeding records during the visits are excluded.

- All occurrences of [primary position bleeding] or [bleeding related disorders with bleeding] records observed during an ER-IP visit with no prior events observed during a 30-day washout period. Patients with traumatic and non-traumatic intracranial bleeding records during the visits are excluded.

See Section 15.3.1 for the extracranial MB mediator definitions.

10.4. Data Sources

Data collected are de-identified and specific details cannot be identified due to vendor governance privacy agreements; however, the data include individuals covered by commercial insurance and Medicare supplemental benefits. The databases in this study have previously been used for scientific publications funded by the sponsor.

10.4.1. Database descriptions

10.4.1.1. Merative™ MarketScan® Commercial Claims and Encounters Database

CCAE includes health insurance claims across the continuum of care (e.g. inpatient, outpatient, outpatient pharmacy, carve-out behavioral healthcare) as well as enrollment data from large employers and health plans across the United States who provide private healthcare coverage for more than 155 million employees, their spouses, and dependents. This administrative claims database includes a variety of fee-for-service, preferred provider organizations, and capitated health plans.

10.4.1.2. Merative™ MarketScan® Medicare Supplemental and Coordination of Benefits Database

MDCR represents the health services of approximately 10 million retirees in the United States with Medicare supplemental coverage through employer-sponsored plans. This database contains primarily fee-for-service plans and includes health insurance claims across the continuum of care (e.g. inpatient, outpatient and outpatient pharmacy).

10.4.1.3. Optum® de-identified Electronic Health Record Dataset

Optum® EHR is derived from dozens of healthcare provider organizations in the United States, that include more than 700 Hospitals and 7000 Clinics; treating more than 102 million patients receiving care in the United States. The data is certified as de-identified by an independent statistical expert following HIPAA statistical de-identification rules and managed according to Optum® customer data use agreements. Clinical, claims and other medical administrative data is obtained from both Inpatient and Ambulatory electronic health records (EHRs), practice management systems and numerous other internal systems. Information is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and outpatient visits. Optum® data elements include demographics, medications prescribed and administered, immunizations, allergies, lab results (including microbiology), vital signs and other observable measurements, clinical and inpatient stay administrative data and coded diagnoses and procedures. In addition, Optum® uses natural language processing (NLP) computing technology to transform critical facts from physician notes into usable datasets. The NLP data provides detailed information regarding signs and symptoms, family history, disease related scores (i.e. RAPID3 for RA, or CHADS2 for stroke risk), genetic testing, medication changes, and physician rationale behind prescribing decisions that might never be recorded in the EHR.

10.4.1.4. Optum's de-identified Clinformatics® Data Mart Database

Clinformatics® is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans. The database includes approximately 17-19 million annual covered lives, for a total of over 65 million unique lives over a 12 year period (1/2007 through 12/2019). Clinformatics® is statistically de-identified under the Expert Determination method consistent with HIPAA and managed according to Optum® customer data use agreements. Administrative claims submitted for payment by providers and pharmacies are verified, adjudicated and de-identified prior to inclusion. This data, including patient-level enrollment information, is derived from claims submitted for all medical and pharmacy health care services with information related to healthcare costs and resource utilization. The population is geographically diverse, spanning all 50 states. Clinformatics® Data of Death also provides date of death (month and year only) for members with both medical and pharmacy coverage from the Social Security Death Master File (however after 2011 reporting frequency changed due to changes in reporting requirements) and location information for patients is at the US state level.

10.4.1.5. IQVIA™ Adjudicated Health Plan Claims Data

The IQVIA™ Adjudicated Health Plan Claims Data (PharMetrics) is a US database is comprised of fully adjudicated health plan claims data and enrollment information for commercial individuals. The information is comprised of over 70 contributing health plans and self-insured employer groups throughout the United States for over more than 170 million unique enrollees over the last 5 years. This anonymous, patient-centric database includes all medical and pharmacy claims data (costs and descriptive services). Claims represent payments to providers for services rendered to covered health plan individuals. The data also includes patient-level enrollment which is a record of demographic variables including eligibility status (year of birth, gender, US Census region, eligibility by month). The enrollee population in the database is generally representative

of the <65 years of age, commercially insured population with a subset of Commercial Medicare and Medicaid in the US with respect to both age and gender. The average length of enrollment is ≥ 39 months and ≥ 47 million patients have 3 or more years of continuous enrollment (medical and pharmacy coverage). Each contributing plan's data undergoes rigorous data quality review by IQVIA™ prior to its addition to the IQVIA™ Adjudicated Health Plan Claims - US database.

The extent of patient overlap between databases is unknown and because all data sources have been de-identified, it is not possible or allowable to link patients across sources. Overlap that may exist is expected to be minimal and would not impact the study results within each database.

10.4.2. Data Suitability Assessment

See Section 10.4.3.

10.4.3. 'Fit-for-Purpose' and Data Feasibility Assessment(s)

The DatabaseDiagnostics package (Blacketer, 2023) was used to select those databases that include the required data elements for the estimation questions.

10.4.4. Data Standardization Methods

All databases were transformed to the OMOP CDM, which provides a standardized representation of database structure and clinical content to enable consistent analysis across disparate healthcare databases (Hripcsak 2015, Voss 2015).

The data for this study are de-identified in compliance with the HIPAA Act of 1996, such that no individual can be re-identified in any of the data sources.

Data elements included in the dataset include closed claims. While closed claims are associated with an enrollment file, open claims do not have information on individuals' enrollment in an insurance plan or eligibility for healthcare payments. Closed payer claims data are derived from health insurance providers, representing nearly all of an individual's healthcare activities during a specific enrollment period and are the most accurate record of health care utilization and events. Closed claims include medical claims and outpatient pharmacy transactions sourced from provider-submitted claims, adjudicated insurance claims, and pharmacy benefit manager billing. Closed claims include details on service dates, medications, diagnoses, and procedures.

10.5. Study Size

For retrospective analysis of secondary data, it is not critical or absolutely necessary to conduct traditional sample size calculations used in prospective studies. The target, comparator, mediator, and outcome cohort count in each study database before any analysis restrictions are reported in Table 3.

Table 3. Target, comparator, mediator, outcome cohort counts before study design restrictions

Cohort	Optum® EHR	Clinformatics®	CCAE	MDCR	PharMetrics
T: rivaroxaban	281,296	150,769	62,183	73,087	83,891
T: DOACs	735,422	537,581	154,895	206,325	298,437
C: warfarin	461,343	235,828	100,296	198,650	44,933
M: IP extracranial MB	801,267	814,377	230,730	193,577	176,222
M: ER-IP extracranial MB	1,758,266	2,021,232	359,095	284,619	362,609
O: AMI	957,165	1,211,533	564,681	547,255	761,438
O: ischemic stroke	752,190	1,122,933	412,276	528,597	539,191
O: AMI or ischemic stroke	1,602,778	2,127,055	230,730	976,281	1,232,244

T: target cohort, C: comparator cohort, M: mediator cohort, O: outcome cohort, Optum® EHR: Optum® de-identified Electronic Health Record dataset, Clinformatics®: Optum's de-identified Clinformatics® Data Mart Database, CCAE: Merative™ MarketScan® Commercial Database, MDCR: Merative™ MarketScan® Medicare Supplemental Database , PharMetrics: IQVIA PharMetrics Plus Database.

10.6. Data Collection and Management

Data have been curated and aggregated by vendors from whom the sponsor licenses databases for clinical research. All databases were transformed to the OMOP CDM, which provides a standardized representation of database structure and clinical content to enable consistent analysis across disparate healthcare databases. The extract-transform-load process of standardizing data to the OMOP CDM is also performed routinely and data quality improvement exercise whereby data or poor quality are removed (e.g., patients with year of birth < 1900). Licensed data are managed in relational databases by the sponsor. Study data are retrieved from databases using structured query language and analyzed using software developed by the OHDSI community (Schuemie 2023).

10.7. Data Analysis

Statistical analyses will be performed by or under the authority of the sponsor. Analytic code to execute the study has been developed and is publicly available at https://github.com/schuemie/MediationAnalysis/tree/main/RealWorldExample.

10.7.1. Estimands of interest

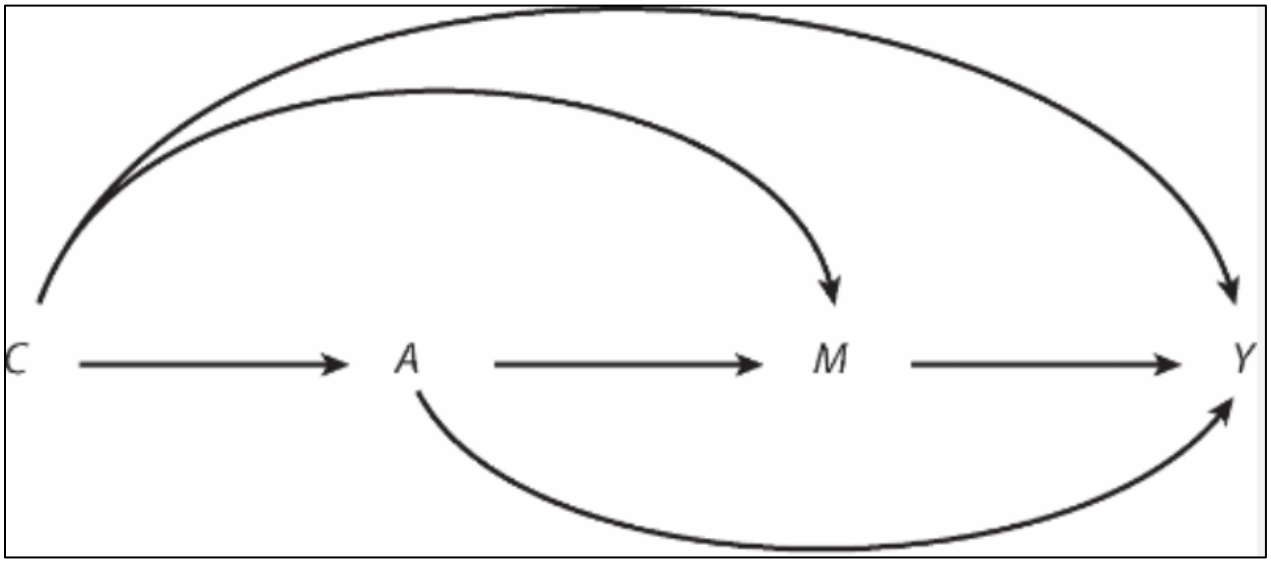
For each target-comparator-outcome triplet, two Cox modes will be fitted, one with the mediator and one without. From these two models, the following estimands will be reported, each on the hazard ratio scale, including their 95% confidence intervals (VanderWeele 2011):

- **Main effect (A→Y)+(A→M→Y)**: The total effect of the target on the outcome, relative to the comparator, which can be decomposed as the following:
  - **Direct effect** (A→Y): The effect of the target on the outcome, relative to the comparator, *not* mediated by the mediator.
  - **Indirect effect** (A→M→Y): The effect of the target on the outcome, relative to the comparator, mediated by the mediator.

The indirect effect is estimated using the difference method, subtracting the (log) direct effect from the (log) main effect.

Figure 1 depicts the causal mediation model as a directed acyclic graph indicating the direct and indirect effect which constitute the main effect (VanderWeele 2016). Confounders C will bias the causal association between target and outcome and between mediator and outcome and must be accounted for valid causal interpretation further discussed in Section 9.7.2.

Figure 1. Relations between exposure A, mediator M, and outcome Y, and confounders C.



10.7.2. Confounding adjustment

Adjustment for confounding between target and comparator is achieved by LSPS (Tian 2018) used for variable ratio PS matching (Rassen 2012).

Adjustment for confounding between those with the mediator and those without is achieved by a large-scale MRS. The MRS is fitted as a survival regression by using the same set of baseline covariates used in the LSPS, including all demographics, drug exposures, conditions, procedures, etc. observed on or in the year prior to treatment initiation. Similar to the LSPS, the MRS model is fitted using L2 regularization, using 10-fold cross-validation to select the optimal hyperparameter by optimizing out-of-sample likelihood. The MRS is included in the outcome model using a 5-knot bicubic spline. This overall approach to mediation analysis in real-world data proved optimal in a wide range of scenarios in initial simulation studies.

10.7.3. Negative controls

A set of 50 negative control outcomes - outcomes believed to have no causal relationship with neither the target nor the comparator - has been identified or reported (Boyce 2014) (See Section 15.6). We assume that these controls are negative both for the direct effect and the mediated effect. The negative control summary estimates are used to detect residual systematic error (if any) and will be used to calibrate all estimands of interest.

10.7.4. Descriptive Analysis

Not applicable.

10.7.4.1. Data Sets Analyzed

See Section 9.4.1.

10.7.4.2. Baseline Characteristics

Baseline characteristics will be calculated, compared, and reported before and after PS matching.

10.7.4.3. Analysis of Effectiveness/Clinical Response

Not applicable.

10.7.4.4. Safety Analyses

Not applicable.

10.7.5. Statistical Methods

All analyses will be performed independently within each of these five data sources to produce a set of five results. No pooling of results across databases will be performed.

10.7.5.1. Model Specification

PS-matched Cox proportional hazards model estimating the risk of cardiovascular (CV) outcomes for 1) rivaroxaban vs warfarin and 2) DOACs vs warfarin, with the MB mediator as time-varying covariate.

10.7.5.2. Statistical Evaluation

If an analysis fails any of the following validity diagnostics, then the analysis will not proceed because the results cannot be interpreted as causal.

- All baseline characteristics must have covariate balance at ASMD<0.1 after PS matching. Covariate balance diagnostics are reported in Section 18.2. All analyses in all databases pass this diagnostic.
- Target vs comparator empirical equipoise (Walker 2013) must be >0.1. Equipoise diagnostics are reported in Section 18.1. All analyses in all databases pass this diagnostic.
- After design restrictions have been applied (e.g., matching on PS), MDRR will be reported. MDRR results are reported in Section 18.3.
- EASE will be calculated for the indirect, direct, and main effect to assess residual bias unaccounted for by PS matching (Schuemie 2014) and must be <0.25. EASE diagnostics are reported in Section 18.5.

10.7.6. Missing Values

Retrospective database analyses by definition use data that have been previously collected primarily for insurance billing, reimbursement, and clinical care purposes. We assume the presence of clinical events if codes are observed and the absence of clinical events if codes are not observed. We recognize that the presence or absence of codes in secondary healthcare data does not imply

perfect fidelity to underlying medical constructs therefor exposure, mediator, and outcome misclassification is unavoidable so results may be subject to information bias.

10.7.7. Sensitivity Analyses and Bias Assessment

The ER-IP major bleeding definition represents a sensitivity analysis because ER visits for bleeding could capture clinically relevant non-major bleeding events. No other sensitivity analyses will be performed. Observed confounding between exposures and outcomes will be minimized by PS matching and observed confounding between mediator and outcomes will be minimized by the MRS (Section 9.7.2).

10.8. Quality Control

See Section 9.6.

10.8.1. Quality Assurance and Quality Control of the Database

See Section 9.6.

10.9. Strengths and Limitations of the Research Methods

Strengths include using novel methods for mediation analysis that account for the time-to-event nature on longitudinal data commonly used in pharmacoepidemiology.

Limitations inherent to the use of administrative databases for epidemiological research are applicable to this study. Retrospective database analyses by definition use data that have been previously collected. We assume the presence of clinical events if codes are observed and the absence of clinical events if codes are not observed. We recognize that the presence or absence of codes in secondary healthcare data does not imply perfect fidelity to underlying medical constructs therefor exposure, mediator, and outcome misclassification is unavoidable so results may be subject to information bias.

The proposed study design is subject to limitations due to both the study design and secondary use of health care data. Data-related limitations include dependency on the accuracy of codes and algorithms to identify at risk conditions. Exposure ascertainment may be based on pharmacy dispensing records, general practice records, immunization registers, medical records, or other electronic data sources. In addition, dates of events may be missing or not correspond exactly to the onset date of the event.

Limited post-index follow-up time may present another limitation. Right-censoring from database discontinuation may limit the ability to observe mediator events and subsequent outcomes, which could limit the ability to model the hypothesized causal pathway exposure → mediator → outcome. The post-index database observation time for the study population will be evaluated and reported.

10.10. Other Aspects

Not applicable.

11. PROTECTION OF HUMAN SUBJECTS

This study does not qualify as human subject research and does not require informed consent, as the New England IRB has waived the need for ethical approval and informed consent for studies conducted in Merative™ MarketScan® Commercial Claims and Encounters and Optum® de-Identified Clinformatics® Data Mart databases. Both databases include anonymized person-level data. The study was performed in accordance with relevant guidelines and regulations.

12. COLLECTION AND REPORTING OF SAFETY DATA

This study uses coded data that already exist in electronic databases. In these types of databases, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any specific individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspected product, and event) are not available and adverse events are not reportable as individual adverse event reports. The study results will be assessed for medically important findings.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in scientific conferences and peer reviewed scientific publications. Patient identifiers will not be used in the publication of results. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating physician) shall be the property of the sponsor as author and owner of copyright in such work.

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15. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

15.1. Annex 1.1: List of Standalone Documents

No standalone documents included. Code sets for exposure, mediator, and outcome cohorts are available in Section 16. Casual validity diagnostic results are reported in Section 18 *Validity Diagnostics Supplement*.

16. ADDITIONAL INFORMATION

None.

16.1. Target cohort definitions

16.1.1. Rivaroxaban new users

[EPI_1001] New users of rivaroxaban with non-valvular atrial fibrillation

Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of 'Rivaroxaban' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

Inclusion Criteria

1. Aged 18 or older

Entry events with the following event criteria: who are >= 18 years old. #### 2. Non-valvular atrial fibrillation in prior 365 days

Entry events having at least 1 condition occurrence of 'Nonvalvular atrial fibrillation', starting between 365 days before and 0 days after cohort entry start date.

Cohort Exit

The cohort end date will be based on a continuous exposure to 'Rivaroxaban': allowing 30 days between exposures, adding 30 days after exposure ends, and using days supply and exposure end date for exposure duration.

Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

Rivaroxaban

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
40241330	rivaroxaban	1114195	RxNorm	NO	YES	NO

Nonvalvular atrial fibrillation

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
313217	Atrial fibrillation	49436004	SNOMED	NO	YES	NO
319843	Mitral valve disorder	11851006	SNOMED	YES	YES	NO
37395820	Familial atrial fibrillation	715395008	SNOMED	YES	YES	NO

16.1.2.

16.1.3. DOAC new users

[EPI_1001] New users of DOACs with non-valvular atrial fibrillation

Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug era of 'DOAC' for the first time in the person's history.

Inclusion Criteria

1. Aged 18 or older

Entry events with the following event criteria: who are >= 18 years old. #### 2. Non-valvular atrial fibrillation in prior 365 days

Entry events having at least 1 condition occurrence of 'Nonvalvular atrial fibrillation', starting between 365 days before and 0 days after cohort entry start date.

Cohort Exit

The cohort end date will be based on a continuous exposure to 'DOAC': allowing 30 days between exposures, adding 30 days after exposure ends, and using days supply and exposure end date for exposure duration.

Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

DOAC

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43013020	apixaban	1364430	RxNorm	NO	YES	NO
45892850	edoxaban	1599538	RxNorm	NO	YES	NO
45775370	dabigatran	1546356	RxNorm	NO	YES	NO
40241330	rivaroxaban	1114195	RxNorm	NO	YES	NO
40228150	dabigatran etexilate	1037042	RxNorm	NO	YES	NO

Nonvalvular atrial fibrillation

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
313217	Atrial fibrillation	49436004	SNOMED	NO	YES	NO
319843	Mitral valve disorder	11851006	SNOMED	YES	YES	NO
37395820	Familial atrial fibrillation	715395008	SNOMED	YES	YES	NO

16.2. Comparator cohort definition

16.2.1. Warfarin new users

[EPI_1001] New users of warfarin with non-valvular atrial fibrillation

Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug era of 'Warfarin' for the first time in the person's history.

Inclusion Criteria

1. Aged 18 or older

Entry events with the following event criteria: who are >= 18 years old

2. Non-valvular atrial fibrillation in prior 365 days

Entry events having at least 1 condition occurrence of 'Nonvalvular atrial fibrillation', starting between 365 days before and 0 days after cohort entry start date.

Cohort Exit

The cohort end date will be based on a continuous exposure to 'Warfarin': allowing 30 days between exposures, adding 30 days after exposure ends, and using days supply and exposure end date for exposure duration.

Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

Warfarin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1310149	warfarin	11289	RxNorm	NO	YES	NO

Nonvalvular atrial fibrillation

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
313217	Atrial fibrillation	49436004	SNOMED	NO	YES	NO
319843	Mitral valve disorder	11851006	SNOMED	YES	YES	NO

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
37395820	Familial atrial fibrillation	715395008	SNOMED	YES	YES	NO

16.3. Mediator cohort definitions

16.3.1. IP extracranial MB

[EPI_1001] Extracranial major bleeding IP visit

Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of '[EPI_1001] Bleeding', a condition status that is: "primary diagnosis".

2. condition occurrences of '[EPI_1001] Bleeding related disorders', a condition status that is: "primary diagnosis"; having at least 1 condition occurrence of '[EPI_1001] Bleeding', starting between 0 days before and 0 days after '[EPI_1001] Bleeding related disorders' start date.

Inclusion Criteria

1. During IP visit

Entry events having at least 1 visit occurrence of 'Inpatient Visit', starting anytime on or before cohort entry start date and ending between 0 days after and all days after cohort entry start date.

2. no ICH

Entry events with all of the following criteria:

1. having no condition occurrences of '[Phenotype Phebruary][Bleed] Intracranial hemorrhage no trauma - definite w desc', starting between 0 days before and 0 days after cohort entry start date.

2. having no condition occurrences of '[Phenotype Phebruary][Bleed] Intracranial hemorrhage trauma - definite w desc', starting between 0 days before and 0 days after cohort entry start date.

Cohort Exit

The cohort end date will be offset from index event's start date plus 30 days.

Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

[EPI_1001] Bleeding

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
437312	Bleeding	131148009	SNOMED	NO	YES	NO

[EPI_1001] Bleeding related disorders

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
195562	Hemorrhoids	70153002	SNOMED	NO	YES	NO
193252	Diverticulosis of small intestine	8114009	SNOMED	NO	YES	NO
42535740	Diverticulosis of colon	733657002	SNOMED	NO	YES	NO
439777	Anemia	271737000	SNOMED	NO	YES	NO
4027663	Peptic ulcer	13200003	SNOMED	NO	YES	NO
30753	Esophagitis	16761005	SNOMED	NO	YES	NO
201340	Gastritis	4556007	SNOMED	NO	YES	NO
4306267	Coag./bleeding tests abnormal	165563002	SNOMED	NO	YES	NO
433516	Duodenitis	72007001	SNOMED	NO	YES	NO

Inpatient Visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
9201	Inpatient Visit	IP	Visit	NO	YES	NO

[Phenotype Phebruary][Bleed] Intracranial hemorrhage no trauma - definite w desc

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4319328	Brain stem hemorrhage	95454007	SNOMED	NO	YES	NO
376713	Cerebral hemorrhage	274100004	SNOMED	NO	YES	NO
43530850	Chronic non-traumatic intracranial subdural hemorrhage	609382000	SNOMED	NO	YES	NO
4176892	Cortical hemorrhage	49422009	SNOMED	NO	YES	NO
4110186	Intracerebral hemorrhage, multiple localized	195169004	SNOMED	NO	YES	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	YES	NO
436430	Nontraumatic extradural hemorrhage	397809001	SNOMED	NO	YES	NO
4144154	Non-traumatic intracerebral ventricular hemorrhage	425957003	SNOMED	NO	YES	NO
4111709	Non-traumatic subdural hemorrhage	195176009	SNOMED	NO	YES	NO
43530670	Spontaneous cerebellar hemorrhage	142851000119103	SNOMED	NO	YES	NO
43530730	Spontaneous cerebral hemorrhage	291571000119106	SNOMED	NO	YES	NO
42535430	Spontaneous hemorrhage of cerebral hemisphere	291531000119108	SNOMED	NO	YES	NO
4148906	Spontaneous subarachnoid hemorrhage	270907008	SNOMED	NO	YES	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	YES	NO

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4108952	Subarachnoid hemorrhage from carotid siphon and bifurcation	195155004	SNOMED	NO	YES	NO
4111708	Subarachnoid hemorrhage from vertebral artery	195160000	SNOMED	NO	YES	NO
4049659	Subcortical hemorrhage	20908003	SNOMED	NO	YES	NO
439040	Subdural hemorrhage	35486000	SNOMED	NO	YES	NO

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808
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810
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812 *[Phenotype Phebruary][Bleed] Intracranial hemorrhage trauma - definite w desc*

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4014781	Closed traumatic subdural hemorrhage	209947002	SNOMED	NO	YES	NO
4306943	Epidural hemorrhage	82999001	SNOMED	NO	YES	NO
42873160	Intracranial hemorrhage following injury	450410005	SNOMED	NO	YES	NO
444197	Intracranial hemorrhage following injury with brief loss of consciousness	127309004	SNOMED	NO	YES	NO
444198	Intracranial hemorrhage following injury with loss of consciousness	127308007	SNOMED	NO	YES	NO
444196	Intracranial hemorrhage following injury with moderate loss of consciousness	127310009	SNOMED	NO	YES	NO
436526	Intracranial hemorrhage following injury with prolonged loss of consciousness AND return to pre-existing conscious level	127311008	SNOMED	NO	YES	NO
437106	Intracranial hemorrhage following injury with prolonged loss of consciousness without return to pre-existing conscious level	127312001	SNOMED	NO	YES	NO
4134162	Subarachnoid hemorrhage due to traumatic injury	262955000	SNOMED	NO	YES	NO
438595	Subdural hemorrhage following injury without open intracranial wound AND with no loss of consciousness	40135004	SNOMED	NO	YES	NO
4196276	Traumatic extradural hematoma without open intracranial wound	315048006	SNOMED	NO	YES	NO
37205200	Traumatic intracranial extradural hemorrhage	784573006	SNOMED	NO	YES	NO
4154699	Traumatic intracranial subdural hematoma with brief loss of consciousness	371050006	SNOMED	NO	YES	NO

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4196275	Traumatic subdural hematoma without open intracranial wound	315046005	SNOMED	NO	YES	NO
4017107	Traumatic subdural hemorrhage	209987007	SNOMED	NO	YES	NO

16.3.2. ER-IP Extracranial MB

[EPI_1001] Extracranial major bleeding IP-ER visit

Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of '[EPI_1001] Bleeding', a condition status that is: "primary diagnosis".
2. condition occurrences of '[EPI_1001] Bleeding related disorders', a condition status that is: "primary diagnosis"; having at least 1 condition occurrence of '[EPI_1001] Bleeding', starting between 0 days before and 0 days after '[EPI_1001] Bleeding related disorders' start date.

Inclusion Criteria

1. During ER-IP visit

Entry events having at least 1 visit occurrence of '[HowOften] Inpatient or ER visit', starting anytime on or before cohort entry start date and ending between 0 days after and all days after cohort entry start date.

3. no ICH

Entry events with all of the following criteria:

1. having no condition occurrences of '[Phenotype Phebruary][Bleed] Intracranial hemorrhage no trauma - definite w desc', starting between 0 days before and 0 days after cohort entry start date.
2. having no condition occurrences of '[Phenotype Phebruary][Bleed] Intracranial hemorrhage trauma - definite w desc', starting between 0 days before and 0 days after cohort entry start date.

Cohort Exit

The cohort end date will be offset from index event's start date plus 30 days.

Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

[EPI_1001] Bleeding

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
437312	Bleeding	131148009	SNOMED	NO	YES	NO

[EPI_1001] Bleeding related disorders

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
195562	Hemorrhoids	70153002	SNOMED	NO	YES	NO
193252	Diverticulosis of small intestine	8114009	SNOMED	NO	YES	NO
42535740	Diverticulosis of colon	733657002	SNOMED	NO	YES	NO
439777	Anemia	271737000	SNOMED	NO	YES	NO
4027663	Peptic ulcer	13200003	SNOMED	NO	YES	NO
30753	Esophagitis	16761005	SNOMED	NO	YES	NO
201340	Gastritis	4556007	SNOMED	NO	YES	NO
4306267	Coag./bleeding tests abnormal	165563002	SNOMED	NO	YES	NO
433516	Duodenitis	72007001	SNOMED	NO	YES	NO

Inpatient Visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
9201	Inpatient Visit	IP	Visit	NO	YES	NO

[Phenotype Phebruary][Bleed] Intracranial hemorrhage no trauma - definite w desc

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4319328	Brain stem hemorrhage	95454007	SNOMED	NO	YES	NO
376713	Cerebral hemorrhage	274100004	SNOMED	NO	YES	NO
43530850	Chronic non-traumatic intracranial subdural hemorrhage	609382000	SNOMED	NO	YES	NO
4176892	Cortical hemorrhage	49422009	SNOMED	NO	YES	NO
4110186	Intracerebral hemorrhage, multiple localized	195169004	SNOMED	NO	YES	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	YES	NO
436430	Nontraumatic extradural hemorrhage	397809001	SNOMED	NO	YES	NO
4144154	Non-traumatic intracerebral ventricular hemorrhage	425957003	SNOMED	NO	YES	NO
4111709	Non-traumatic subdural hemorrhage	195176009	SNOMED	NO	YES	NO
43530670	Spontaneous cerebellar hemorrhage	142851000119103	SNOMED	NO	YES	NO
43530730	Spontaneous cerebral hemorrhage	291571000119106	SNOMED	NO	YES	NO
42535430	Spontaneous hemorrhage of cerebral hemisphere	291531000119108	SNOMED	NO	YES	NO
4148906	Spontaneous subarachnoid hemorrhage	270907008	SNOMED	NO	YES	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	YES	NO
4108952	Subarachnoid hemorrhage from carotid siphon and bifurcation	195155004	SNOMED	NO	YES	NO

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4111708	Subarachnoid hemorrhage from vertebral artery	195160000	SNOMED	NO	YES	NO
4049659	Subcortical hemorrhage	20908003	SNOMED	NO	YES	NO
439040	Subdural hemorrhage	35486000	SNOMED	NO	YES	NO

[Phenotype Phebruary][Bleed] Intracranial hemorrhage trauma - definite w desc

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4014781	Closed traumatic subdural hemorrhage	209947002	SNOMED	NO	YES	NO
4306943	Epidural hemorrhage	82999001	SNOMED	NO	YES	NO
42873160	Intracranial hemorrhage following injury	450410005	SNOMED	NO	YES	NO
444197	Intracranial hemorrhage following injury with brief loss of consciousness	127309004	SNOMED	NO	YES	NO
444198	Intracranial hemorrhage following injury with loss of consciousness	127308007	SNOMED	NO	YES	NO
444196	Intracranial hemorrhage following injury with moderate loss of consciousness	127310009	SNOMED	NO	YES	NO
436526	Intracranial hemorrhage following injury with prolonged loss of consciousness AND return to pre-existing conscious level	127311008	SNOMED	NO	YES	NO
437106	Intracranial hemorrhage following injury with prolonged loss of consciousness without return to pre-existing conscious level	127312001	SNOMED	NO	YES	NO
4134162	Subarachnoid hemorrhage due to traumatic injury	262955000	SNOMED	NO	YES	NO
438595	Subdural hemorrhage following injury without open intracranial wound AND with no loss of consciousness	40135004	SNOMED	NO	YES	NO
4196276	Traumatic extradural hematoma without open intracranial wound	315048006	SNOMED	NO	YES	NO
37205200	Traumatic intracranial extradural hemorrhage	784573006	SNOMED	NO	YES	NO
4154699	Traumatic intracranial subdural hematoma with brief loss of consciousness	371050006	SNOMED	NO	YES	NO
4196275	Traumatic subdural hematoma without open intracranial wound	315046005	SNOMED	NO	YES	NO
4017107	Traumatic subdural hemorrhage	209987007	SNOMED	NO	YES	NO

[HowOften] Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

16.4. Outcome cohort definitions

16.4.1. AMI

[PL] All events of Acute Myocardial Infarction, inpatient setting with washout period of 365 days

Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of 'Myocardial Infarction and complication'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or Inpatient/ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

Inclusion Criteria

1. has no events in prior 'clean window' - 365 days

Entry events having no condition occurrences of 'Myocardial Infarction and complication', starting in the 365 days prior to cohort entry start date; allow events outside observation period; having at least 1 visit occurrence of 'Inpatient or Inpatient/ER visit', starting anytime on or before 'Myocardial Infarction and complication' start date and ending between 0 days before and all days after 'Myocardial Infarction and complication' start date.

Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

Inpatient or Inpatient/ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

Myocardial Infarction and complication

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
4108680	Thrombosis of atrium, auricular appendage, and ventricle due to and following acute myocardial infarction	194868001	SNOMED	NO	YES	NO
4108678	Hemopericardium due to and following acute myocardial infarction	194862000	SNOMED	NO	YES	NO
438172	Atrial septal defect due to and following acute myocardial infarction	194863005	SNOMED	NO	YES	NO
4124687	Cardiac rupture due to and following acute myocardial infarction	233847009	SNOMED	NO	YES	NO
45766210	Mitral valve regurgitation due to and following acute myocardial infarction	703326006	SNOMED	NO	YES	NO
37109910	Ventricular aneurysm due to and following acute myocardial infarction	723858002	SNOMED	NO	YES	NO
37109910	Pulmonary embolism due to and following acute myocardial infarction	723859005	SNOMED	NO	YES	NO
37109910	Arrhythmia due to and following acute myocardial infarction	723860000	SNOMED	NO	YES	NO
314666	Old myocardial infarction	1755008	SNOMED	YES	YES	NO

16.4.2. Ischemic stroke

Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘Cerebral infarction’.

Restrict entry events to having at least 1 visit occurrence of ‘Inpatient or Inpatient/ER visit’, starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

Inclusion Criteria

1. has no events in prior ‘clean window’ - 365 days

Entry events having no condition occurrences of ‘Cerebral infarction’, starting in the 365 days prior to cohort entry start date; allow events outside observation period; having at least 1 visit occurrence of ‘Inpatient or Inpatient/ER visit’, starting anytime on or before ‘Cerebral infarction’ start date and ending between 0 days before and all days after ‘Cerebral infarction’ start date.

Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

Inpatient or Inpatient/ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

Cerebral infarction

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
443454	Cerebral infarction	432504007	SNOMED	NO	YES	NO
40479570	Infarct of cerebrum due to iatrogenic cerebrovascular accident	441526008	SNOMED	YES	YES	NO
4046360	Lacunar infarction	230698000	SNOMED	YES	YES	NO
372435	Periventricular leukomalacia	230769007	SNOMED	YES	NO	NO
377254	Multi-infarct dementia, uncomplicated	70936005	SNOMED	YES	NO	NO
379778	Multi-infarct dementia	56267009	SNOMED	YES	NO	NO
443790	Multi-infarct dementia with delusions	25772007	SNOMED	YES	NO	NO
443864	Multi-infarct dementia with depression	14070001	SNOMED	YES	NO	NO
444091	Multi-infarct dementia with delirium	10349009	SNOMED	YES	NO	NO
4046089	Vascular dementia of acute onset	230285003	SNOMED	YES	NO	NO
4046090	Mixed cortical and subcortical vascular dementia	230287006	SNOMED	YES	NO	NO
4129534	Pituitary apoplexy	237701005	SNOMED	YES	NO	NO

16.4.3. Composite ischemic stroke or AMI

[EPI_1001] Composite outcome Non-hemorrhagic Stroke or Acute Myocardial Infarction

Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of 'Cerebral infarction'.
2. condition occurrences of 'Myocardial Infarction and complication'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or Inpatient/ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

Inclusion Criteria

1. has no events in prior 'clean window' - 365 days

Entry events with all of the following criteria:

1. having no condition occurrences of 'Cerebral infarction', starting in the 365 days prior to cohort entry start date; allow events outside observation period; having at least 1 visit occurrence of 'Inpatient or Inpatient/ER visit', starting anytime on or before 'Cerebral infarction' start date and ending between 0 days before and all days after 'Cerebral infarction' start date.
2. having at least 0 condition occurrences of 'Myocardial Infarction and complication', starting in the 365 days prior to cohort entry start date; allow events outside observation period; having at least 1 visit occurrence of 'Inpatient or Inpatient/ER visit', starting anytime on or before 'Myocardial Infarction and complication' start date and ending between 0 days before and all days after 'Myocardial Infarction and complication' start date.

Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

Inpatient or Inpatient/ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

Cerebral infarction

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
443454	Cerebral infarction	432504007	SNOMED	NO	YES	NO
40479570	Infarct of cerebrum due to iatrogenic cerebrovascular accident	441526008	SNOMED	YES	YES	NO
4046360	Lacunar infarction	230698000	SNOMED	YES	YES	NO
372435	Periventricular leukomalacia	230769007	SNOMED	YES	NO	NO
377254	Multi-infarct dementia, uncomplicated	70936005	SNOMED	YES	NO	NO
379778	Multi-infarct dementia	56267009	SNOMED	YES	NO	NO
443790	Multi-infarct dementia with delusions	25772007	SNOMED	YES	NO	NO
443864	Multi-infarct dementia with depression	14070001	SNOMED	YES	NO	NO

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
444091	Multi-infarct dementia with delirium	10349009	SNOMED	YES	NO	NO
4046089	Vascular dementia of acute onset	230285003	SNOMED	YES	NO	NO
4046090	Mixed cortical and subcortical vascular dementia	230287006	SNOMED	YES	NO	NO
4129534	Pituitary apoplexy	237701005	SNOMED	YES	NO	NO

Myocardial Infarction and complication

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
4108680	Thrombosis of atrium, auricular appendage, and ventricle due to and following acute myocardial infarction	194868001	SNOMED	NO	YES	NO
4108678	Hemopericardium due to and following acute myocardial infarction	194862000	SNOMED	NO	YES	NO
438172	Atrial septal defect due to and following acute myocardial infarction	194863005	SNOMED	NO	YES	NO
4124687	Cardiac rupture due to and following acute myocardial infarction	233847009	SNOMED	NO	YES	NO
45766210	Mitral valve regurgitation due to and following acute myocardial infarction	703326006	SNOMED	NO	YES	NO
37109910	Ventricular aneurysm due to and following acute myocardial infarction	723858002	SNOMED	NO	YES	NO
37109910	Pulmonary embolism due to and following acute myocardial infarction	723859005	SNOMED	NO	YES	NO
37109910	Arrhythmia due to and following acute myocardial infarction	723860000	SNOMED	NO	YES	NO
314666	Old myocardial infarction	1755008	SNOMED	YES	YES	NO

16.5. Negative control outcomes

Concept ID	Name
437643	Abnormal gait
260139	Acute bronchitis
257007	Allergic rhinitis
442077	Anxiety disorder
4153359	Arthritis of spine
4324765	Arthropathy of knee joint
261880	Atelectasis
443344	Barrett’s esophagus

Concept ID	Name
378425	Blepharitis
256449	Bronchiectasis
313791	Bundle branch block
435613	Cellulitis
257012	Chronic sinusitis
134441	Chronic ulcer of skin
4150614	Communication disorder
201606	Crohn’s disease
73302	Curvature of spine
4242416	Cutis laxa
74726	Dislocation of joint
192279	Disorder of kidney due to diabetes mellitus
443730	Disorder of nervous system due to diabetes mellitus
435657	Dyssomnia
197684	Dysuria
79903	Effusion of joint
4050747	Fracture of upper limb
196456	Gallstone
4007453	Gammopathy
441788	Human papilloma virus infection
197032	Hyperplasia of prostate
4208390	Inflammation of sacroiliac joint
139099	Ingrowing nail
4112853	Malignant tumor of breast
374919	Multiple sclerosis
24134	Neck pain
433736	Obesity
141663	Osteomyelitis
372328	Otitis media
78162	Peripheral vertigo
4002650	Plantar fasciitis
373478	Presbyopia
199876	Prolapse of female genital organs
436073	Psychotic disorder
4174977	Retinopathy due to diabetes mellitus
141932	Senile hyperkeratosis
141825	Simple goiter
313459	Sleep apnea
4077081	Superficial mycosis
193326	Urge incontinence of urine
81902	Urinary tract infectious disease
140641	Verruca vulgaris

939

17. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

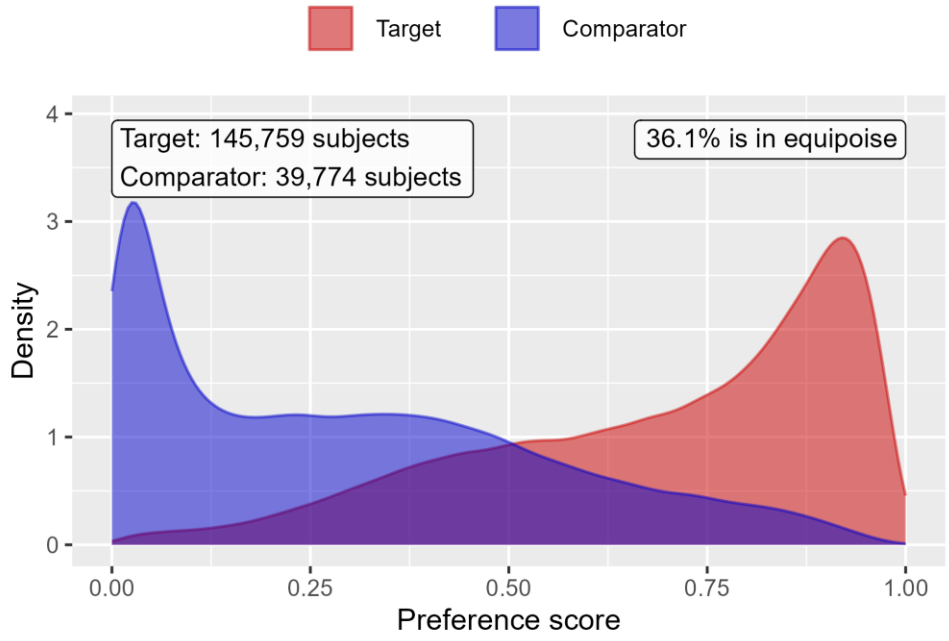
18. VALIDITY DIAGNOSTICS SUPPLEMENT

18.1. Propensity score distribution and equipoise

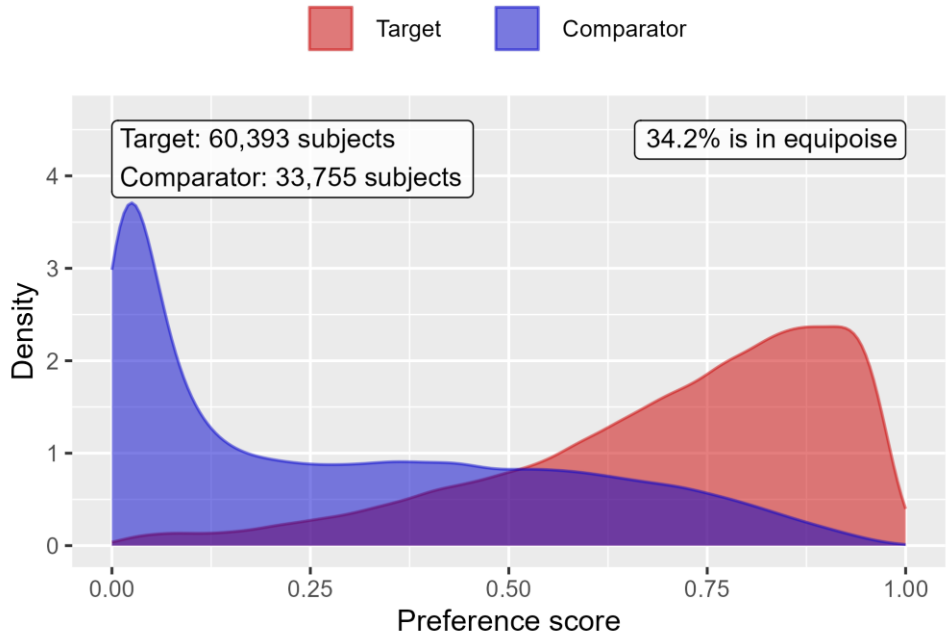
Table 1.1: Overview of empirical equipoise per database and comparison

Database	Target	Comparator	Equipoise
CCAE	DOACs	Warfarin	36.1%
CCAE	Rivaroxaban	Warfarin	34.2%
Clinformatics®	DOACs	Warfarin	36.0%
Clinformatics®	Rivaroxaban	Warfarin	45.3%
Optum® EHR	DOACs	Warfarin	36.2%
Optum® EHR	Rivaroxaban	Warfarin	39.8%
PharMetrics	DOACs	Warfarin	39.4%
PharMetrics	Rivaroxaban	Warfarin	37.7%
MDCR	DOACs	Warfarin	42.8%
MDCR	Rivaroxaban	Warfarin	45.8%

18.1.1. CCAE

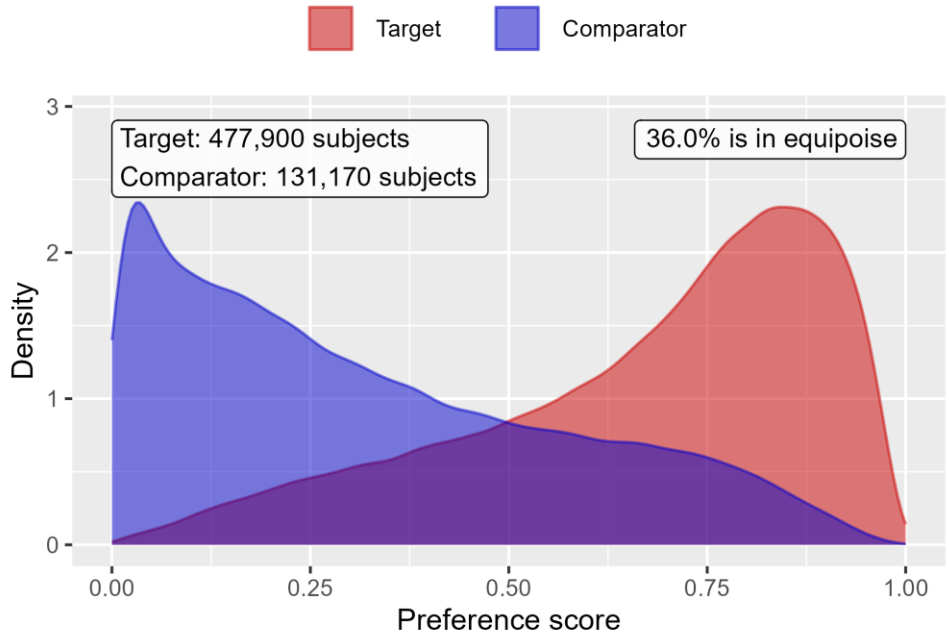


Propensity score distribution comparing DOACs to Warfarin in CCAE.

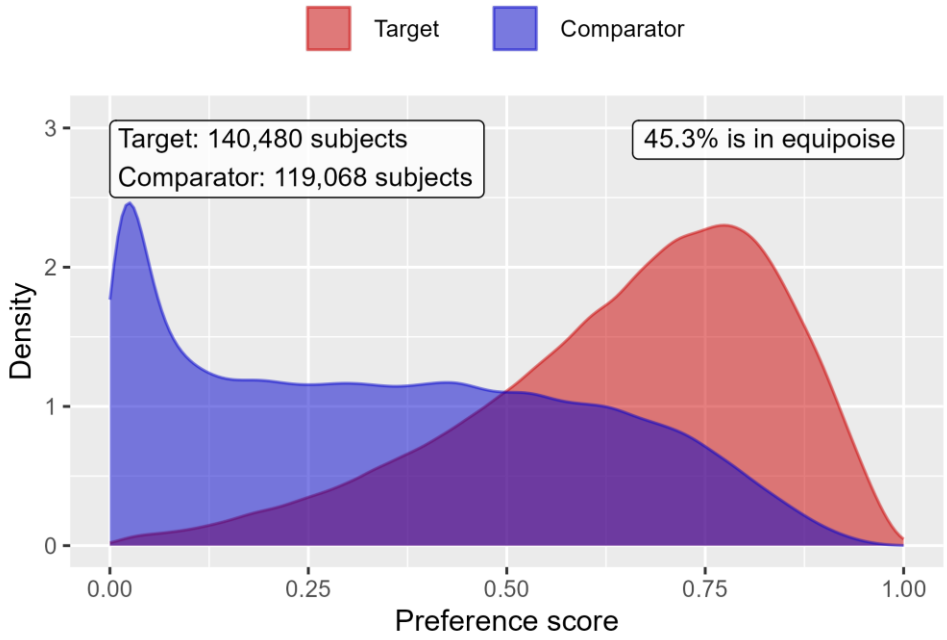


Propensity score distribution comparing Rivaroxaban to Warfarin in CCAE.

18.1.2. Clinformatics®

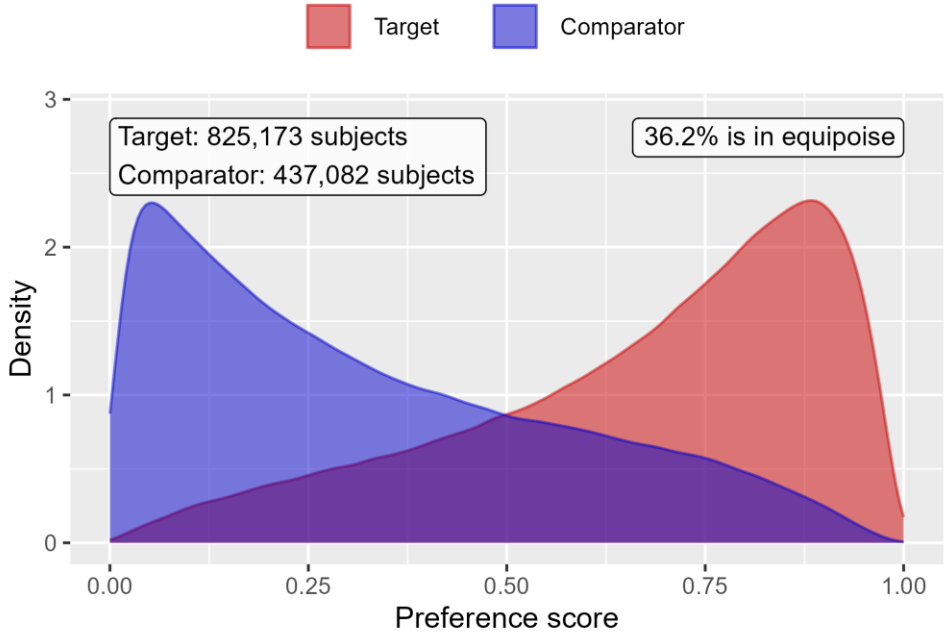


Propensity score distribution comparing DOACs to Warfarin in Clinformatics®.

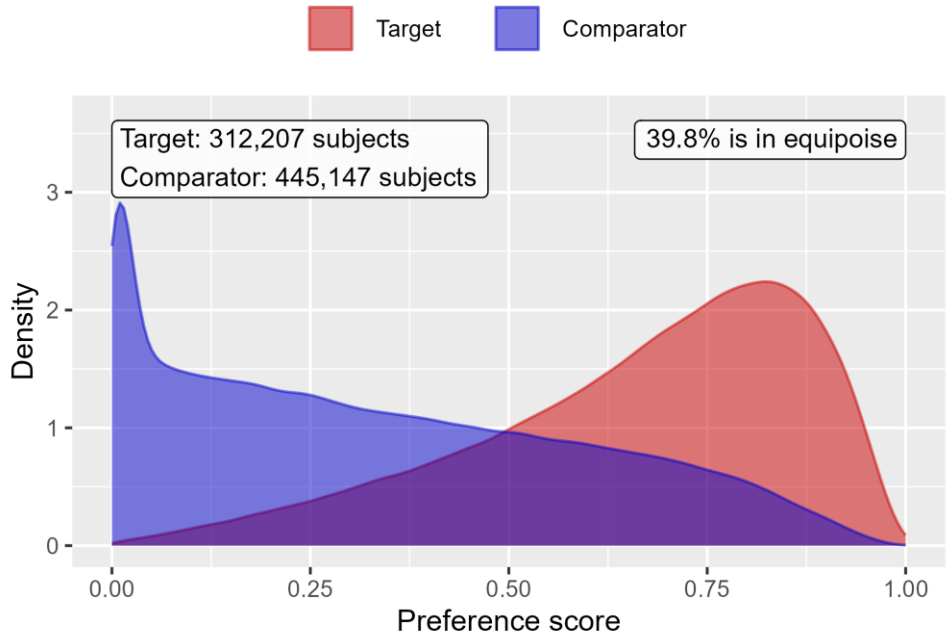


Propensity score distribution comparing Rivaroxaban to Warfarin in Clinformatics®.

18.1.3. Optum® EHR

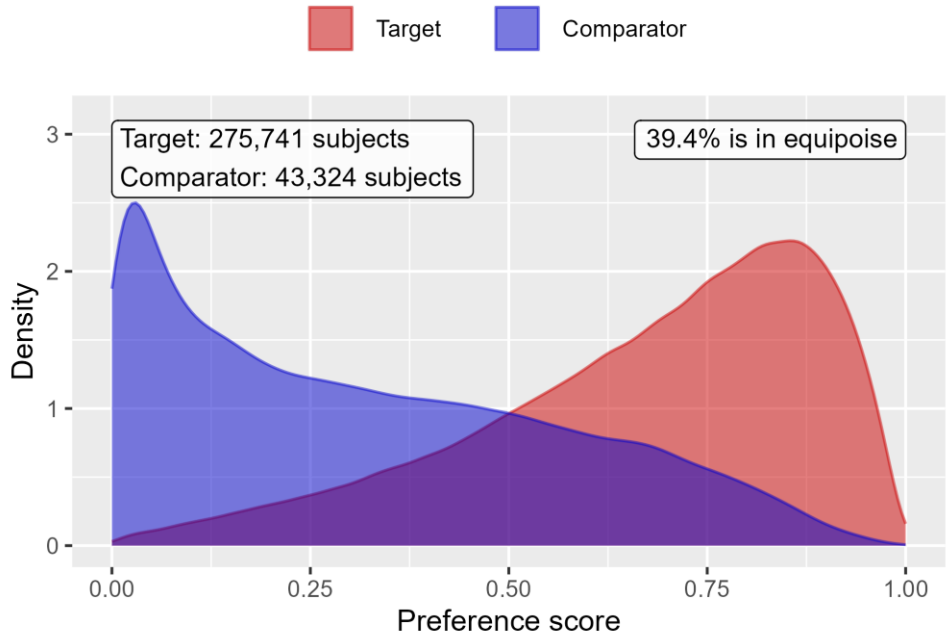


Propensity score distribution comparing DOACs to Warfarin in Optum® EHR.

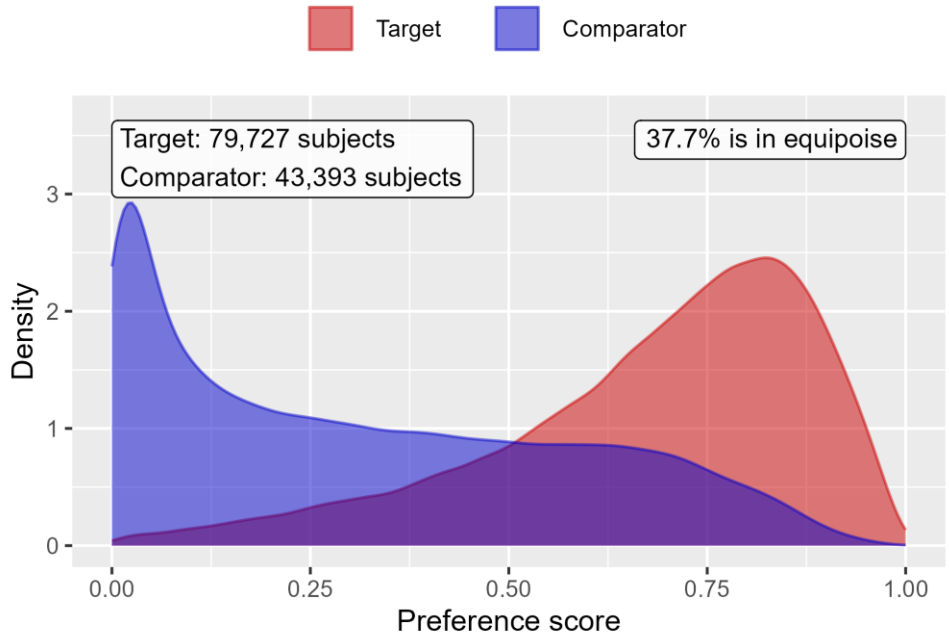


Propensity score distribution comparing Rivaroxaban to Warfarin in Optum® EHR.

18.1.4. PharMetrics

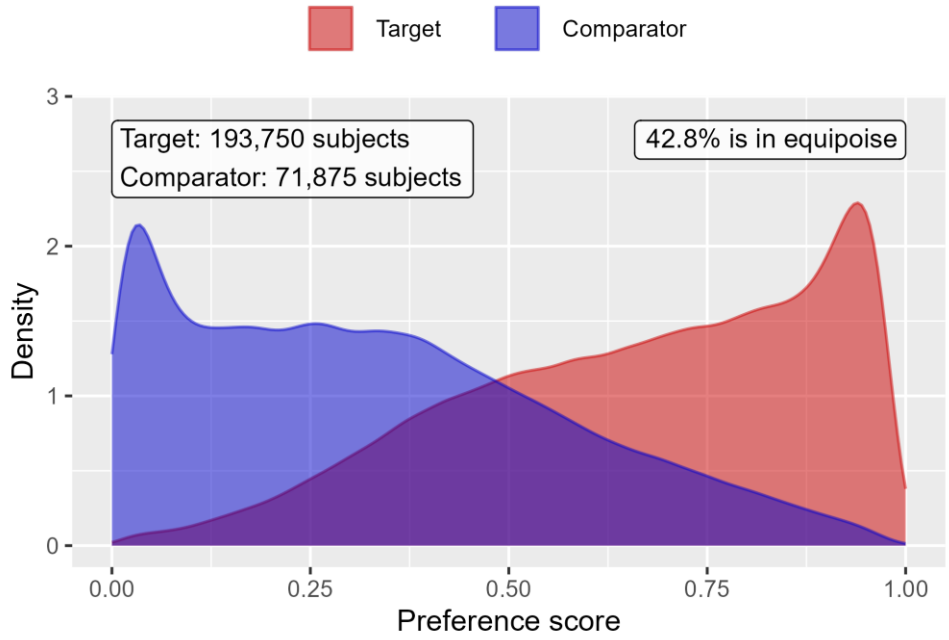


Propensity score distribution comparing DOACs to Warfarin in PharMetrics.

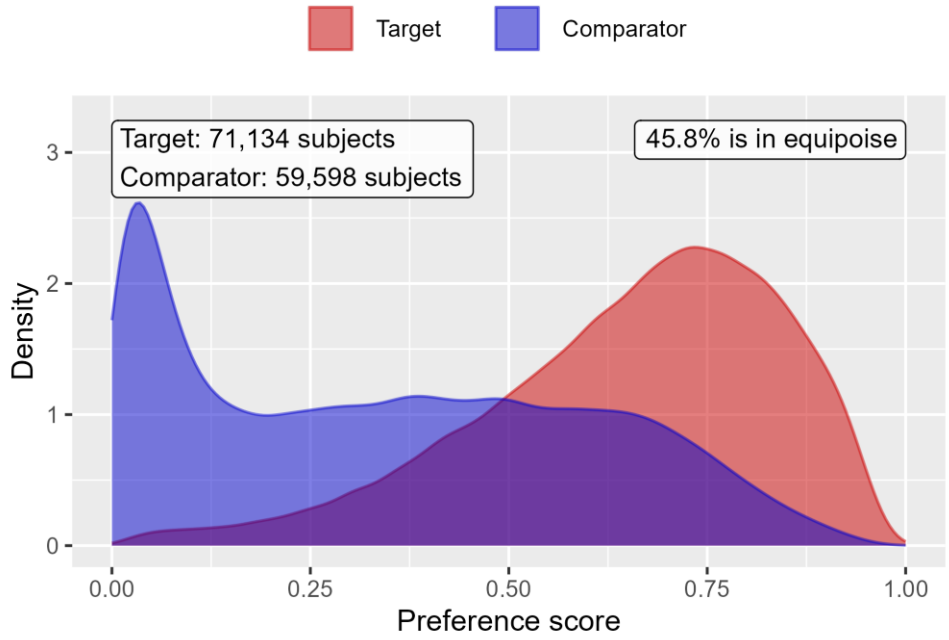


Propensity score distribution comparing Rivaroxaban to Warfarin in PharMetrics.

18.1.5. MDCR



Propensity score distribution comparing DOACs to Warfarin in MDCR.



973

974 Propensity score distribution comparing Rivaroxaban to Warfarin in MDCR.

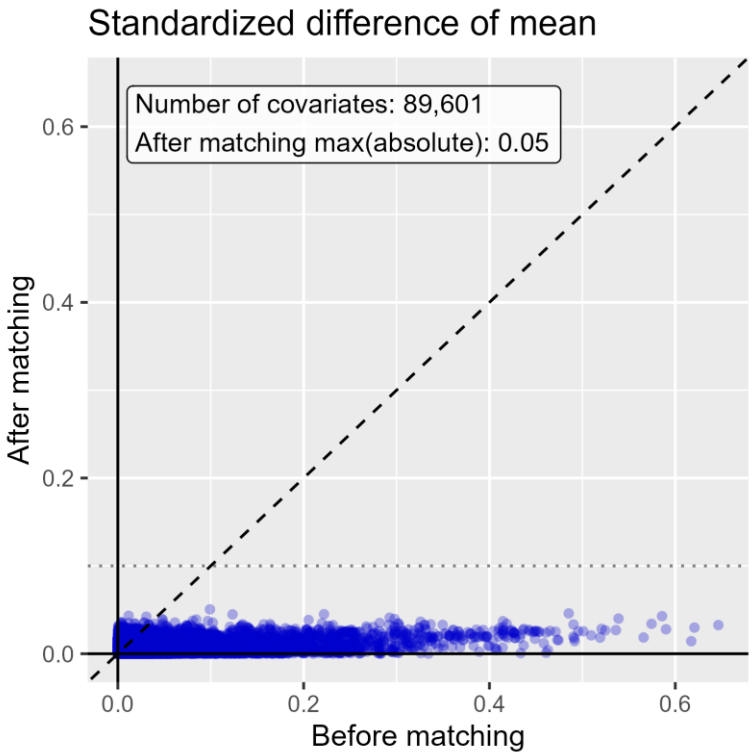
975 ## 18.2. Covariate balance

976 *Table 2.1: Overview of balance per database and comparison*

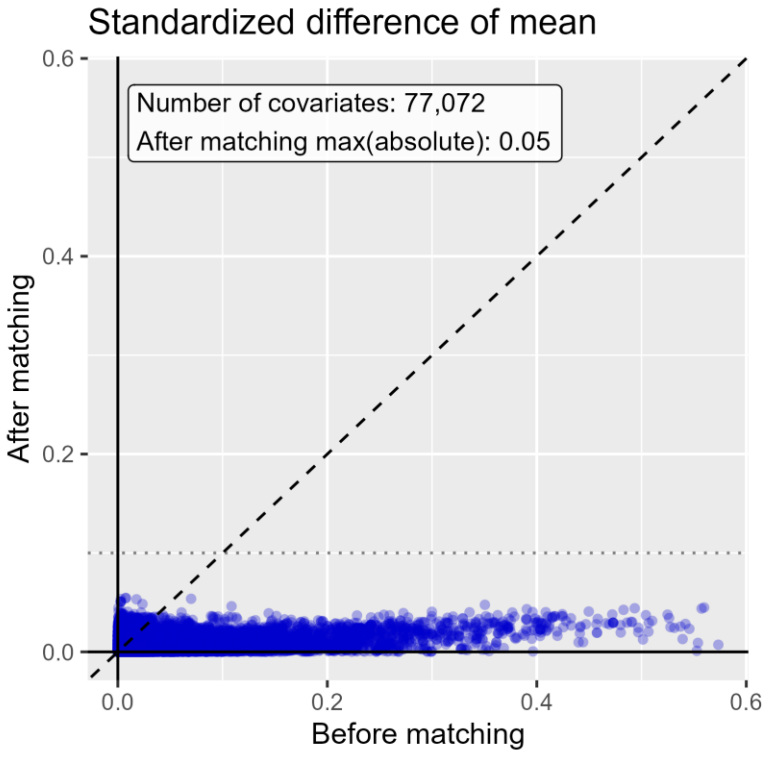
Database	Target	Comparator	Number of covariates	Max ASDM
CCAE	DOACs	Warfarin	89,601	0.05
CCAE	Rivaroxaban	Warfarin	77,072	0.05
Clinformatics®	DOACs	Warfarin	127,326	0.05
Clinformatics®	Rivaroxaban	Warfarin	113,953	0.07
Optum® EHR	DOACs	Warfarin	122,913	0.06
Optum® EHR	Rivaroxaban	Warfarin	118,035	0.08
PharMetrics	DOACs	Warfarin	78,981	0.07
PharMetrics	Rivaroxaban	Warfarin	67,123	0.06
MDCR	DOACs	Warfarin	87,462	0.04
MDCR	Rivaroxaban	Warfarin	74,352	0.05

977

18.2.1. CCAE

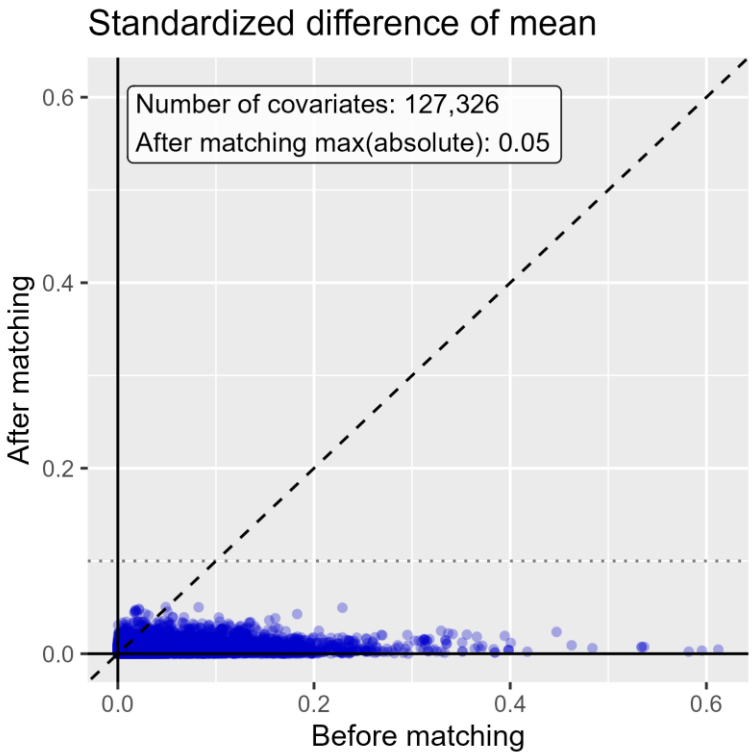


Standardized difference of mean comparing DOACs to Warfarin in CCAE.

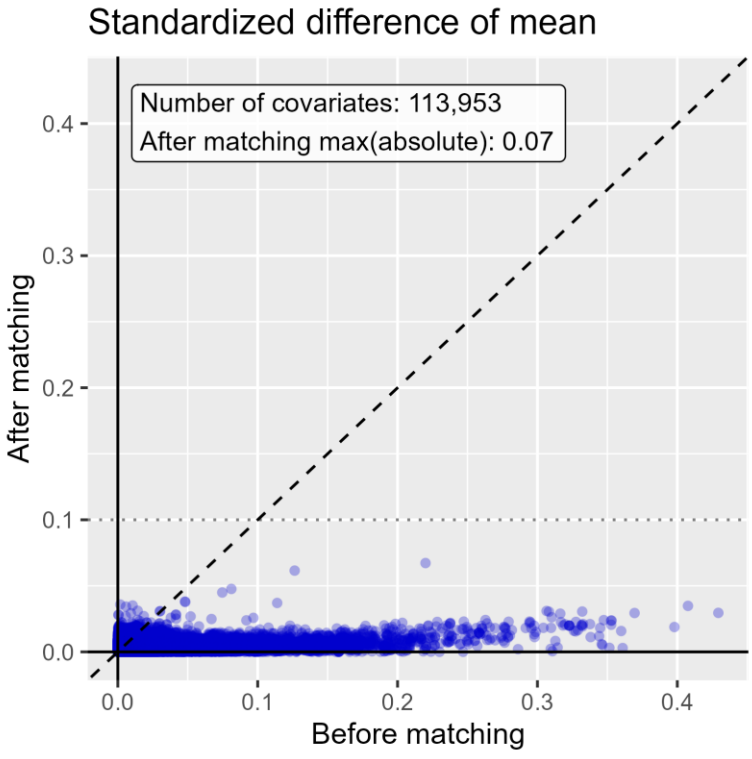


Standardized difference of mean comparing Rivaroxaban to Warfarin in CCAE.

18.2.2. Clinformatics®

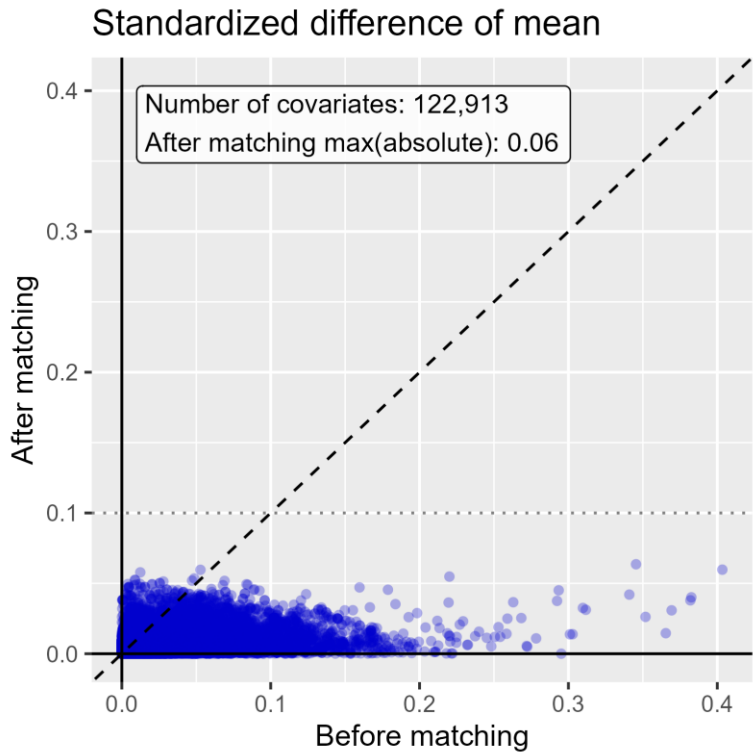


Standardized difference of mean comparing DOACs to Warfarin in Clinformatics®.

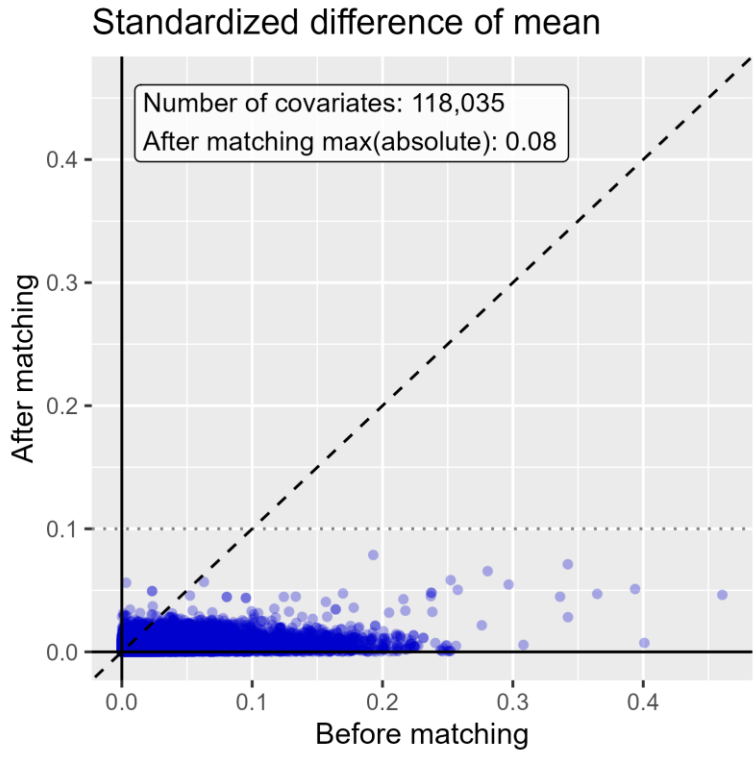


Standardized difference of mean comparing Rivaroxaban to Warfarin in Clinformatics®.

18.2.3. Optum® EHR

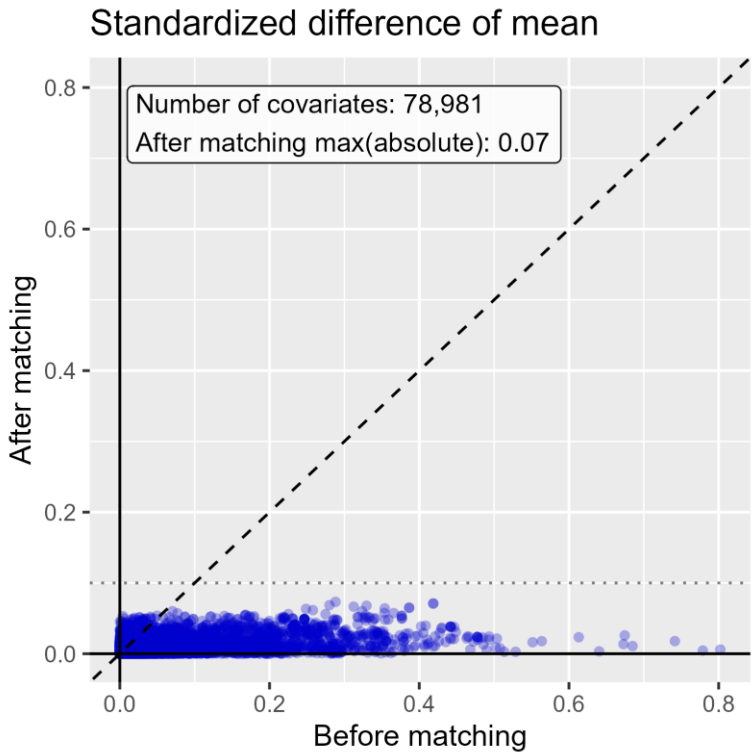


Standardized difference of mean comparing DOACs to Warfarin in Optum® EHR.

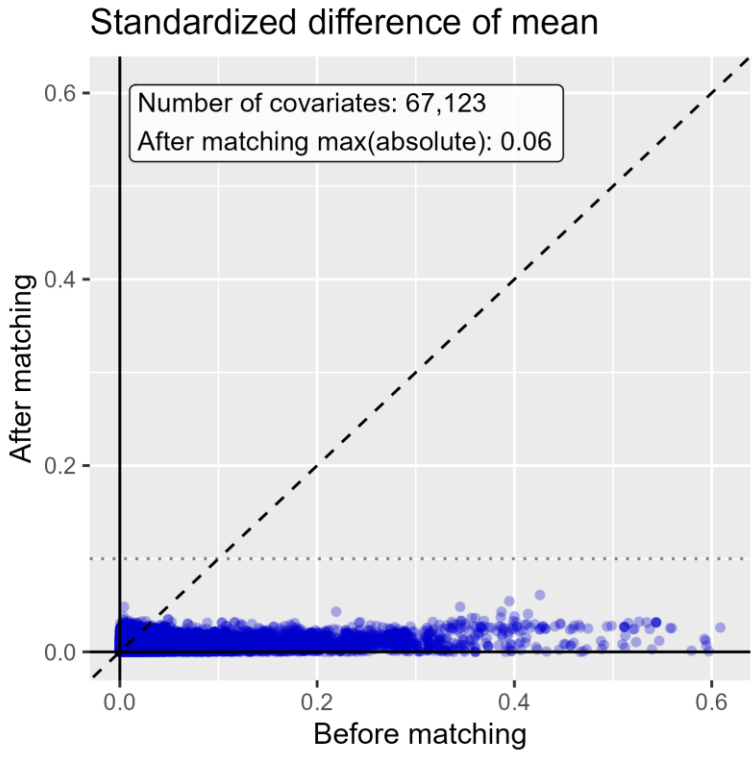


Standardized difference of mean comparing Rivaroxaban to Warfarin in Optum® EHR.

18.2.4. PharMetrics

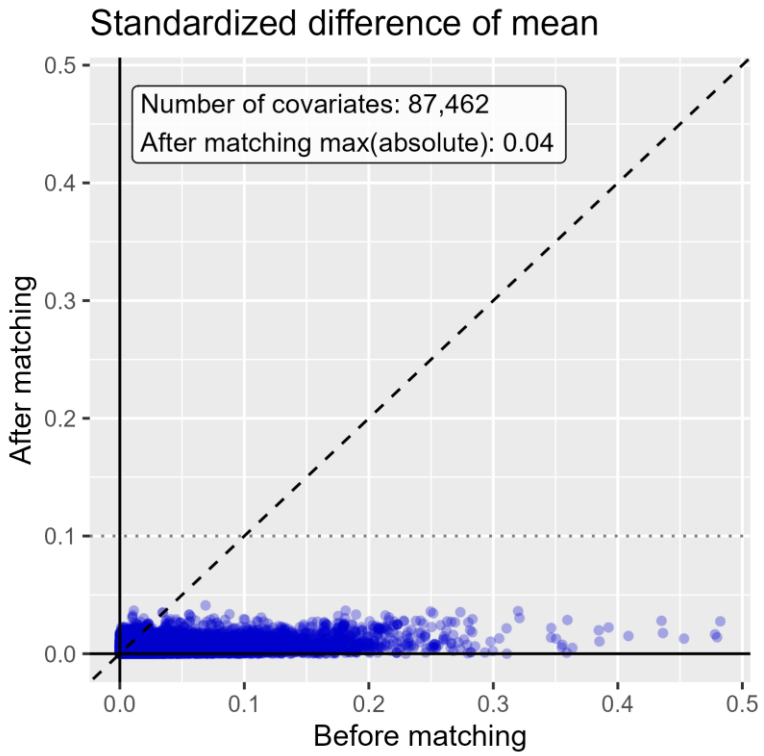


Standardized difference of mean comparing DOACs to Warfarin in Optum® EHR.

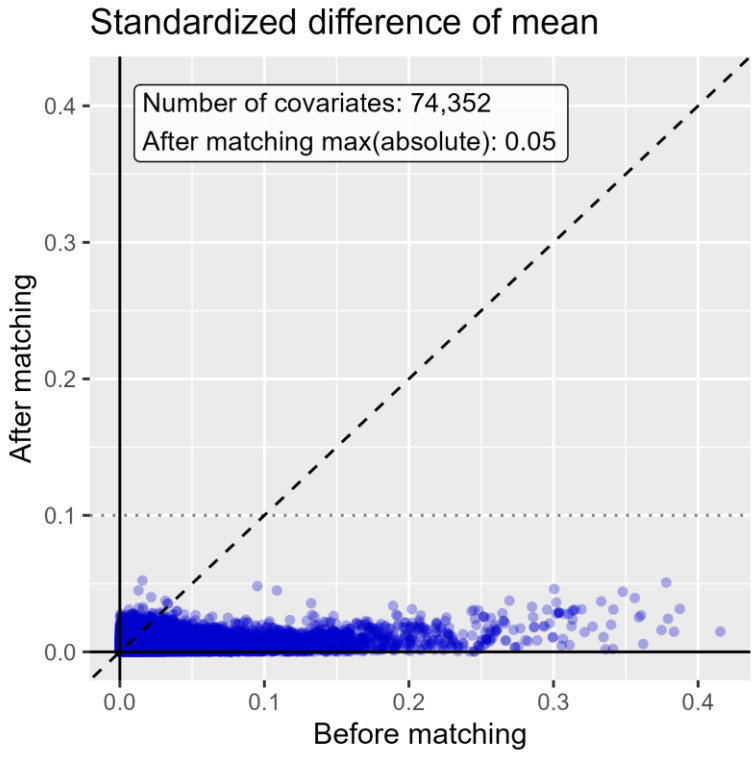


Standardized difference of mean comparing Rivaroxaban to Warfarin in PharMetrics.

18.2.5. MDCR



Standardized difference of mean comparing DOACs to Warfarin in MDCR.



Standardized difference of mean comparing Rivaroxaban to Warfarin in MDCR.

18.3. MDRR and follow-up time

18.3.1. MDRR

Table 3.1: Overview of MDRR per database, comparison, and outcome.

Database	Target	Comparator	Outcome*	Target subjects	Comparator subjects	Total outcomes	MDRR
CCAE	DOACs	Warfarin	AMI	22,025	32,335	634	1.25
CCAE	DOACs	Warfarin	Ischemic stroke	22,182	32,986	532	1.28
CCAE	DOACs	Warfarin	Composite	20,744	30,081	989	1.20
CCAE	Rivaroxaban	Warfarin	AMI	15,053	28,126	526	1.29
CCAE	Rivaroxaban	Warfarin	Ischemic stroke	15,120	28,725	446	1.32
CCAE	Rivaroxaban	Warfarin	Composite	14,220	26,116	808	1.23
Clinformatics®	DOACs	Warfarin	AMI	76,373	105,169	4,775	1.09
Clinformatics®	DOACs	Warfarin	Ischemic stroke	76,134	105,579	4,656	1.09
Clinformatics®	DOACs	Warfarin	Composite	70,206	95,531	7,968	1.07
Clinformatics®	Rivaroxaban	Warfarin	AMI	56,171	100,549	4,148	1.09
Clinformatics®	Rivaroxaban	Warfarin	Ischemic stroke	55,715	100,755	3,984	1.10
Clinformatics®	Rivaroxaban	Warfarin	Composite	52,085	91,126	6,877	1.07
Optum® EHR	DOACs	Warfarin	AMI	210,874	370,657	18,036	1.04
Optum® EHR	DOACs	Warfarin	Ischemic stroke	211,897	374,503	16,426	1.05
Optum® EHR	DOACs	Warfarin	Composite	203,464	358,980	31,485	1.03
Optum® EHR	Rivaroxaban	Warfarin	AMI	155,890	372,100	16,683	1.05
Optum® EHR	Rivaroxaban	Warfarin	Ischemic stroke	156,577	376,897	15,156	1.05
Optum® EHR	Rivaroxaban	Warfarin	Composite	150,696	359,545	28,982	1.04
PharMetrics	DOACs	Warfarin	AMI	26,930	33,632	1,217	1.18
PharMetrics	DOACs	Warfarin	Ischemic stroke	27,550	34,805	933	1.20
PharMetrics	DOACs	Warfarin	Composite	25,051	31,323	1,832	1.14
PharMetrics	Rivaroxaban	Warfarin	AMI	21,298	36,857	1,076	1.19
PharMetrics	Rivaroxaban	Warfarin	Ischemic stroke	21,437	38,072	835	1.22
PharMetrics	Rivaroxaban	Warfarin	Composite	19,988	34,340	1,637	1.15
MDCR	DOACs	Warfarin	AMI	42,182	59,381	2,355	1.12
MDCR	DOACs	Warfarin	Ischemic stroke	41,367	58,971	2,413	1.12
MDCR	DOACs	Warfarin	Composite	38,398	53,530	4,060	1.09
MDCR	Rivaroxaban	Warfarin	AMI	28,377	50,112	1,878	1.14
MDCR	Rivaroxaban	Warfarin	Ischemic stroke	27,735	49,718	1,886	1.14
MDCR	Rivaroxaban	Warfarin	Composite	25,969	45,091	3,183	1.11

*Composite: Ischemic stroke or AMI

18.3.2. Follow-up time in the target cohort

Table 3.2: Overview of follow-up time in days in the target cohort per database, comparison, and outcome.

Database	Target	Comparator	Outcome	p10	p25	Median	p75	p90
CCAE	DOACs	Warfarin	AMI	60.0	60	153	356	706.0

Database	Target	Comparator	Outcome	p10	p25	Median	p75	p90
CCAE	DOACs	Warfarin	Ischemic stroke	60.0	60	151	353	699.0
CCAE	DOACs	Warfarin	Composite	58.0	60	150	351	696.0
CCAE	Rivaroxaban	Warfarin	AMI	54.0	60	151	339	688.0
CCAE	Rivaroxaban	Warfarin	Ischemic stroke	55.0	60	150	337	683.0
CCAE	Rivaroxaban	Warfarin	Composite	53.0	60	149	336	681.0
Clinformatics®	DOACs	Warfarin	AMI	60.0	81	191	439	847.0
Clinformatics®	DOACs	Warfarin	Ischemic stroke	60.0	78	187	430	833.0
Clinformatics®	DOACs	Warfarin	Composite	59.0	77	188	432	836.0
Clinformatics®	Rivaroxaban	Warfarin	AMI	60.0	67	177	416	850.0
Clinformatics®	Rivaroxaban	Warfarin	Ischemic stroke	60.0	65	173	410	843.0
Clinformatics®	Rivaroxaban	Warfarin	Composite	58.0	65	174	411	842.0
Optum® EHR	DOACs	Warfarin	AMI	43.0	60	73	120	213.0
Optum® EHR	DOACs	Warfarin	Ischemic stroke	45.0	60	74	120	215.0
Optum® EHR	DOACs	Warfarin	Composite	34.0	60	72	118	210.0
Optum® EHR	Rivaroxaban	Warfarin	AMI	57.0	60	63	107	179.0
Optum® EHR	Rivaroxaban	Warfarin	Ischemic stroke	60.0	60	64	107	179.0
Optum® EHR	Rivaroxaban	Warfarin	Composite	47.0	60	63	105	177.0
PharMetrics	DOACs	Warfarin	AMI	56.0	71	174	405	811.0
PharMetrics	DOACs	Warfarin	Ischemic stroke	57.0	70	172	400	801.0
PharMetrics	DOACs	Warfarin	Composite	55.0	68	171	399	800.0
PharMetrics	Rivaroxaban	Warfarin	AMI	56.0	60	153	372	793.0
PharMetrics	Rivaroxaban	Warfarin	Ischemic stroke	56.0	60	152	370	788.0
PharMetrics	Rivaroxaban	Warfarin	Composite	54.0	60	152	368	785.9
MDCR	DOACs	Warfarin	AMI	44.0	70	187	454	865.0
MDCR	DOACs	Warfarin	Ischemic stroke	43.0	67	183	446	853.0
MDCR	DOACs	Warfarin	Composite	42.0	67	184	449	857.0
MDCR	Rivaroxaban	Warfarin	AMI	43.0	60	177	431	847.0
MDCR	Rivaroxaban	Warfarin	Ischemic stroke	42.7	60	173	424	841.0
MDCR	Rivaroxaban	Warfarin	Composite	42.0	60	173	425	839.0

1010

1011

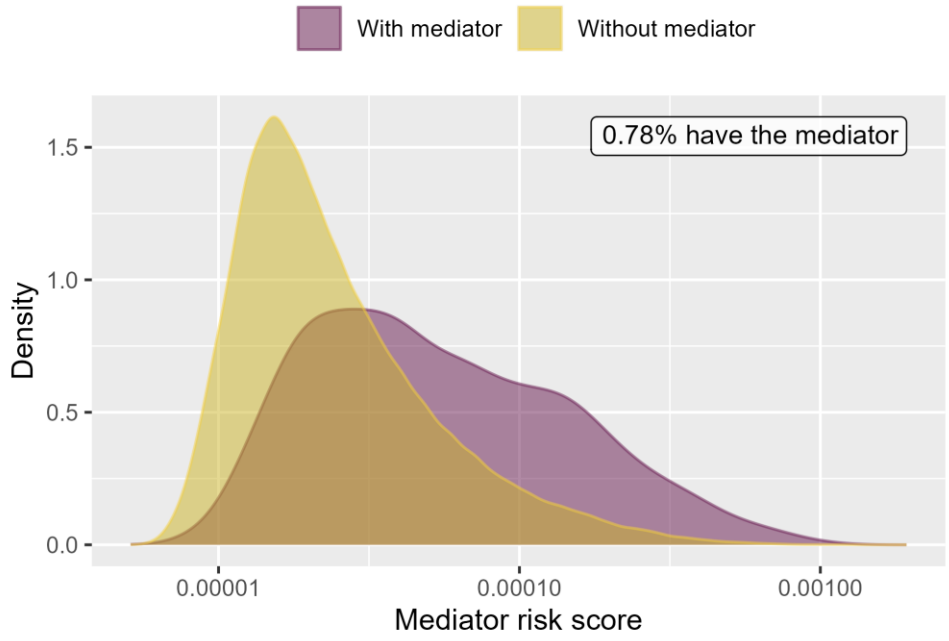
18.3.3. Follow-up time in the comparator cohort

Table 3.3: Overview of follow-up time in days in the comparator cohort per database, comparison, and outcome.

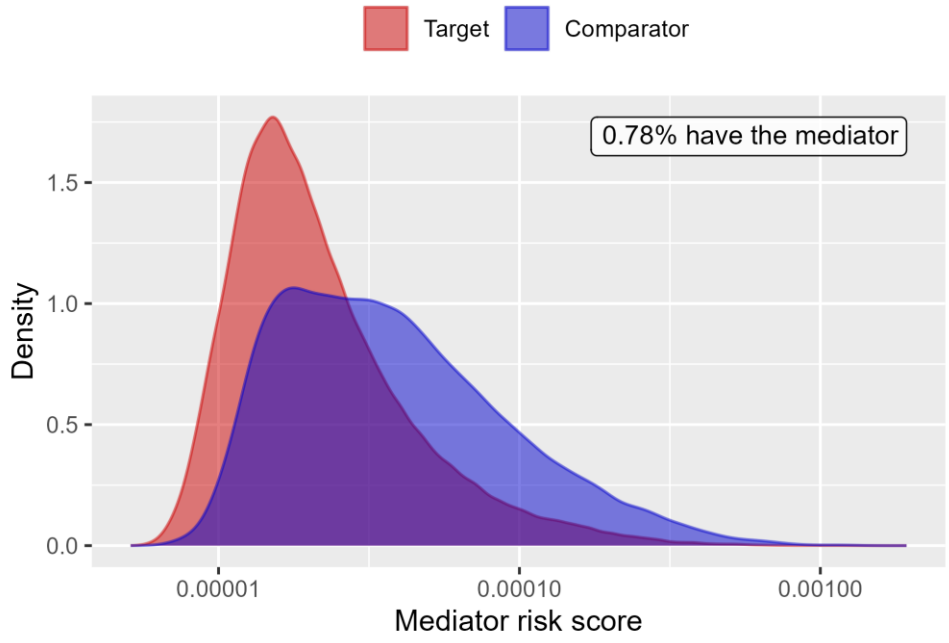
Database	Target	Comparator	Outcome	p10	p25	Median	p75	p90
CCAE	DOACs	Warfarin	AMI	40	60	120	250	493.0
CCAE	DOACs	Warfarin	Ischemic stroke	41	60	120	246	483.0
CCAE	DOACs	Warfarin	Composite	40	60	120	243	481.0
CCAE	Rivaroxaban	Warfarin	AMI	47	60	122	251	492.0
CCAE	Rivaroxaban	Warfarin	Ischemic stroke	48	60	121	247	482.0
CCAE	Rivaroxaban	Warfarin	Composite	45	60	120	244	479.0
Clinformatics®	DOACs	Warfarin	AMI	47	70	152	356	713.0
Clinformatics®	DOACs	Warfarin	Ischemic stroke	46	68	149	347	701.0
Clinformatics®	DOACs	Warfarin	Composite	45	67	149	350	705.0
Clinformatics®	Rivaroxaban	Warfarin	AMI	57	75	154	357	711.0
Clinformatics®	Rivaroxaban	Warfarin	Ischemic stroke	57	74	151	349	697.0
Clinformatics®	Rivaroxaban	Warfarin	Composite	54	73	151	351	702.0
Optum® EHR	DOACs	Warfarin	AMI	41	89	122	201	397.0
Optum® EHR	DOACs	Warfarin	Ischemic stroke	42	91	122	202	399.0
Optum® EHR	DOACs	Warfarin	Composite	27	75	121	196	389.0
Optum® EHR	Rivaroxaban	Warfarin	AMI	60	105	123	205	408.0
Optum® EHR	Rivaroxaban	Warfarin	Ischemic stroke	60	108	123	207	411.0
Optum® EHR	Rivaroxaban	Warfarin	Composite	40	87	122	201	400.0
PharMetrics	DOACs	Warfarin	AMI	40	63	135	306	622.4
PharMetrics	DOACs	Warfarin	Ischemic stroke	40	62	134	302	614.0
PharMetrics	DOACs	Warfarin	Composite	38	61	133	302	618.0
PharMetrics	Rivaroxaban	Warfarin	AMI	50	70	138	306	622.0
PharMetrics	Rivaroxaban	Warfarin	Ischemic stroke	50	69	137	302	613.0
PharMetrics	Rivaroxaban	Warfarin	Composite	48	68	136	303	617.0
MDCR	DOACs	Warfarin	AMI	42	60	137	299	577.8
MDCR	DOACs	Warfarin	Ischemic stroke	43	60	134	291	569.0
MDCR	DOACs	Warfarin	Composite	40	60	133	291	568.0
MDCR	Rivaroxaban	Warfarin	AMI	45	60	136	297	574.2
MDCR	Rivaroxaban	Warfarin	Ischemic stroke	45	60	133	290	566.0
MDCR	Rivaroxaban	Warfarin	Composite	44	60	132	289	565.0

18.4. Mediator risk score distribution

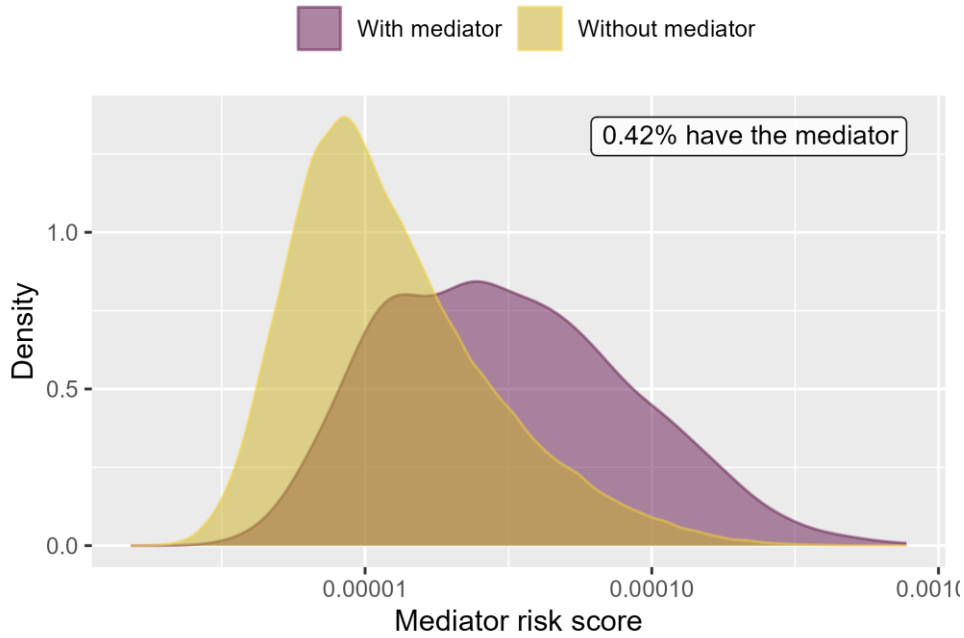
18.4.1. CCAE



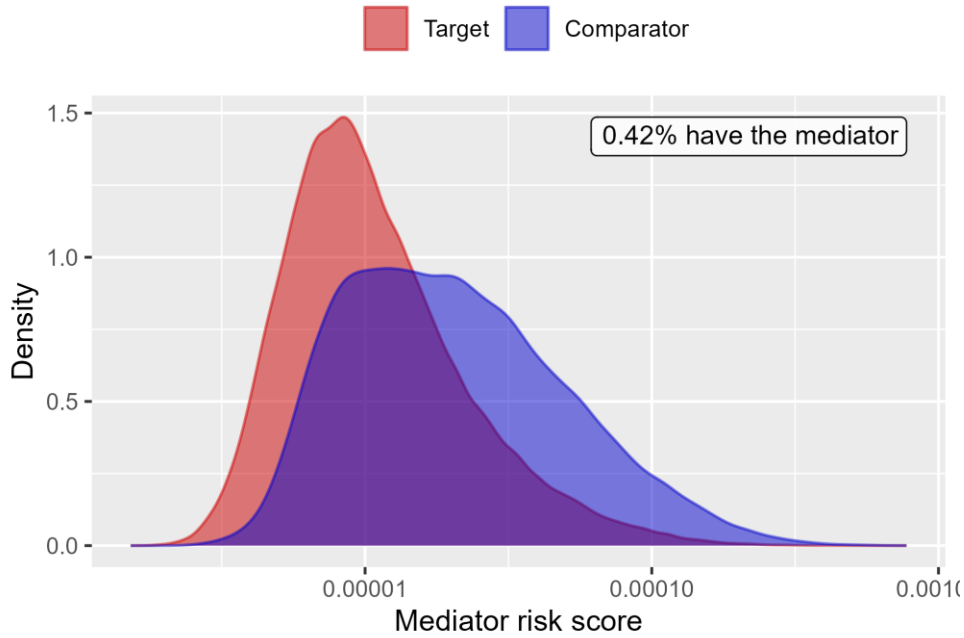
Mediator risk score by mediator status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in CCAE.



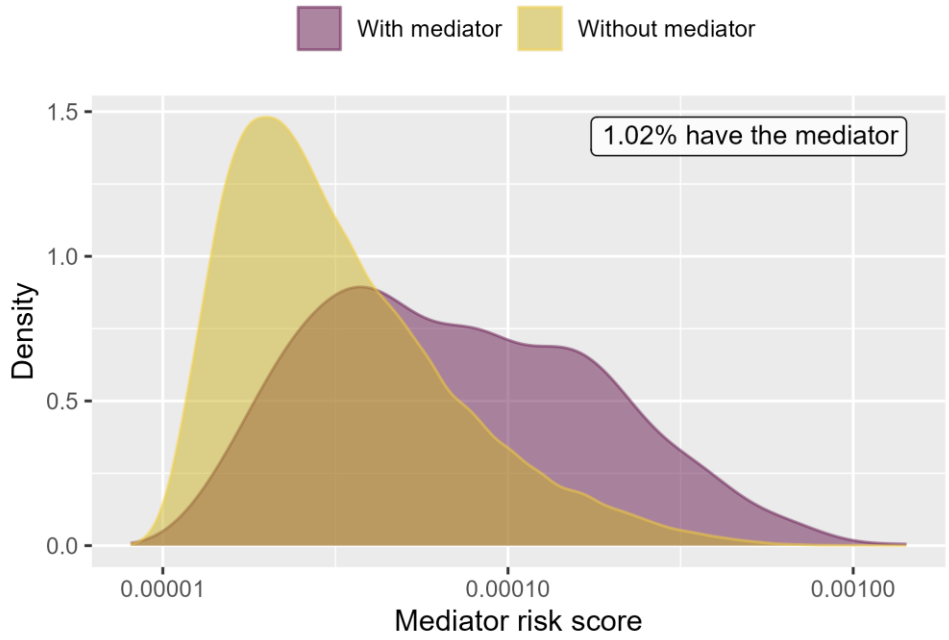
Mediator risk score by exposure status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in CCAE.



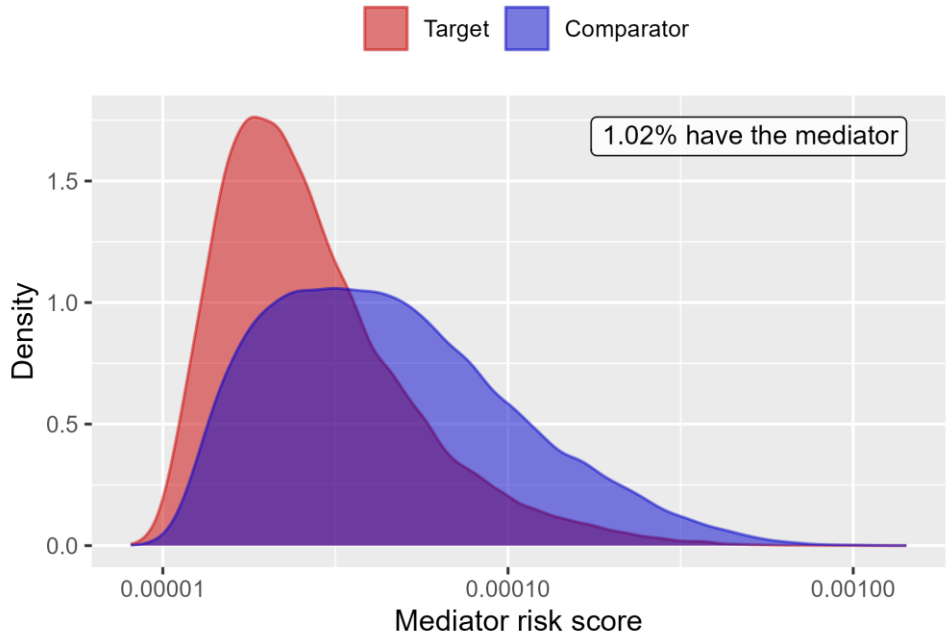
Mediator risk score by mediator status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in CCAE.



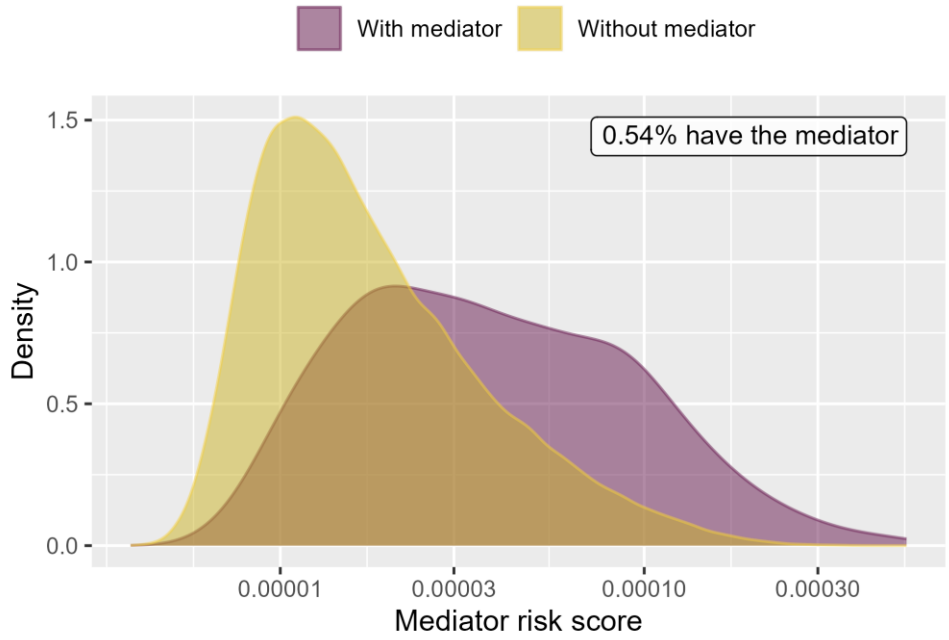
Mediator risk score by exposure status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in CCAE.



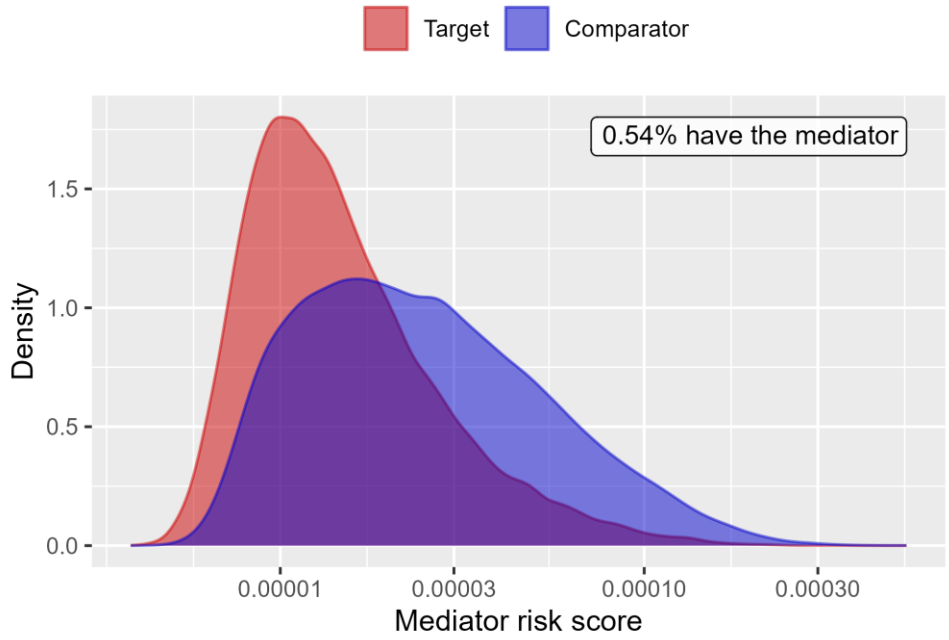
Mediator risk score by mediator status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP-ER in CCAE.



Mediator risk score by exposure status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP-ER in CCAE.

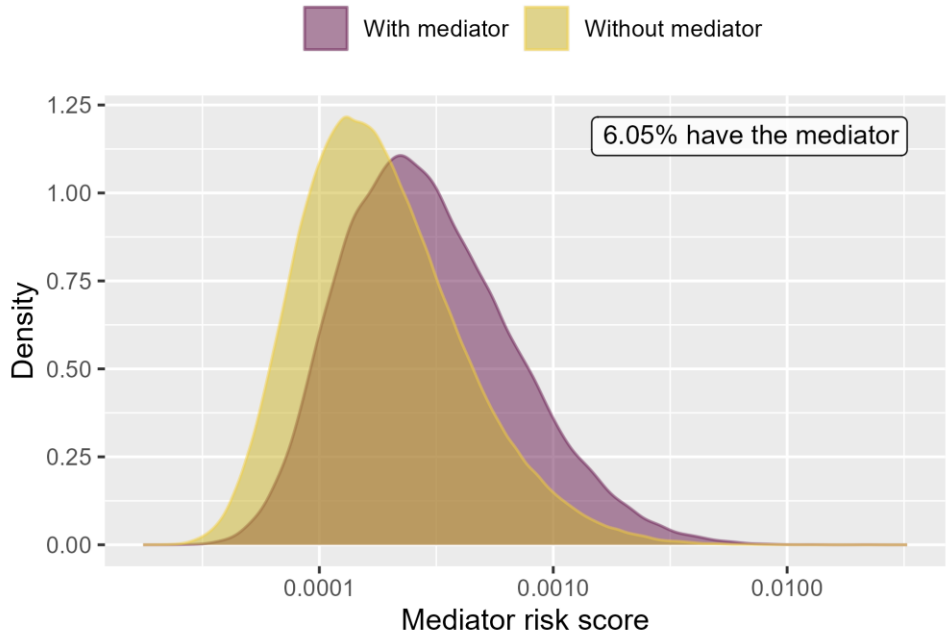


Mediator risk score by mediator status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in CCAE.

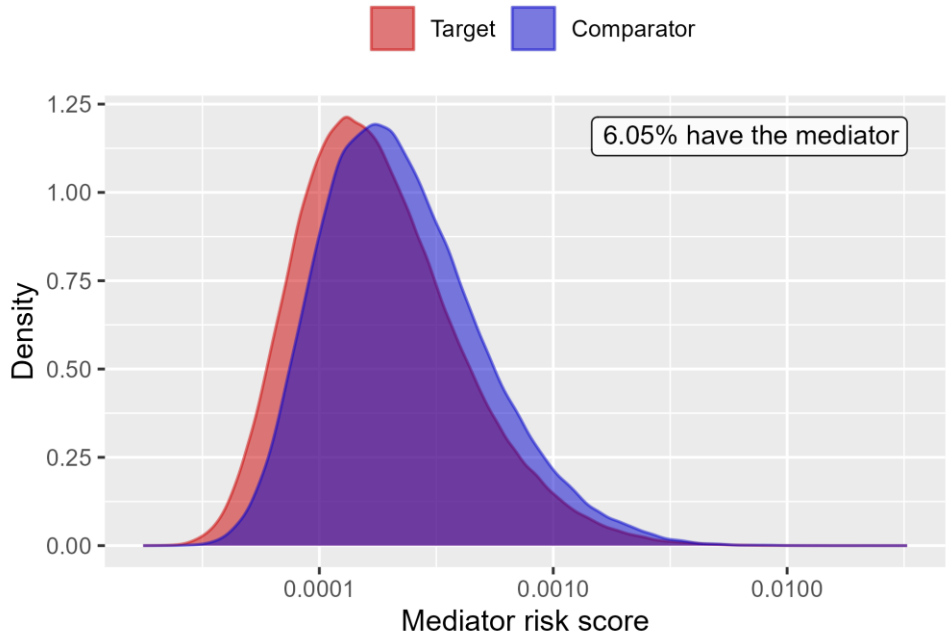


Mediator risk score by exposure status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in CCAE.

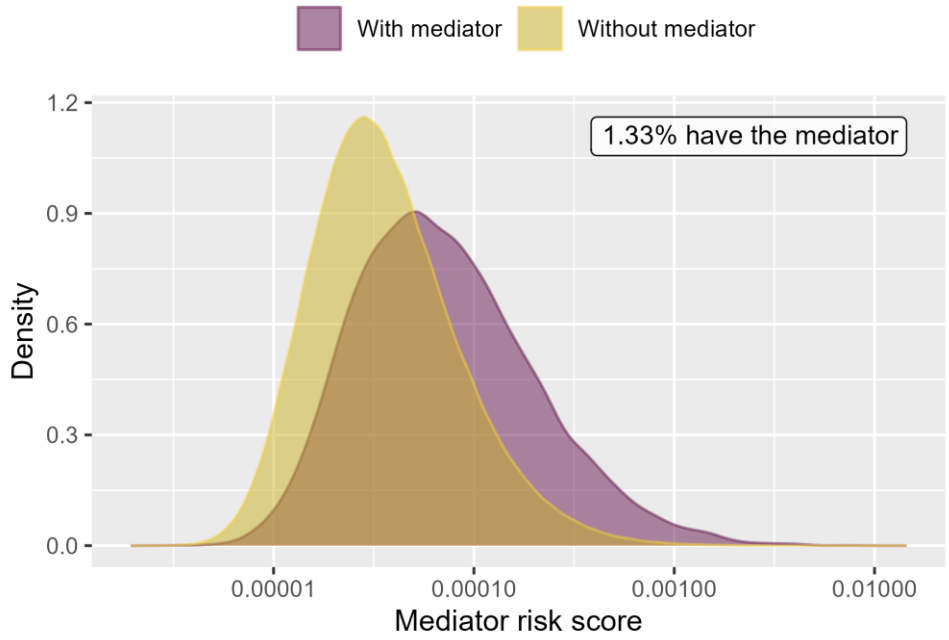
18.4.2. Clinformatics®



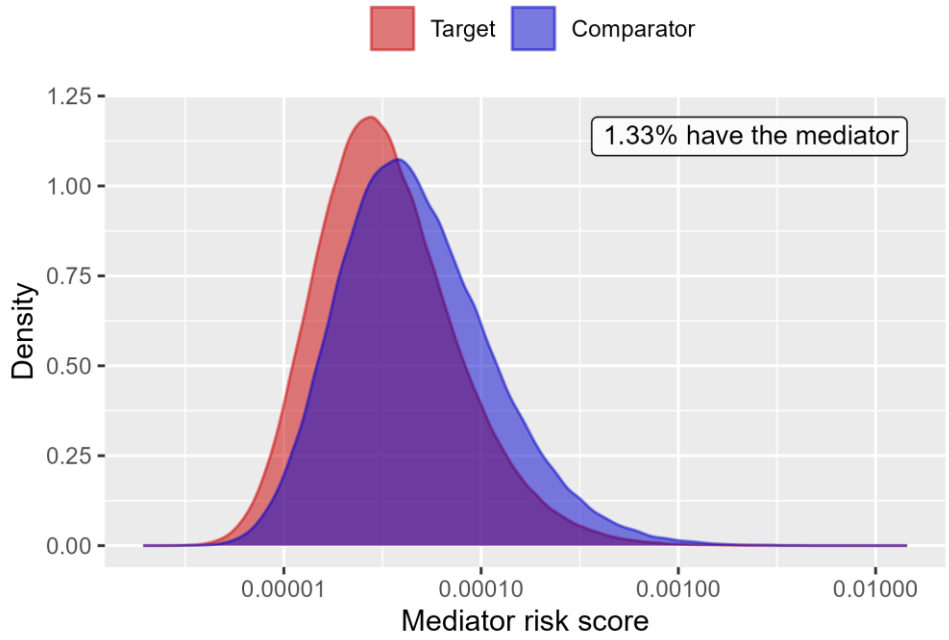
Mediator risk score by mediator status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in Clinformatics®.



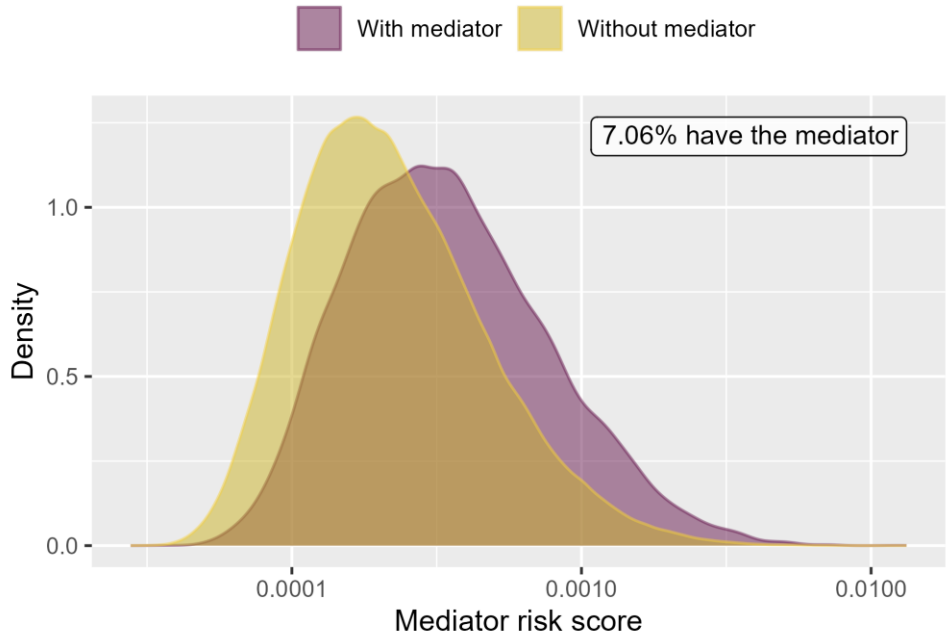
Mediator risk score by exposure status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in Clinformatics®.



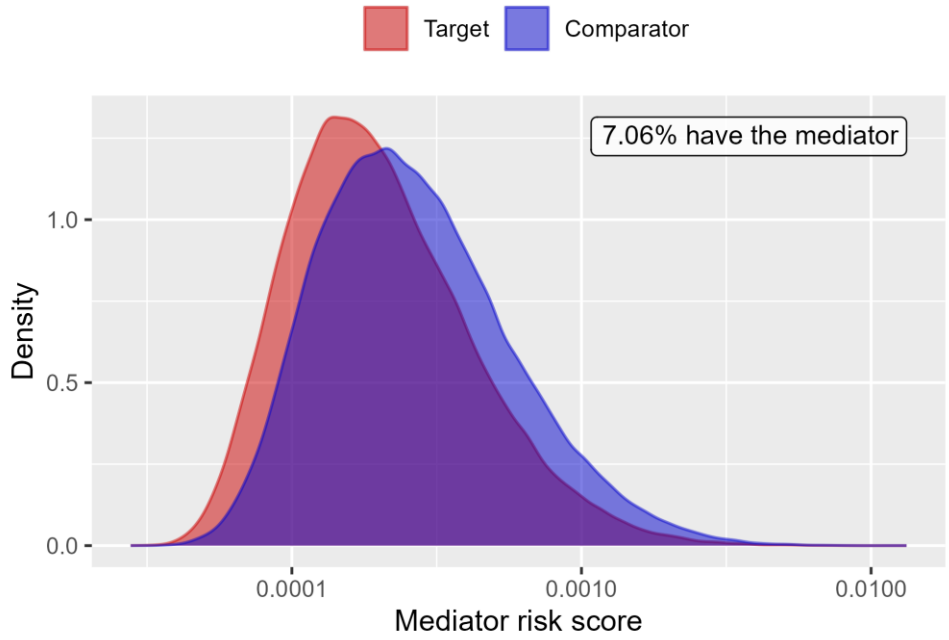
Mediator risk score by mediator status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in Clinformatics®.



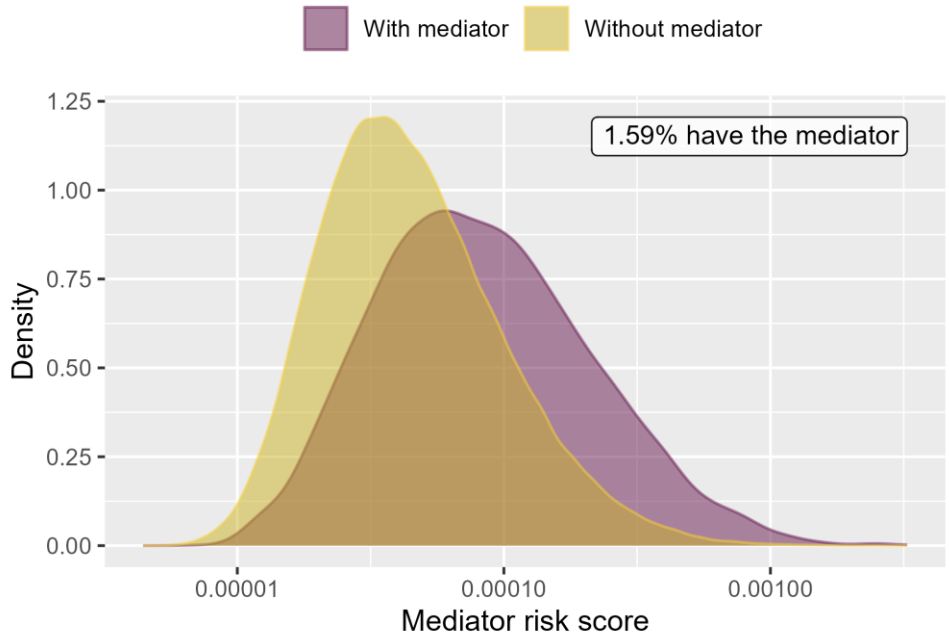
Mediator risk score by exposure status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in Clinformatics®.



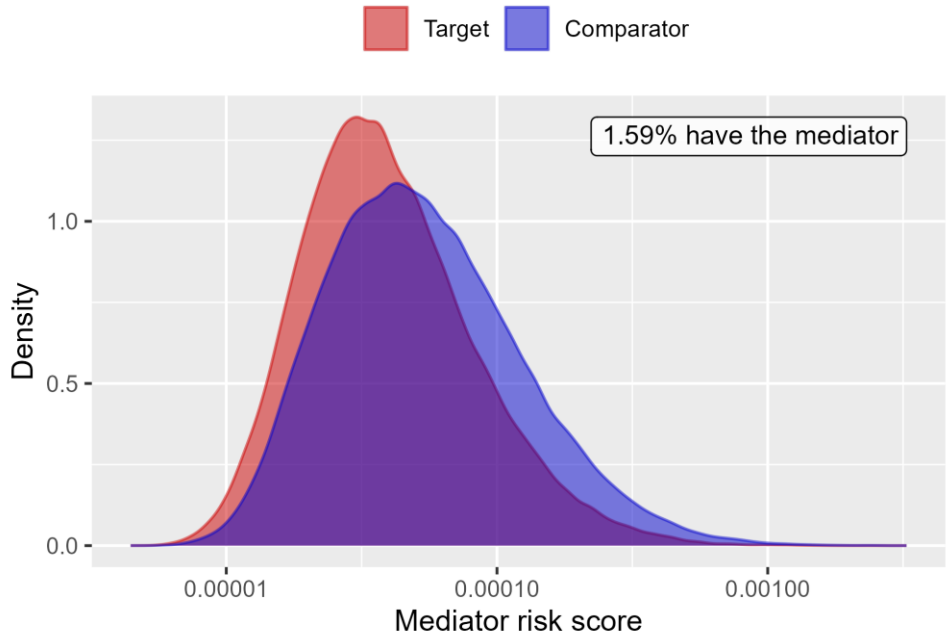
Mediator risk score by mediator status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP-ER in Clinformatics®.



Mediator risk score by exposure status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP-ER in Clinformatics®.

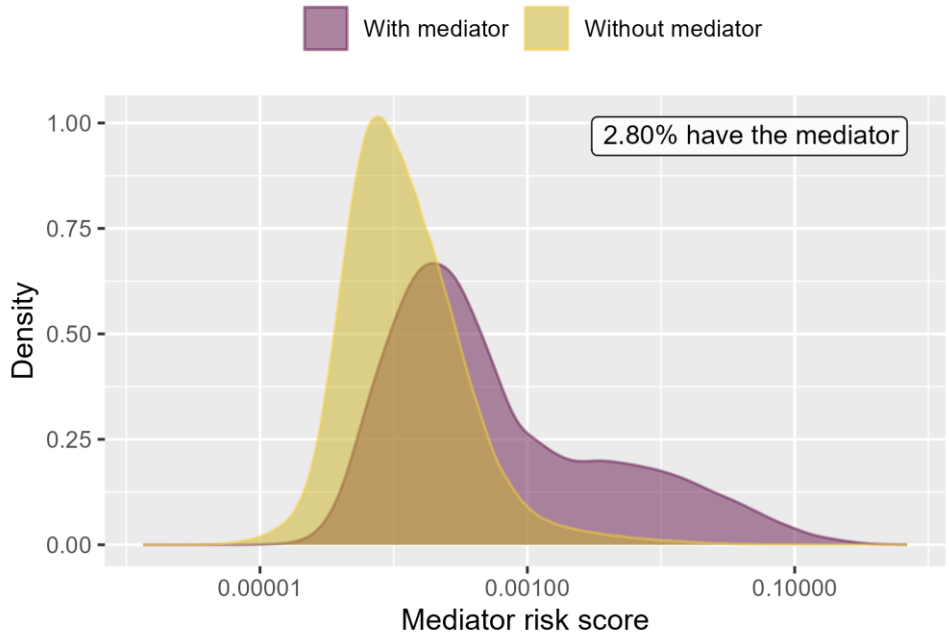


Mediator risk score by mediator status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in Clinformatics®.

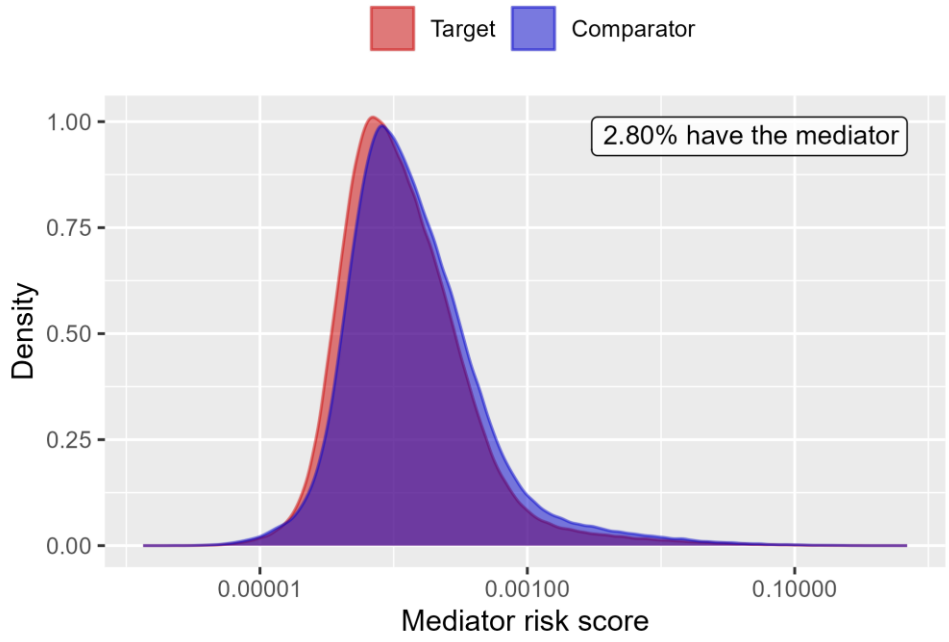


Mediator risk score by exposure status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in Clinformatics®.

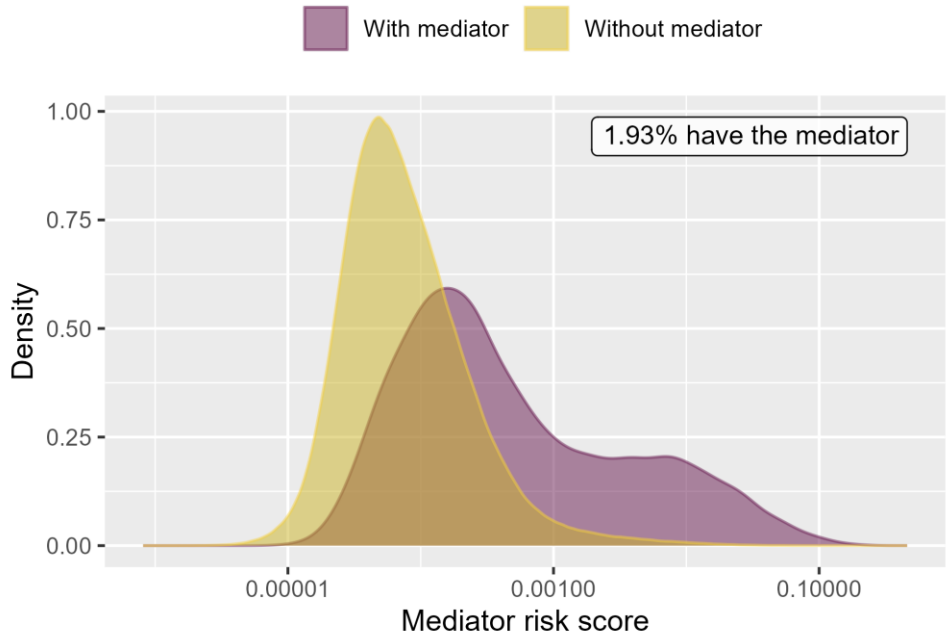
18.4.3. Optum® EHR



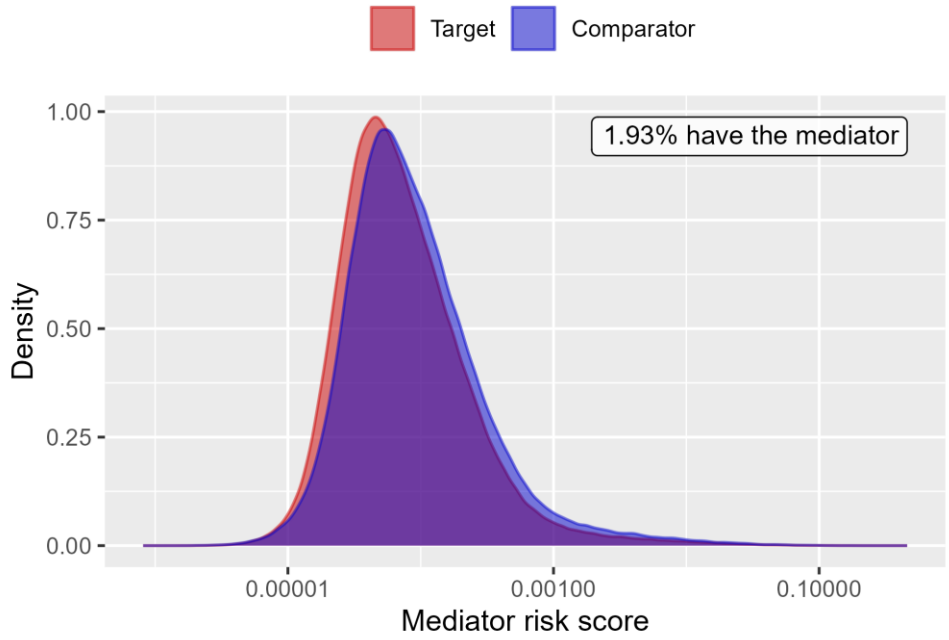
Mediator risk score by mediator status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in Optum® EHR.



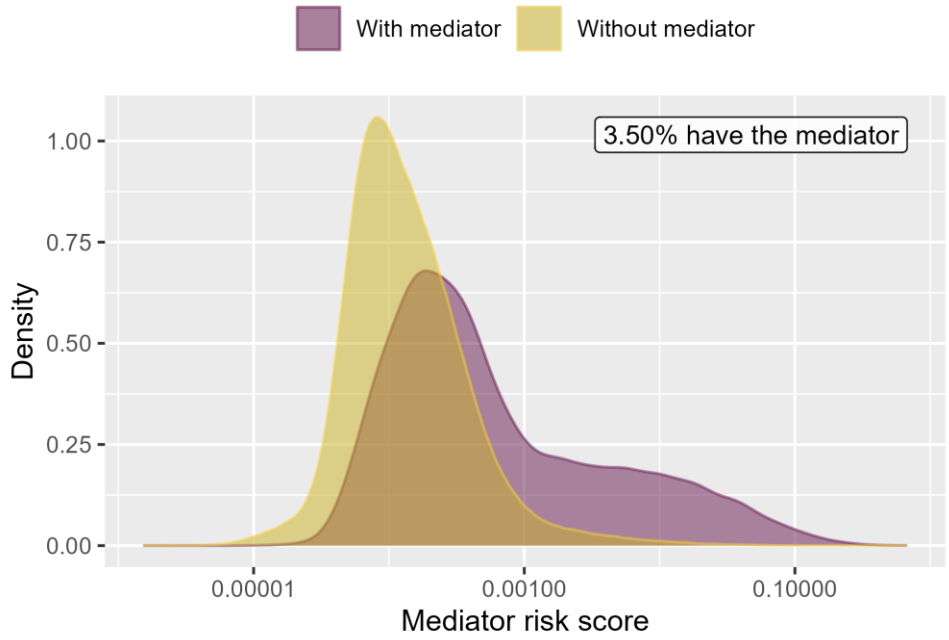
Mediator risk score by exposure status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in Optum® EHR.



Mediator risk score by mediator status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in Optum® EHR.

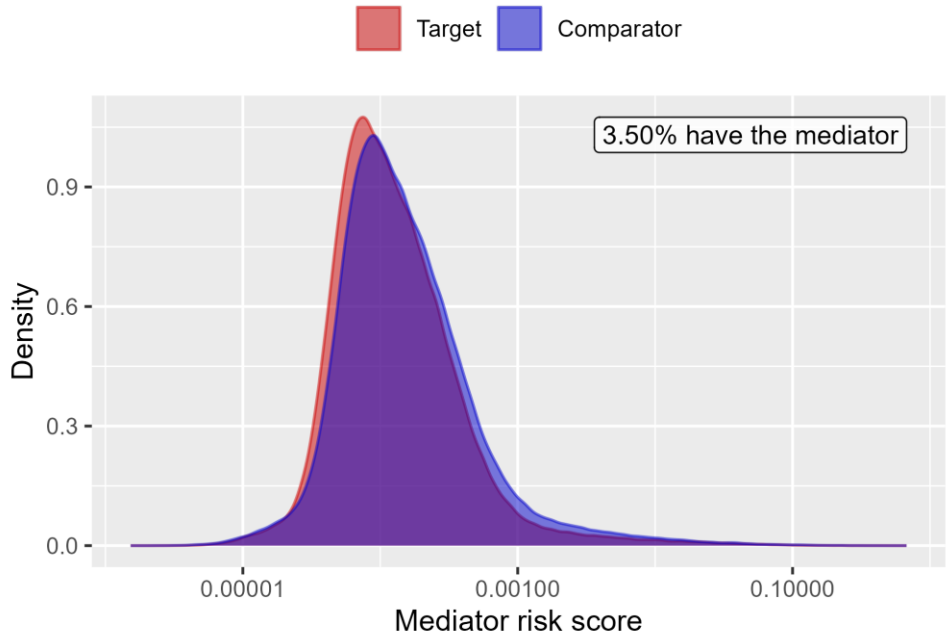


Mediator risk score by exposure status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in Optum® EHR.



1081

1082 *Mediator risk score by mediator status when comparing Rivaroxaban to Warfarin using*
1083 *mediator Extracranial Major bleeding IP-ER in Optum® EHR.*



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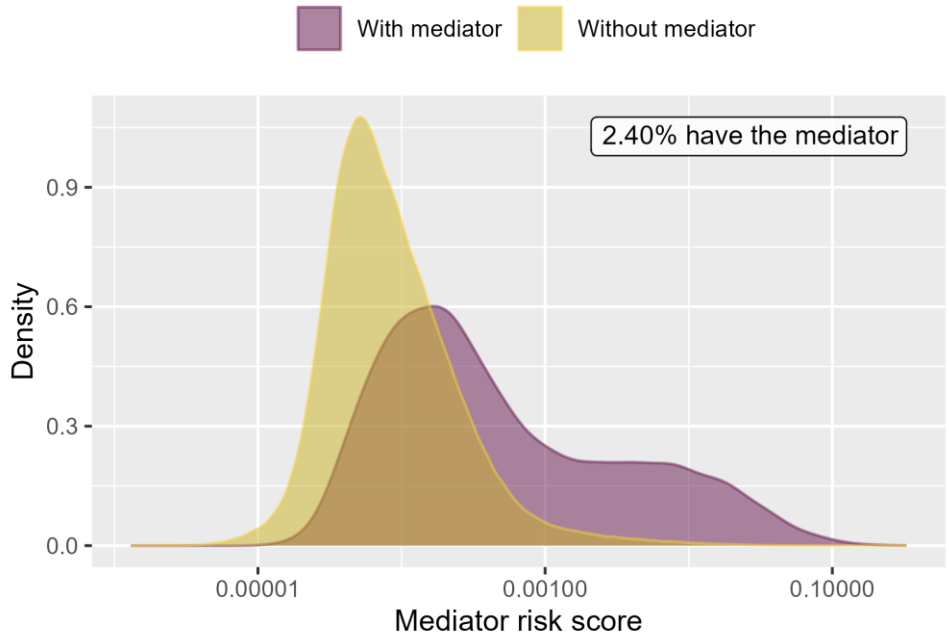
1086 *mediator Extracranial Major bleeding IP-ER in Optum® EHR.*



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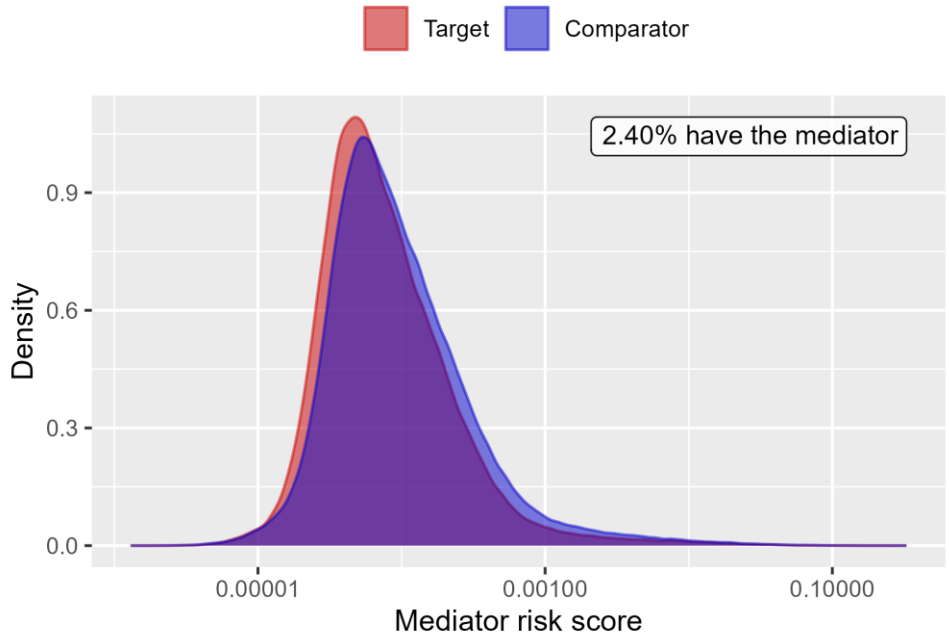

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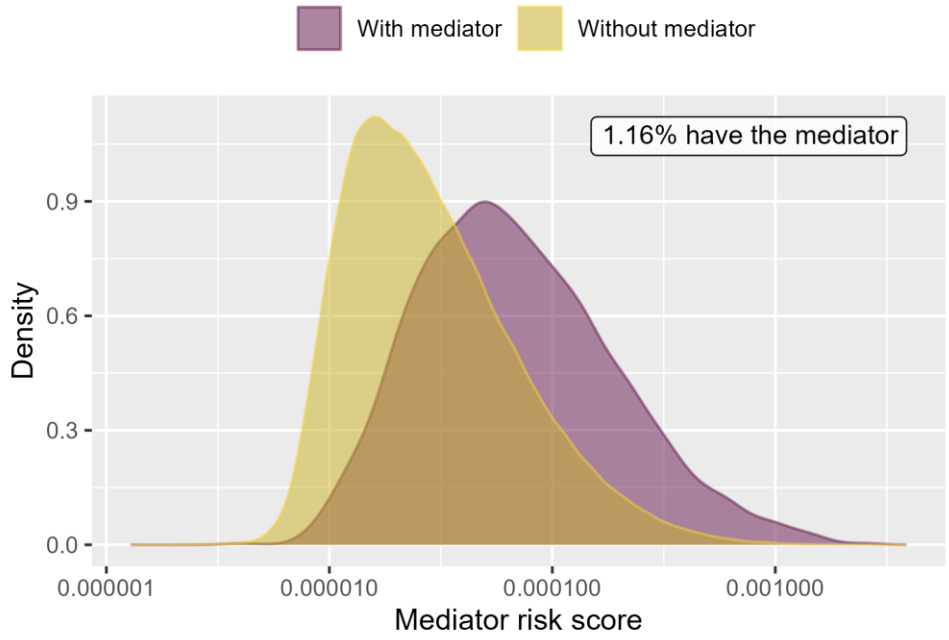
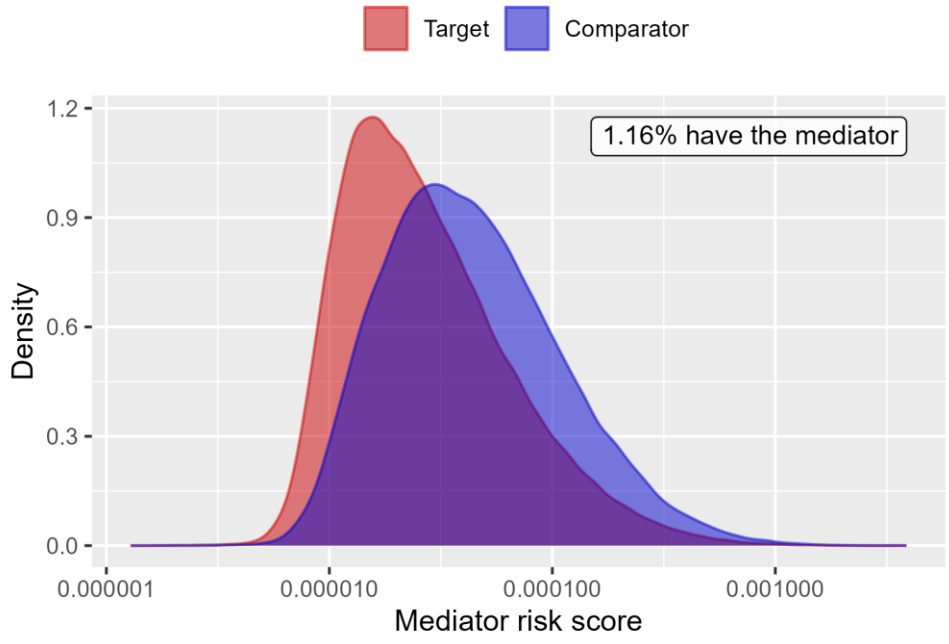
1091 *Mediator risk score by exposure status when comparing Rivaroxaban to Warfarin using*
1092 *mediator Extracranial Major bleeding IP in Optum® EHR.*

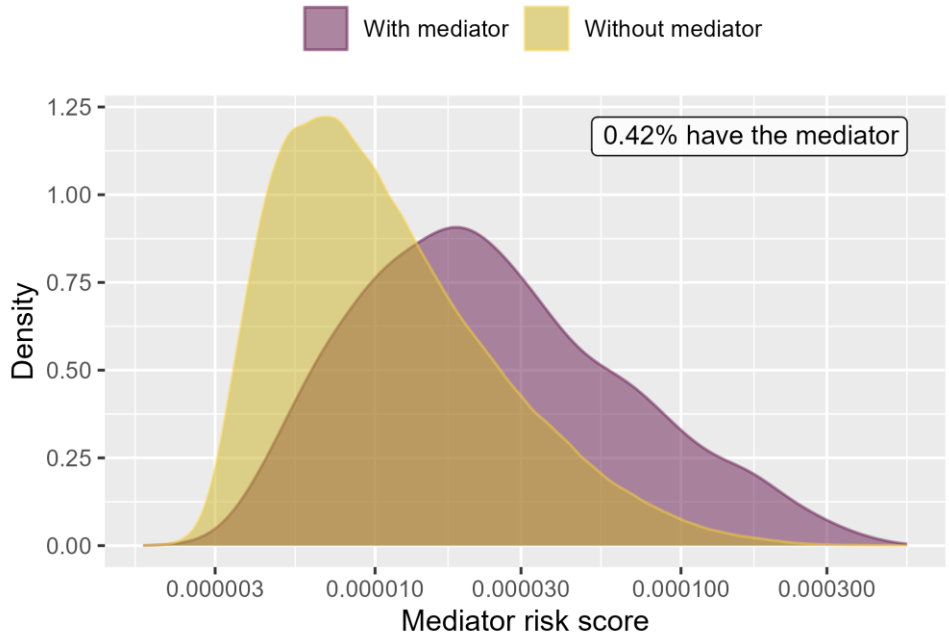
18.4.4. PharMetrics



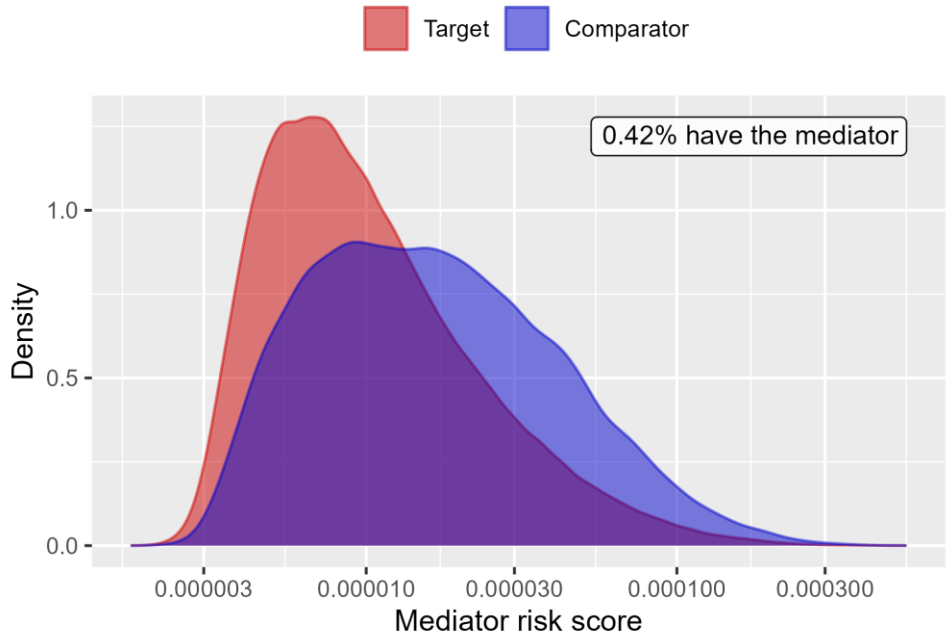
Mediator risk score by mediator status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in PharMetrics.



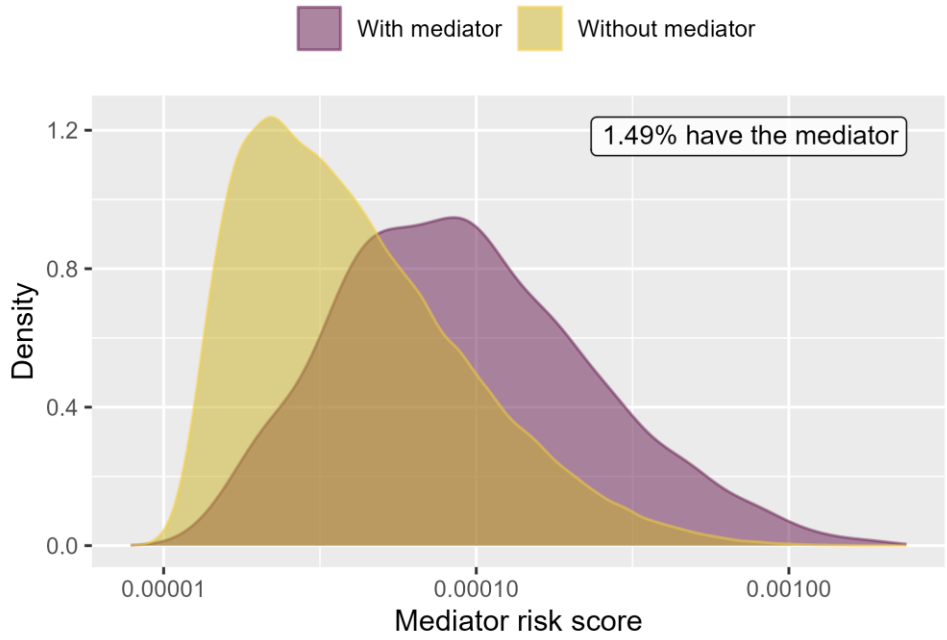
Mediator risk score by exposure status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in PharMetrics.



Mediator risk score by mediator status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in PharMetrics.



Mediator risk score by exposure status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in PharMetrics.



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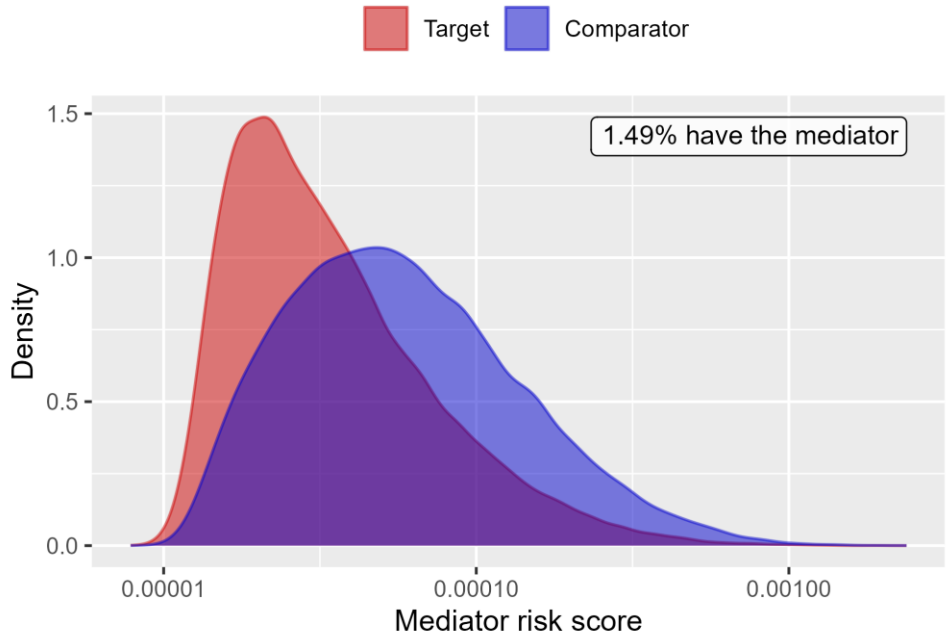
1107 *Mediator risk score by mediator status when comparing Rivaroxaban to Warfarin using*
1108 *mediator Extracranial Major bleeding IP-ER in PharMetrics.*



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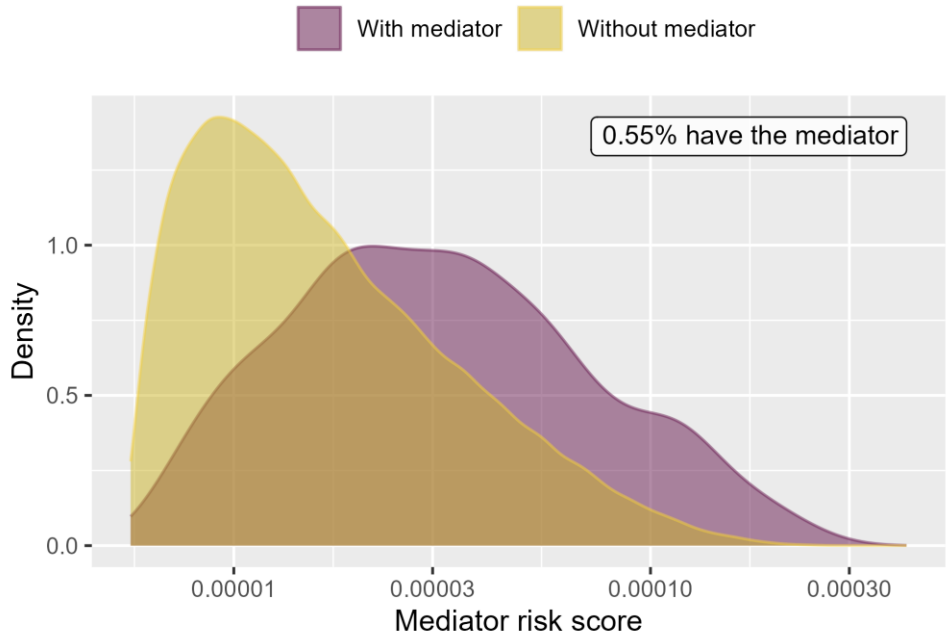
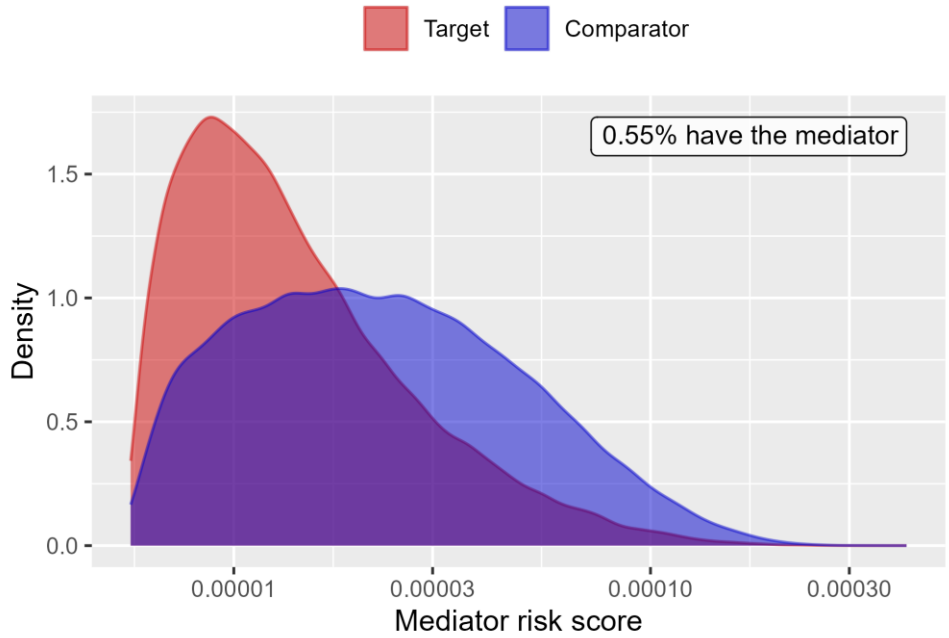
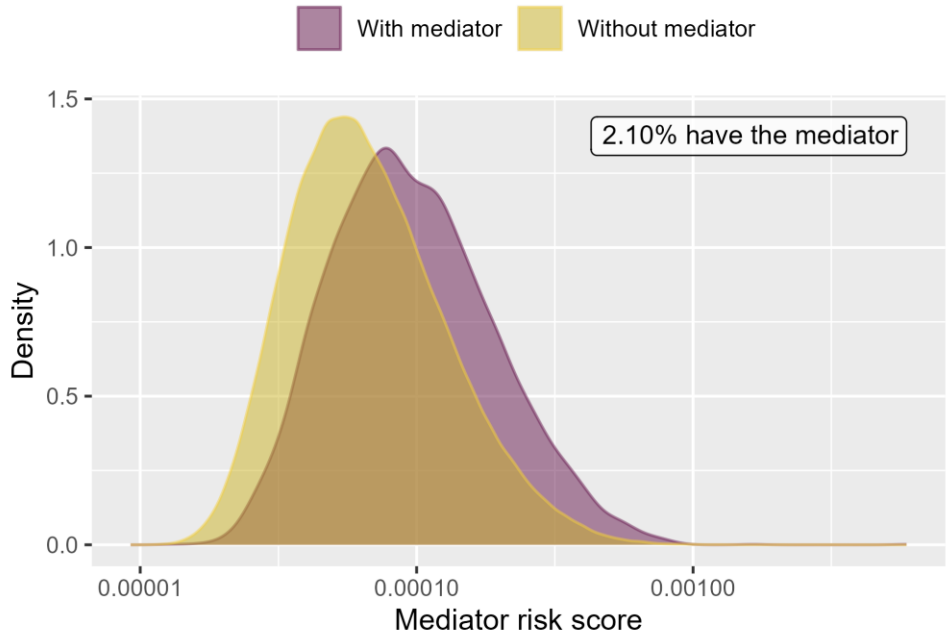


Mediator risk score by mediator status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in PharMetrics.

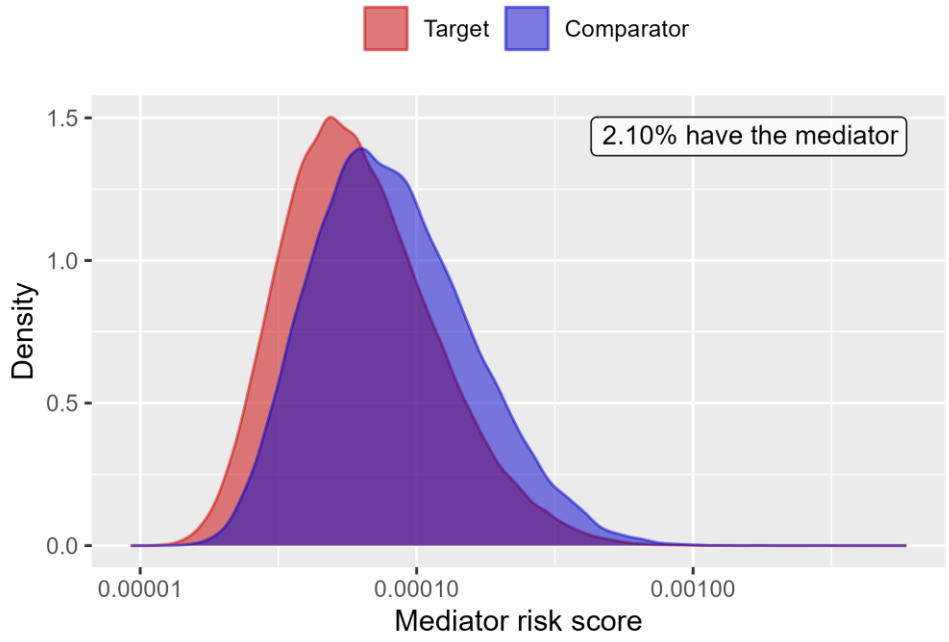


Mediator risk score by exposure status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in PharMetrics.

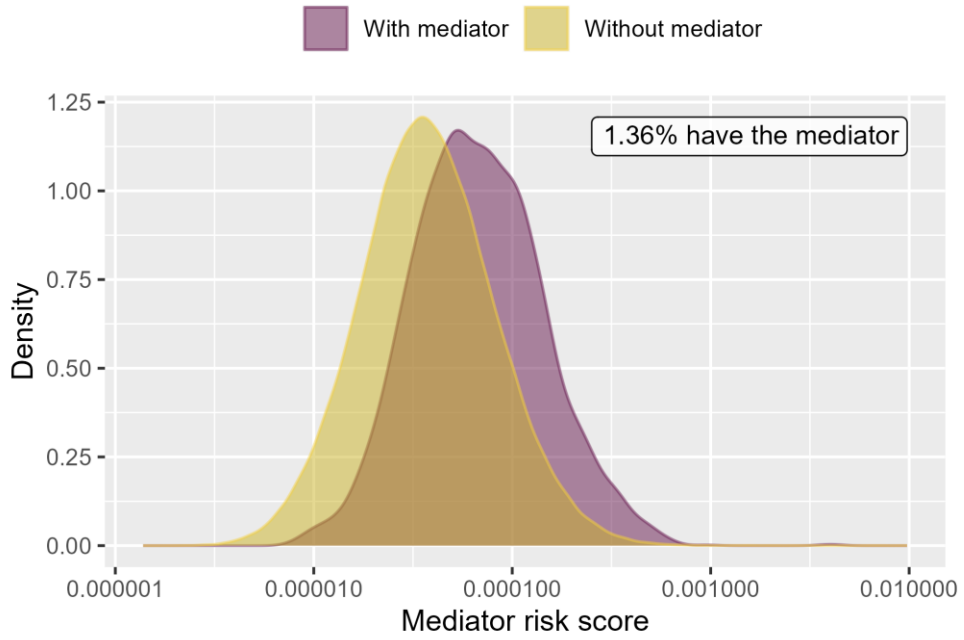
18.4.5. MDCR



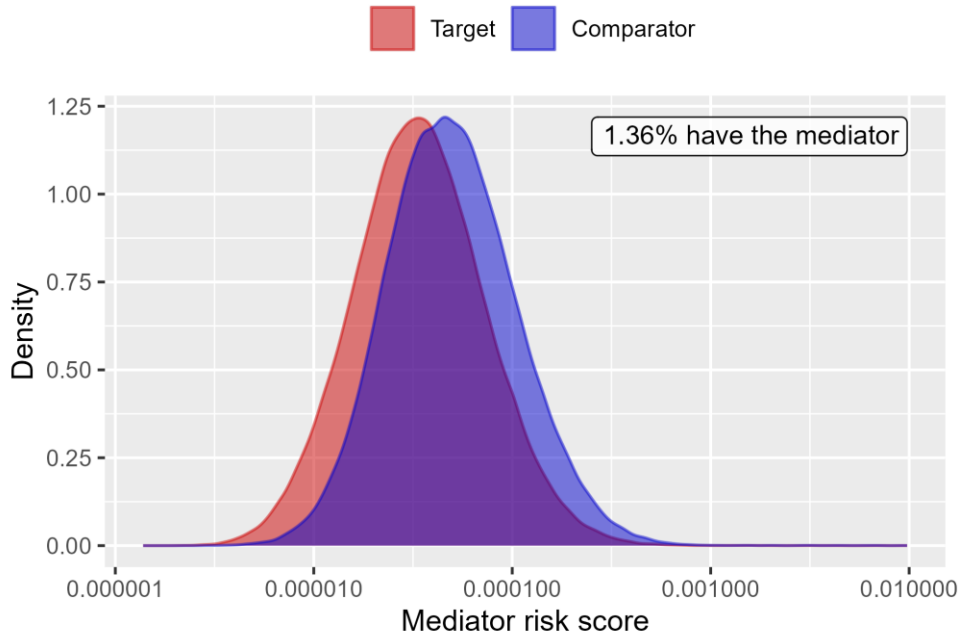
Mediator risk score by mediator status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in MDCR.



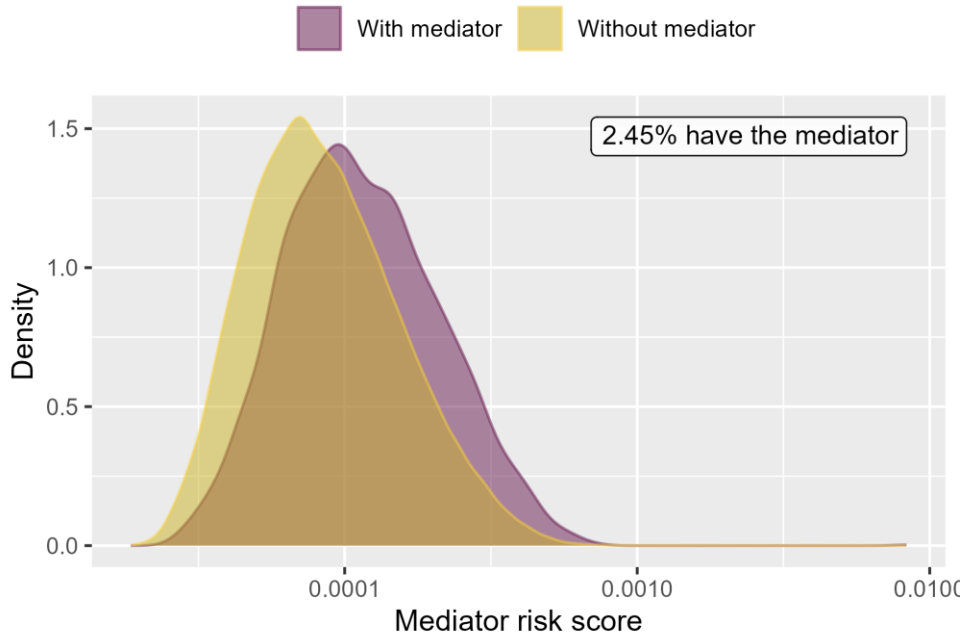
Mediator risk score by exposure status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in MDCR.



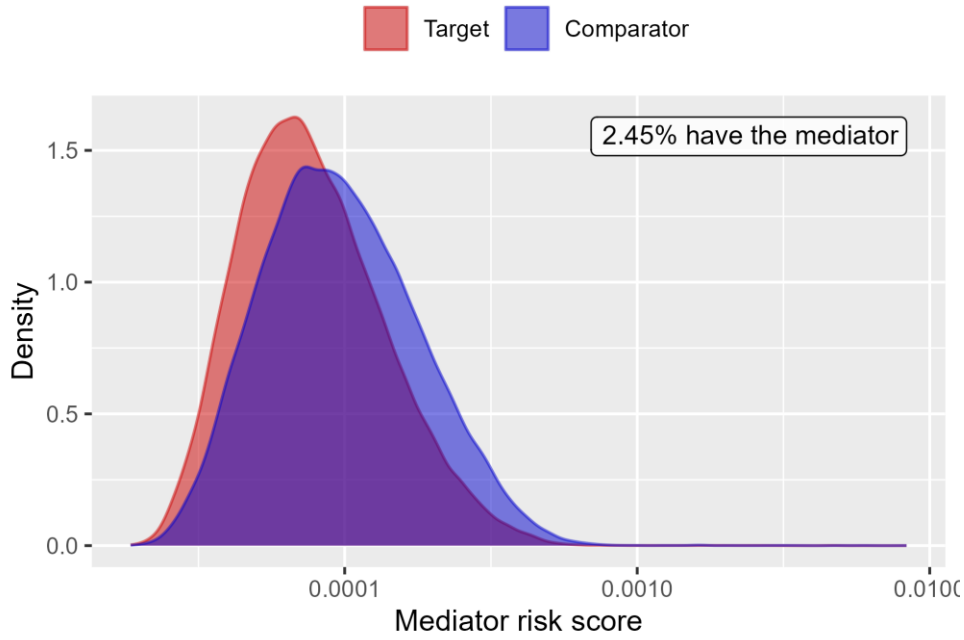
Mediator risk score by mediator status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in MDCR.



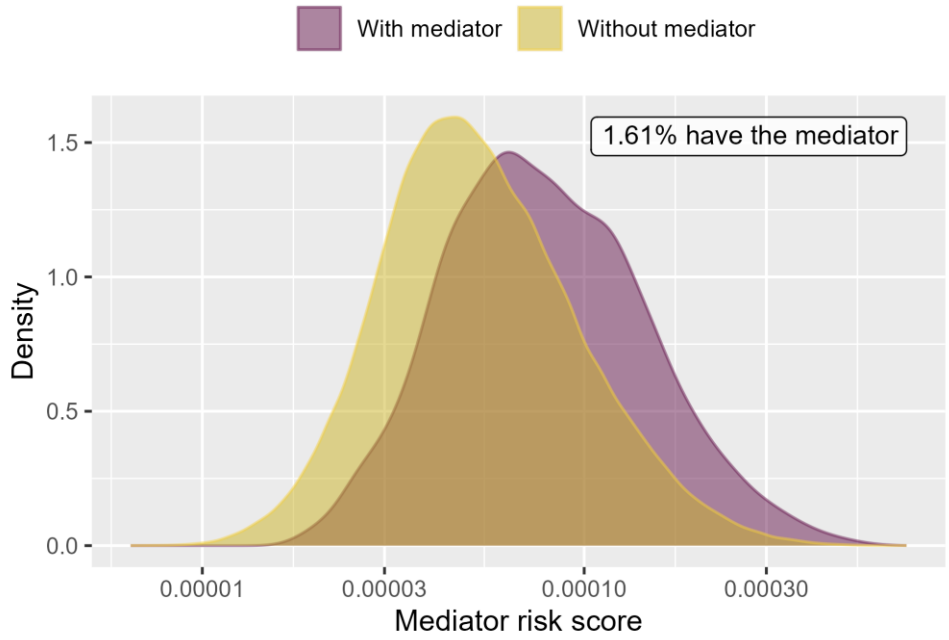
Mediator risk score by exposure status when comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in MDCR.



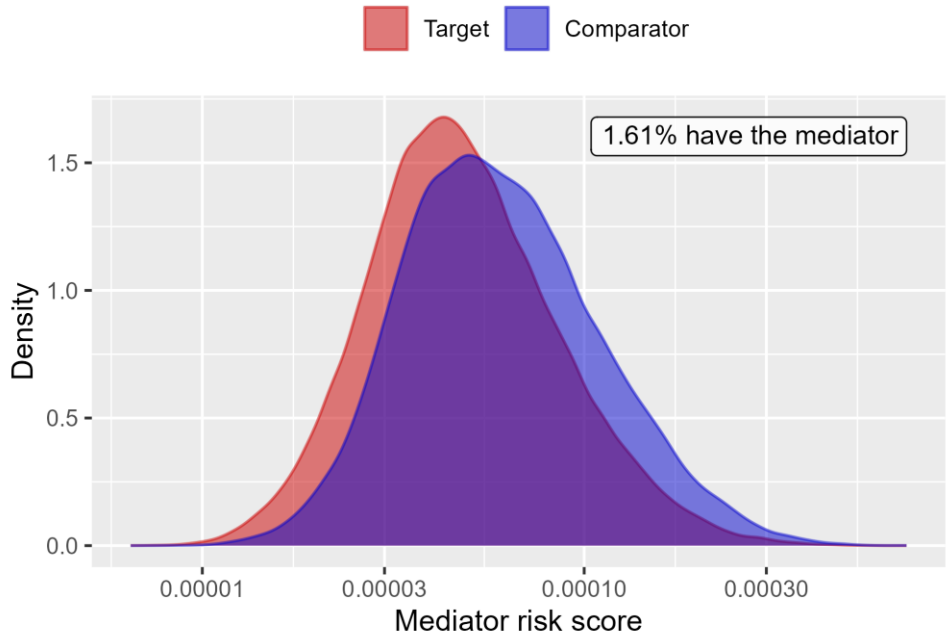
Mediator risk score by mediator status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP-ER in MDCR.



Mediator risk score by exposure status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP-ER in MDCR.



Mediator risk score by mediator status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in MDCR.



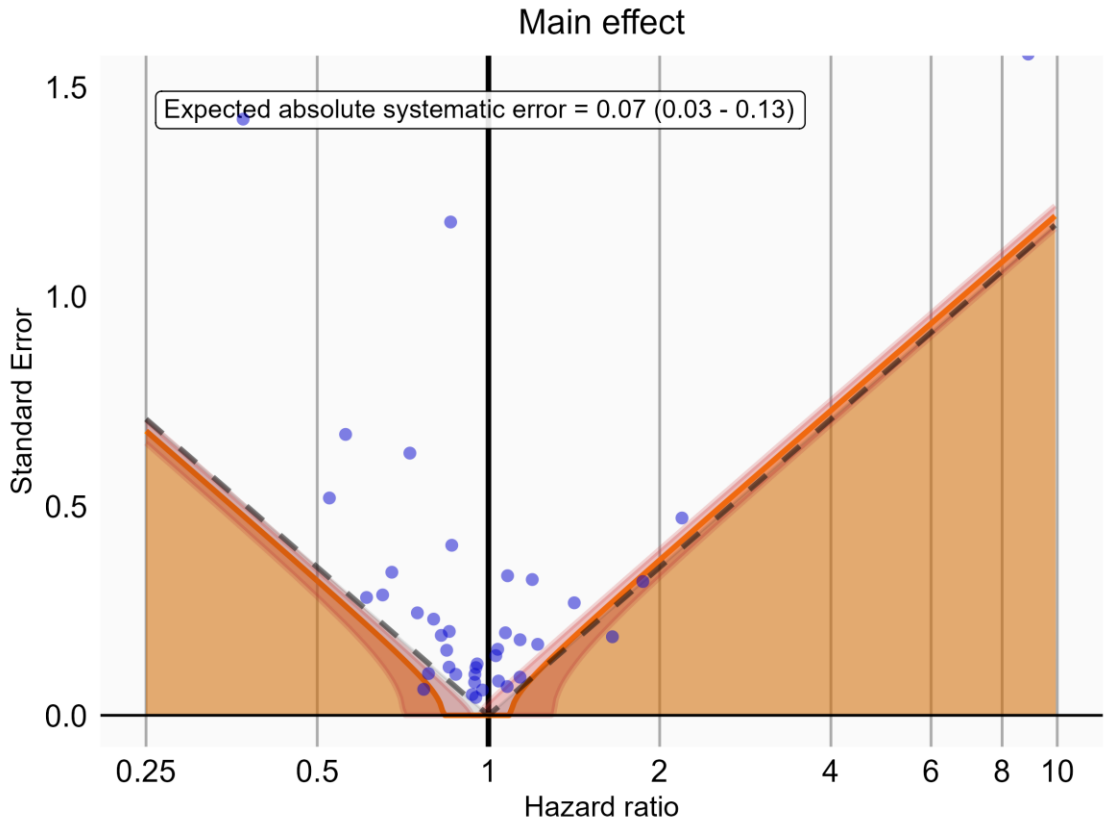
Mediator risk score by exposure status when comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in MDCR.

18.5. Negative controls

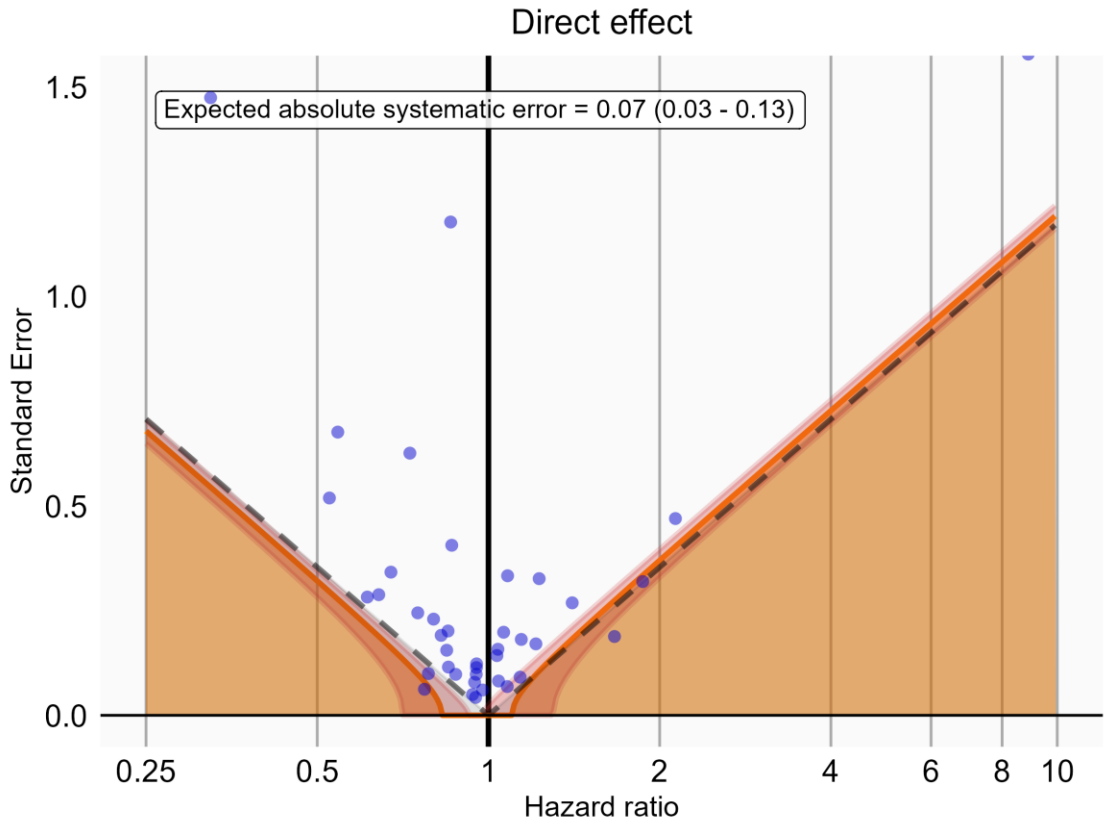
Table 5.1: Expected Absolute Systematic Error (EASE) per database, comparison, and mediator.

Database	Target	Comparator	Mediator	EASE main	EASE direct	EASE indirect
CCAE	DOACs	Warfarin	Extracranial Major bleeding IP-ER	0.07	0.07	0.00
CCAE	DOACs	Warfarin	Extracranial Major bleeding IP	0.07	0.07	0.00
CCAE	Rivaroxaban	Warfarin	Extracranial Major bleeding IP-ER	0.08	0.08	0.01
CCAE	Rivaroxaban	Warfarin	Extracranial Major bleeding IP	0.08	0.08	0.00
Clinformatics®	DOACs	Warfarin	Extracranial Major bleeding IP-ER	0.09	0.09	0.00
Clinformatics®	DOACs	Warfarin	Extracranial Major bleeding IP	0.09	0.09	0.00
Clinformatics®	Rivaroxaban	Warfarin	Extracranial Major bleeding IP-ER	0.06	0.06	0.00
Clinformatics®	Rivaroxaban	Warfarin	Extracranial Major bleeding IP	0.07	0.07	0.00
Optum® EHR	DOACs	Warfarin	Extracranial Major bleeding IP-ER	0.04	0.04	0.00
Optum® EHR	DOACs	Warfarin	Extracranial Major bleeding IP	0.04	0.04	0.00
Optum® EHR	Rivaroxaban	Warfarin	Extracranial Major bleeding IP-ER	0.05	0.05	0.00
Optum® EHR	Rivaroxaban	Warfarin	Extracranial Major bleeding IP	0.05	0.05	0.00
PharMetrics	DOACs	Warfarin	Extracranial Major bleeding IP-ER	0.02	0.02	0.00
PharMetrics	DOACs	Warfarin	Extracranial Major bleeding IP	0.02	0.02	0.00
PharMetrics	Rivaroxaban	Warfarin	Extracranial Major bleeding IP-ER	0.03	0.03	0.00
PharMetrics	Rivaroxaban	Warfarin	Extracranial Major bleeding IP	0.03	0.03	0.00
MDCR	DOACs	Warfarin	Extracranial Major bleeding IP-ER	0.03	0.03	0.00
MDCR	DOACs	Warfarin	Extracranial Major bleeding IP	0.03	0.03	0.00
MDCR	Rivaroxaban	Warfarin	Extracranial Major bleeding IP-ER	0.04	0.05	0.00
MDCR	Rivaroxaban	Warfarin	Extracranial Major bleeding IP	0.05	0.04	0.00

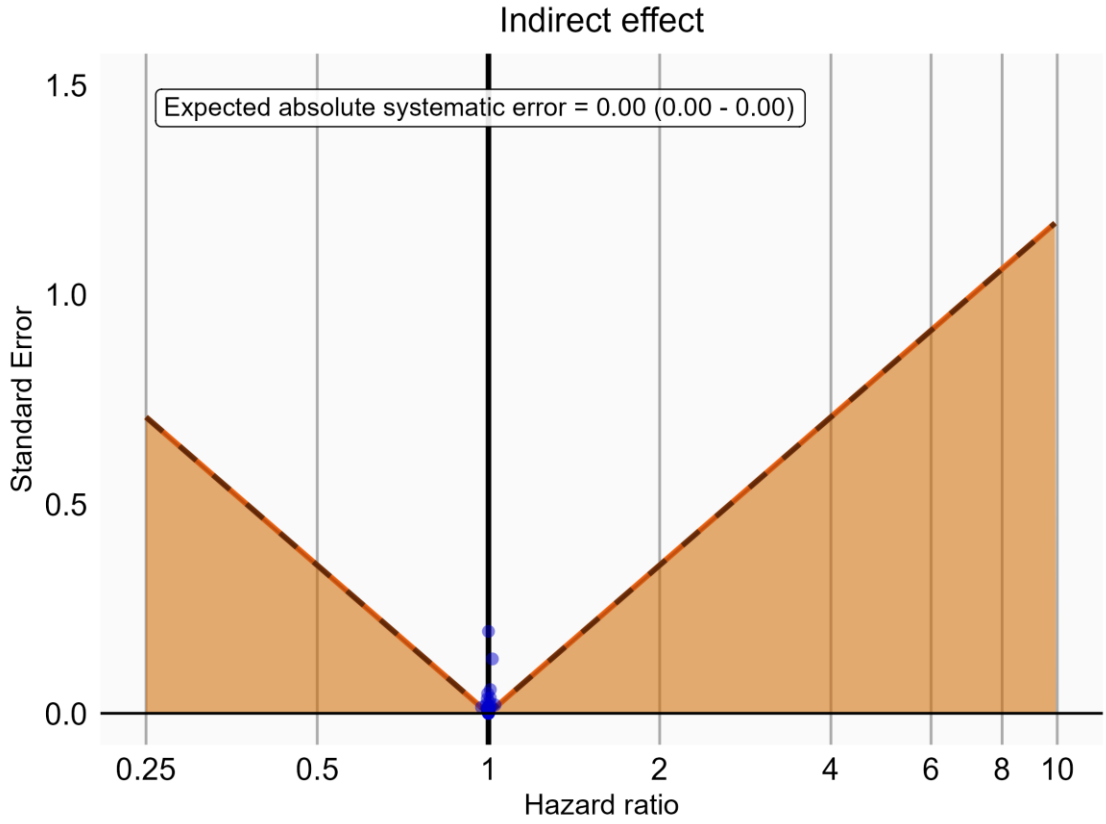
18.5.1. CCAE



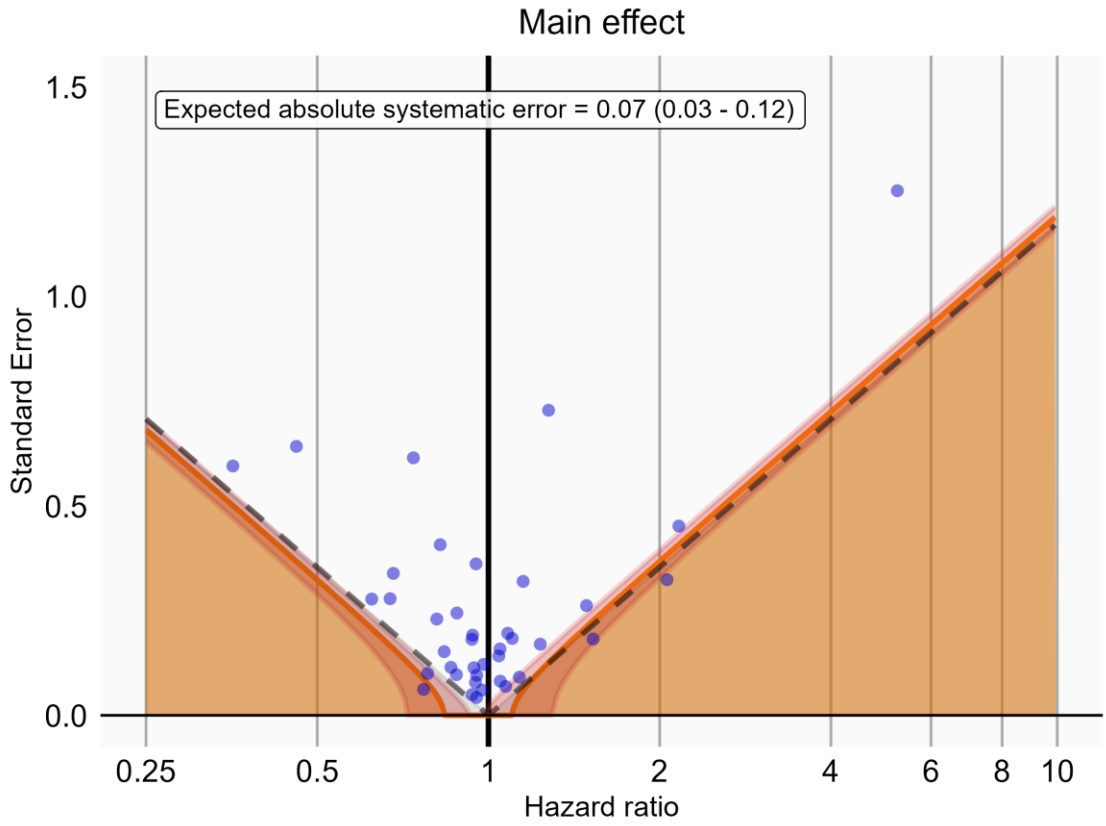
Negative control estimates of the main effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in CCAE.



Negative control estimates of the direct effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in CCAE.

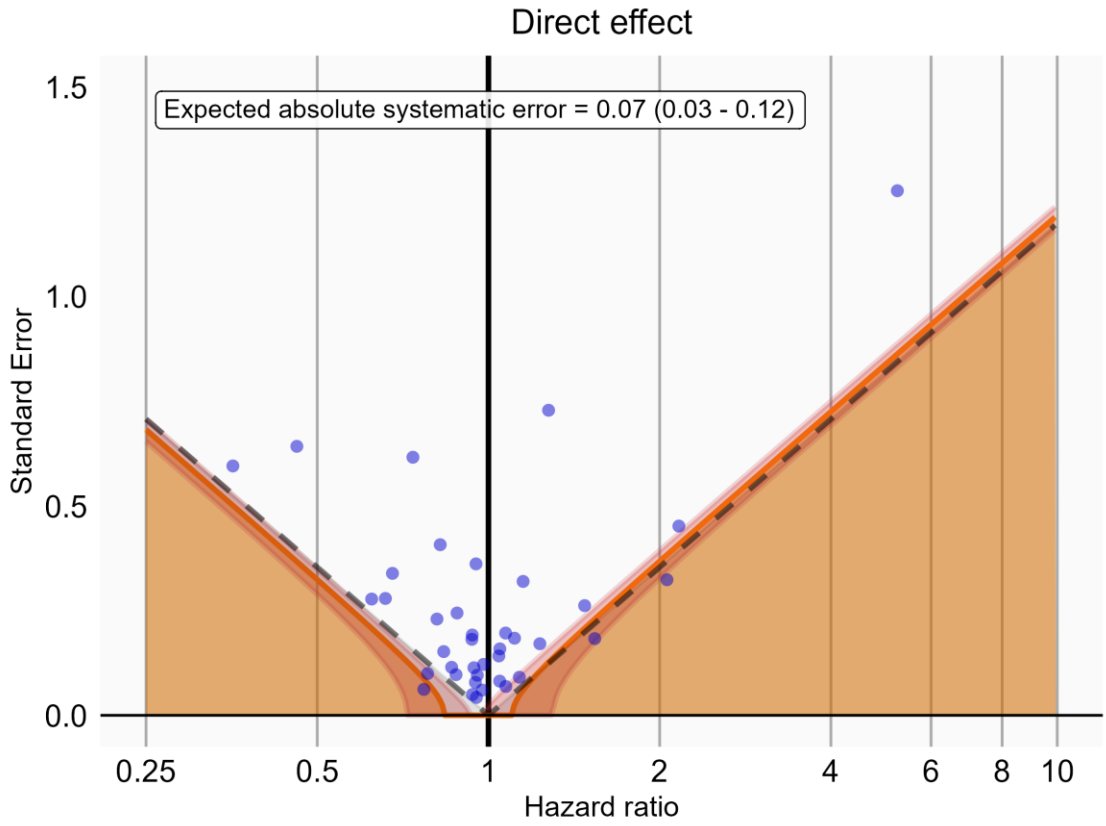


Negative control estimates of the indirect effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in CCAE.



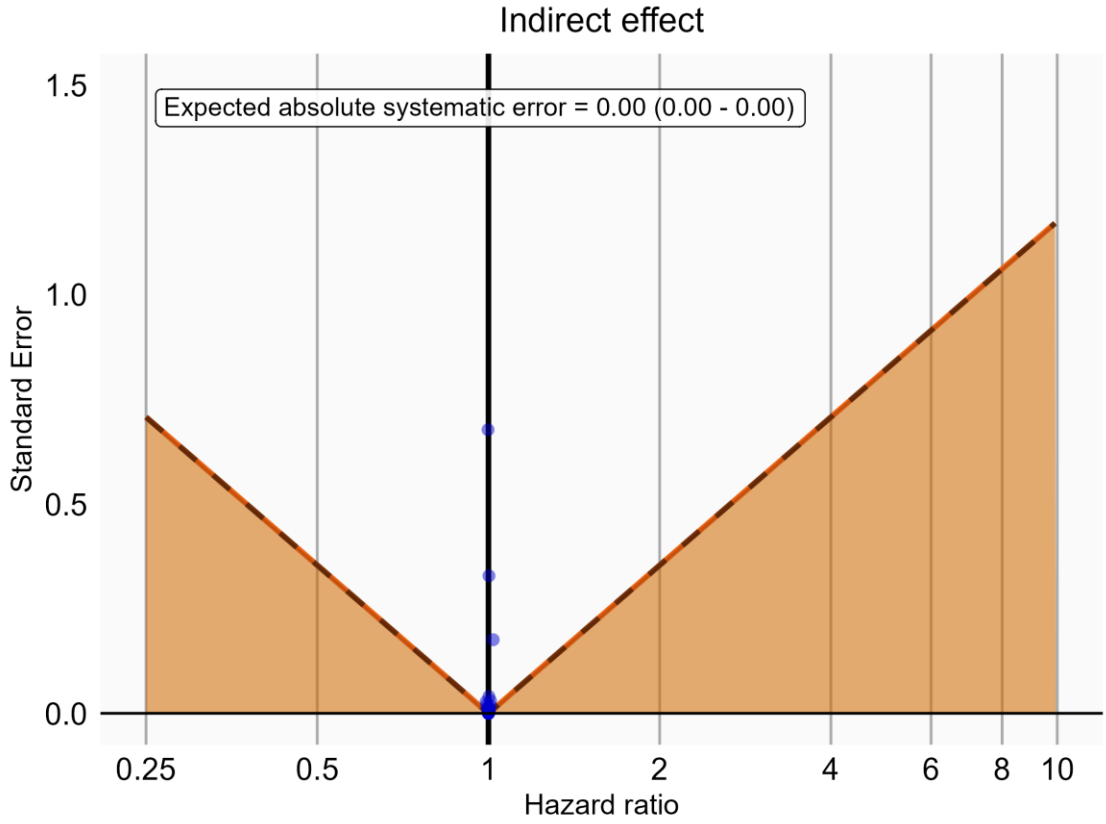
1156

1157 *Negative control estimates of the main effect comparing DOACs to Warfarin using mediator*
1158 *Extracranial Major bleeding IP in CCAE.*

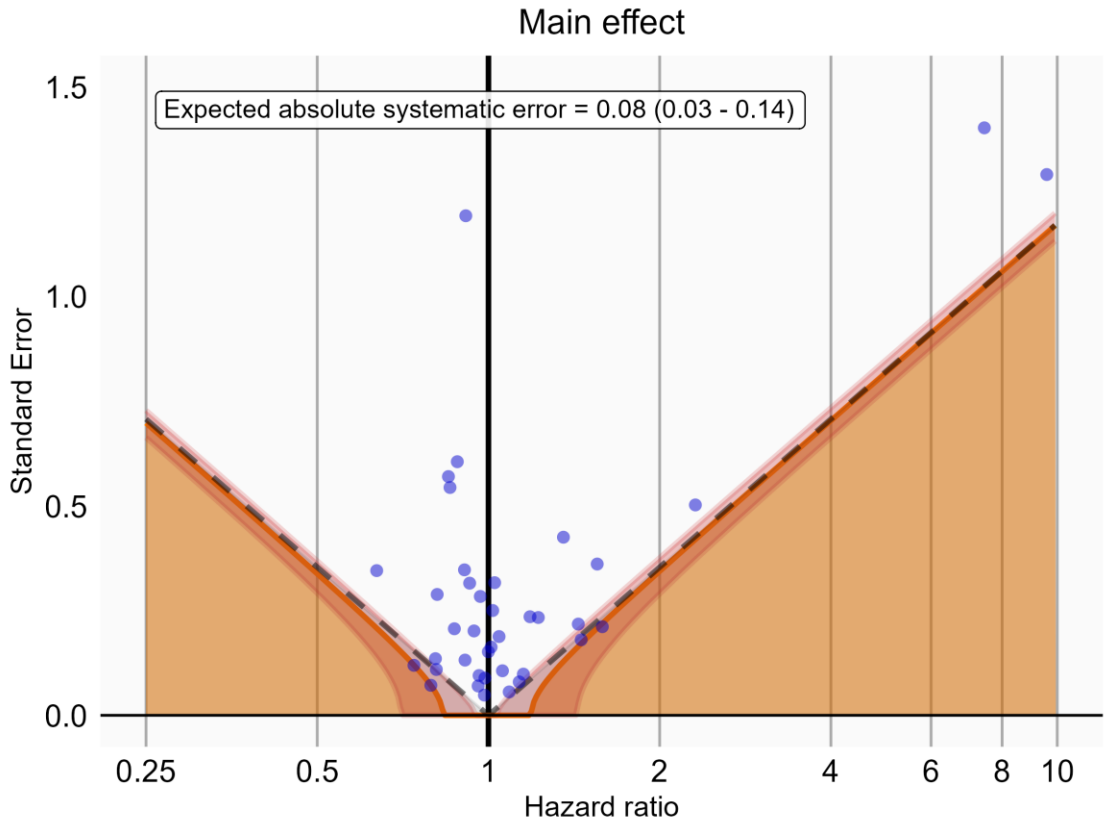


1159

1160 *Negative control estimates of the direct effect comparing DOACs to Warfarin using mediator*
1161 *Extracranial Major bleeding IP in CCAE.*

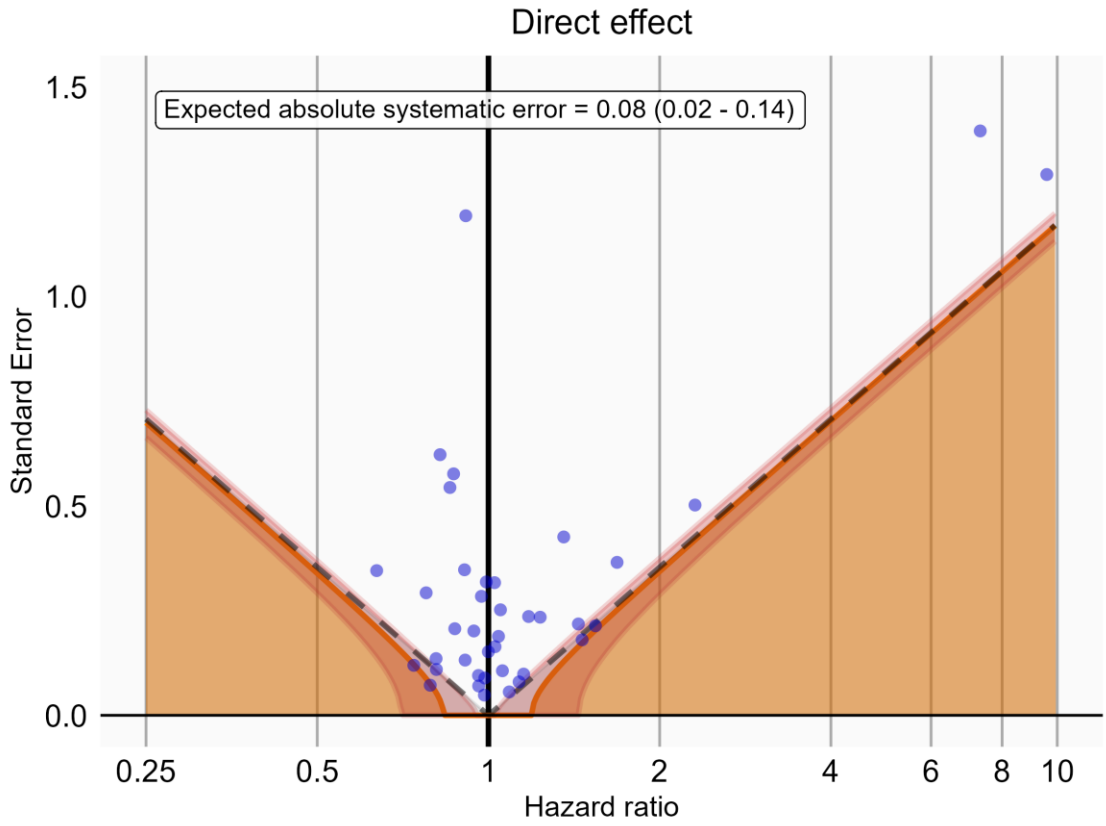


Negative control estimates of the indirect effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in CCAE.

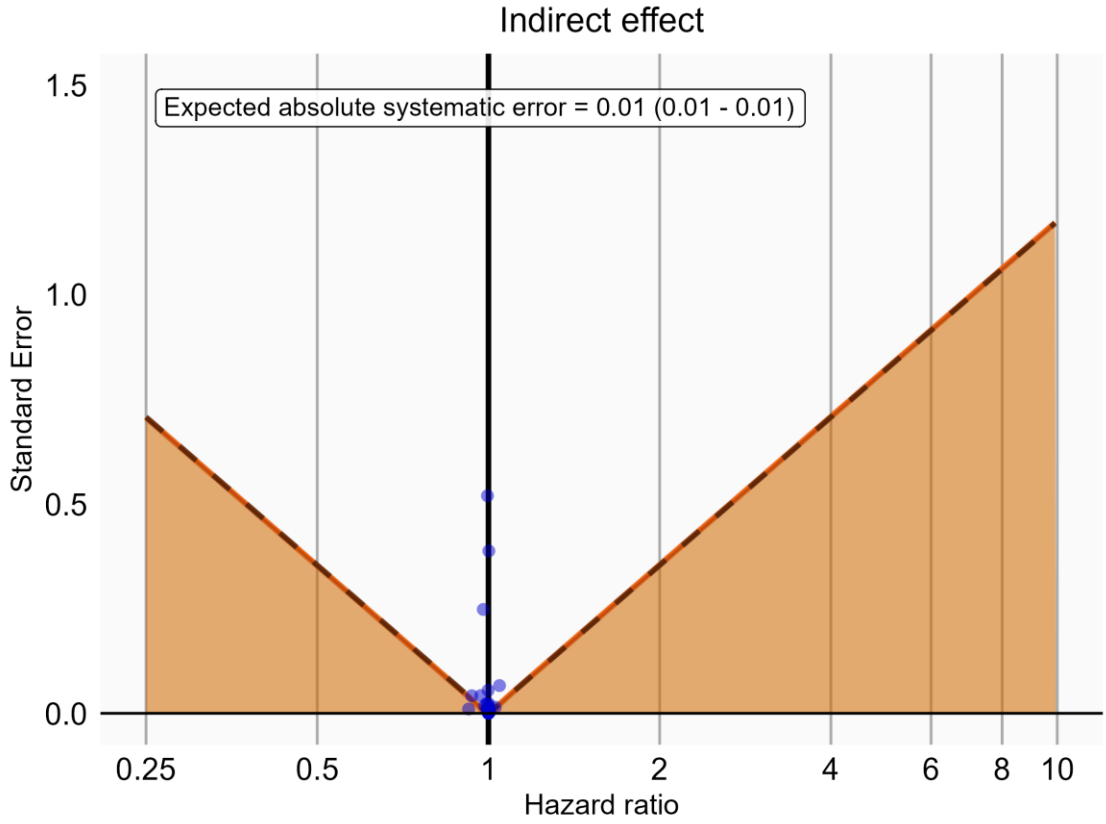


1165

1166 *Negative control estimates of the main effect comparing Rivaroxaban to Warfarin using*
1167 *mediator Extracranial Major bleeding IP-ER in CCAE.*

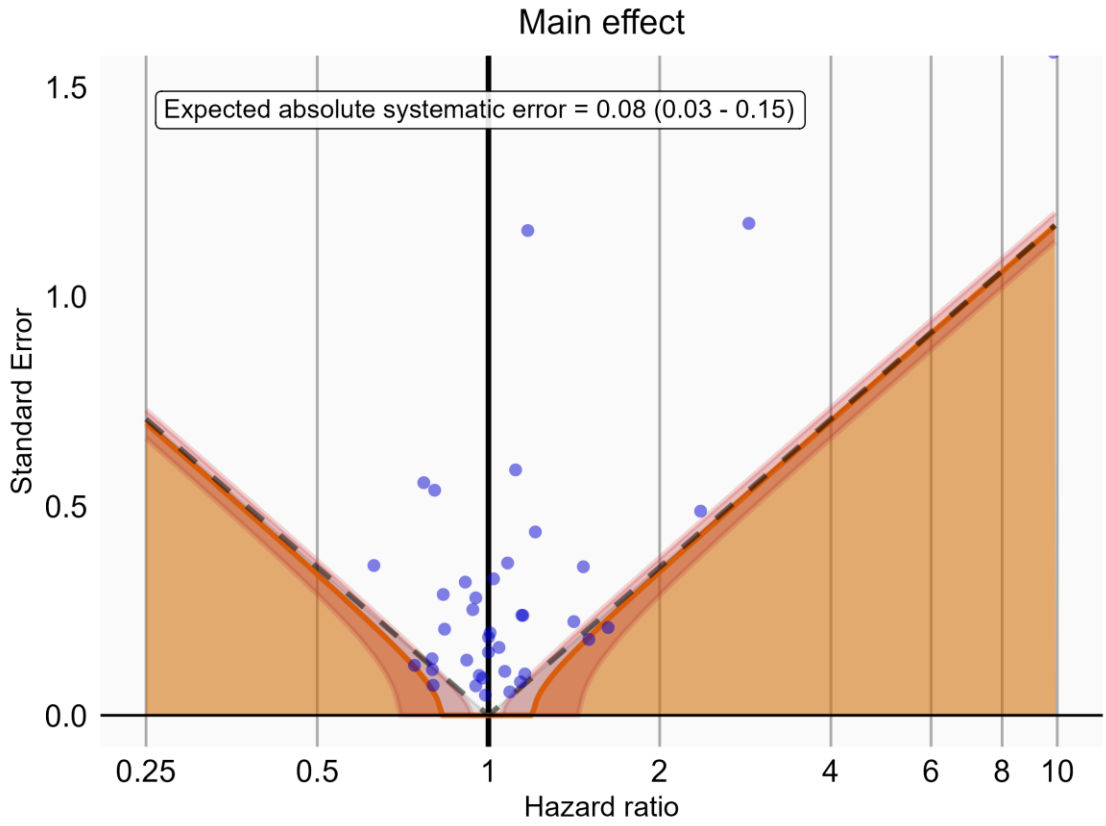


Negative control estimates of the direct effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP-ER in CCAE.

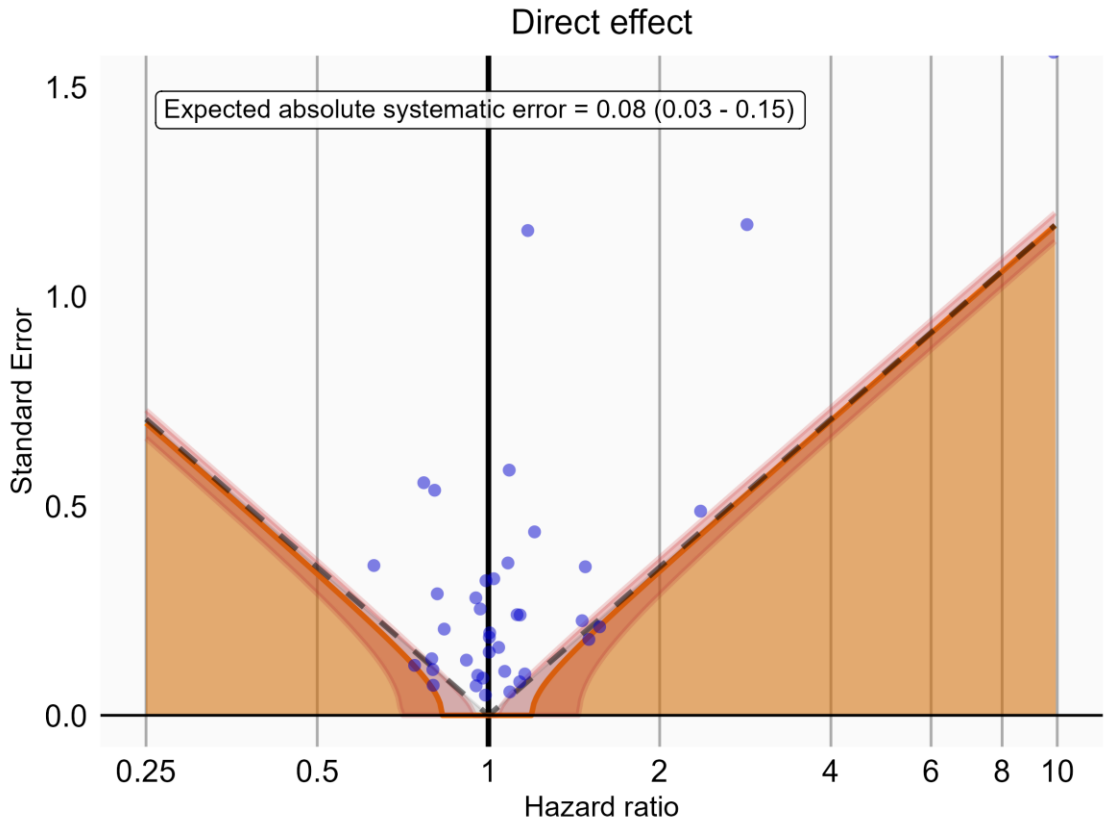


1171

1172 *Negative control estimates of the indirect effect comparing Rivaroxaban to Warfarin using*
1173 *mediator Extracranial Major bleeding IP-ER in CCAE.*

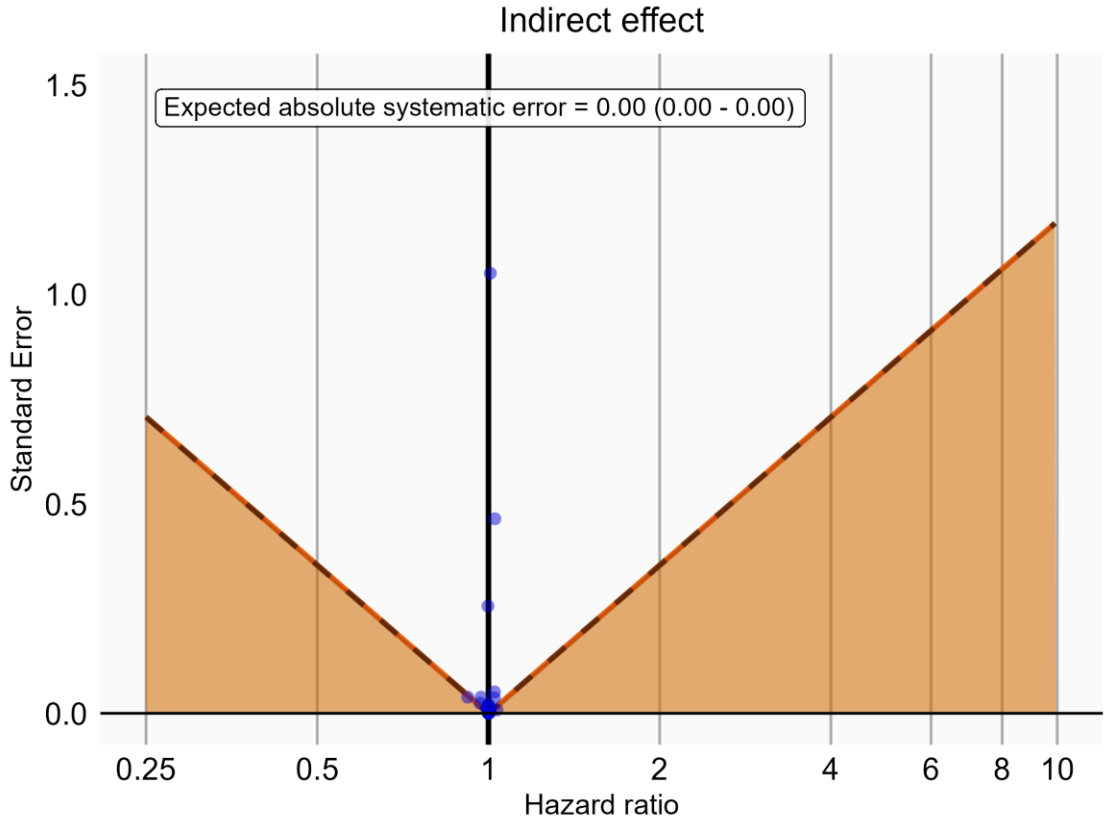


Negative control estimates of the main effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in CCAE.



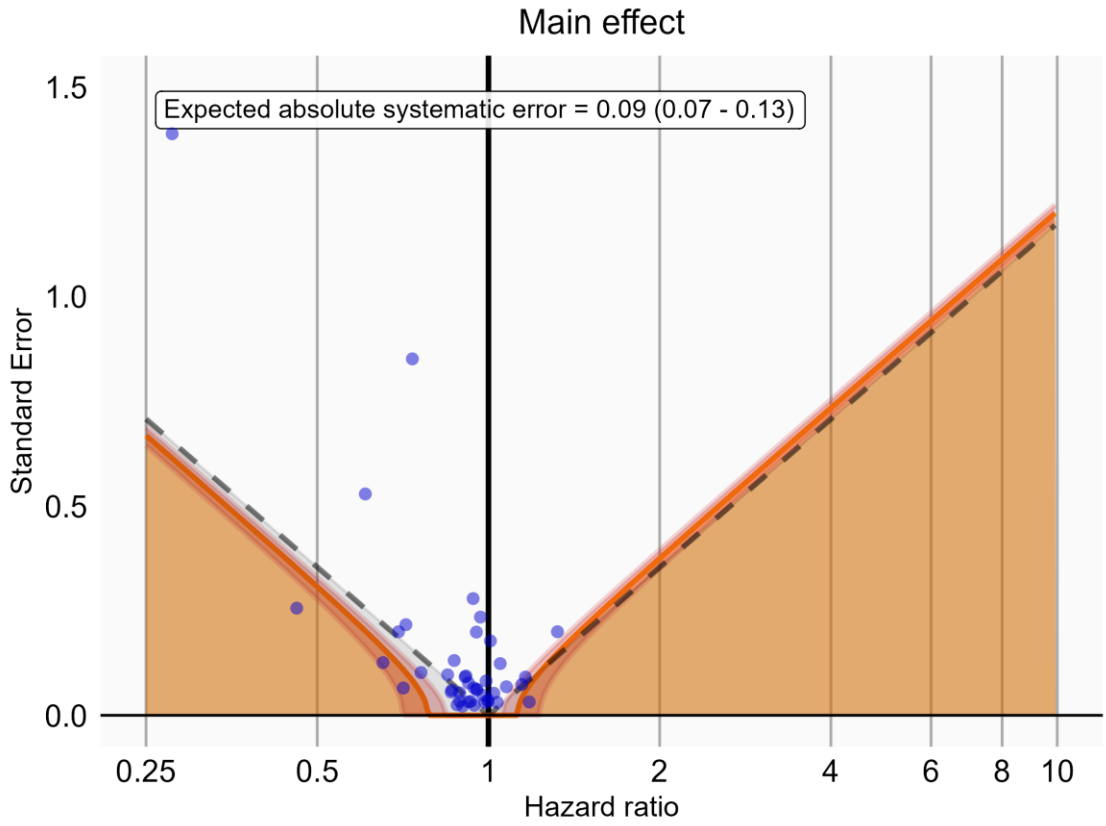
1177

1178 *Negative control estimates of the direct effect comparing Rivaroxaban to Warfarin using*
1179 *mediator Extracranial Major bleeding IP in CCAE.*

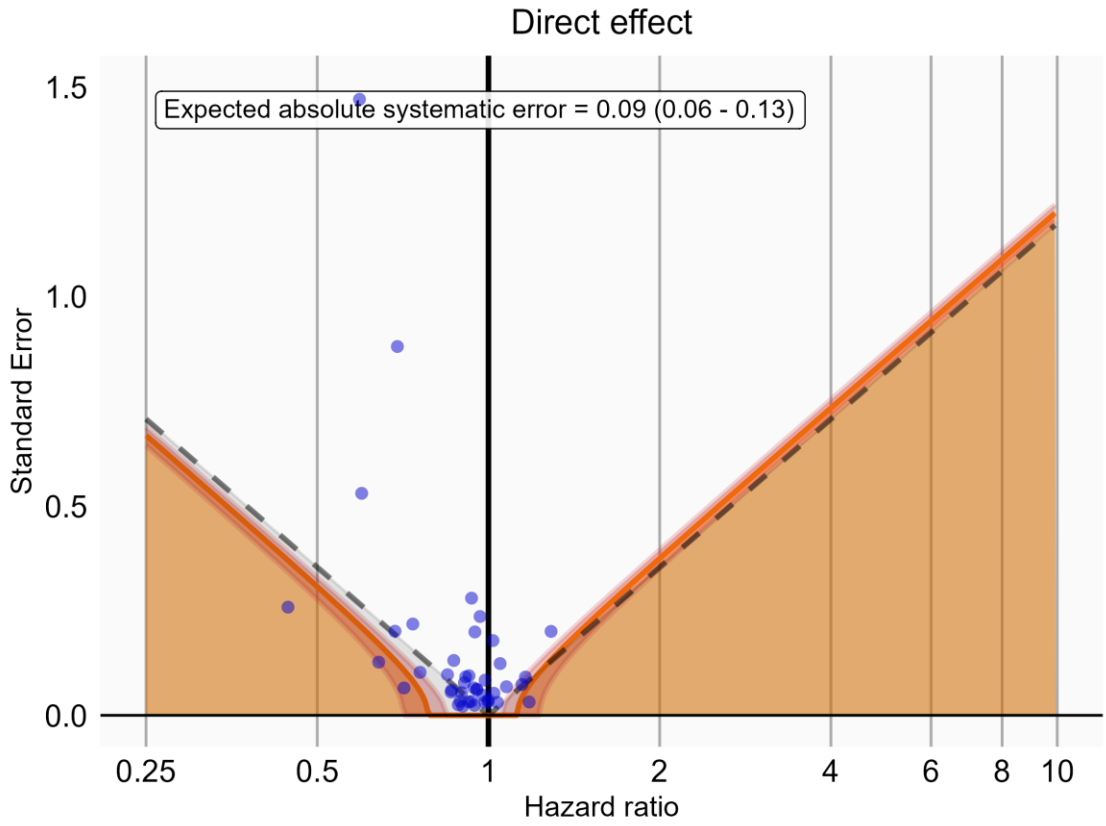


Negative control estimates of the indirect effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in CCAE.

18.5.2. Clinformatics®

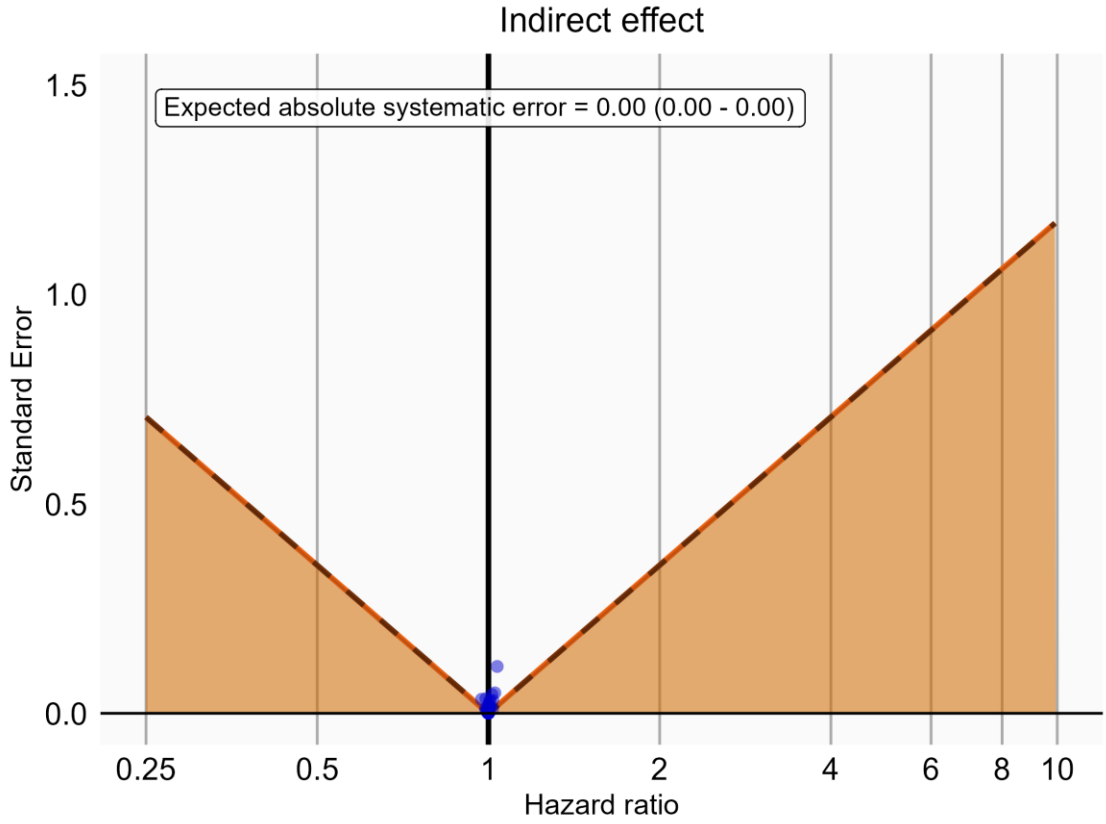


Negative control estimates of the main effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in Clinformatics®.

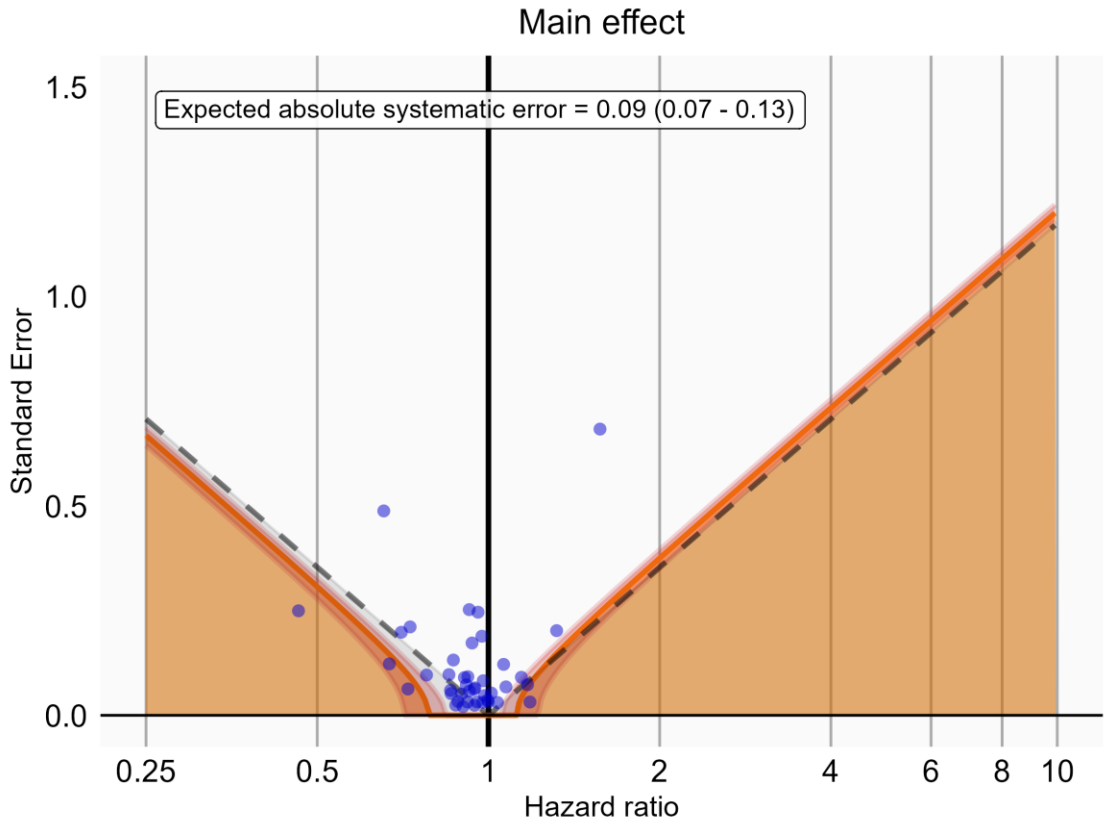


1187

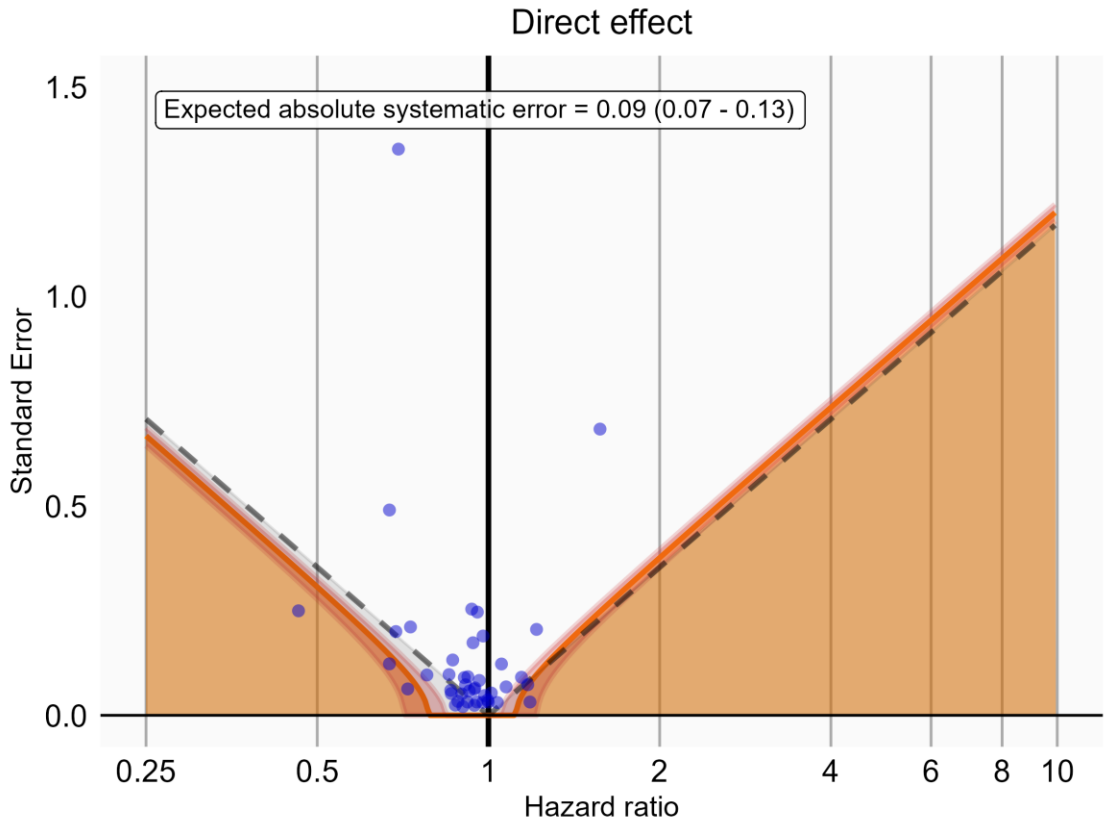
1188 *Negative control estimates of the direct effect comparing DOACs to Warfarin using mediator*
1189 *Extracranial Major bleeding IP-ER in Clinformatics®.*



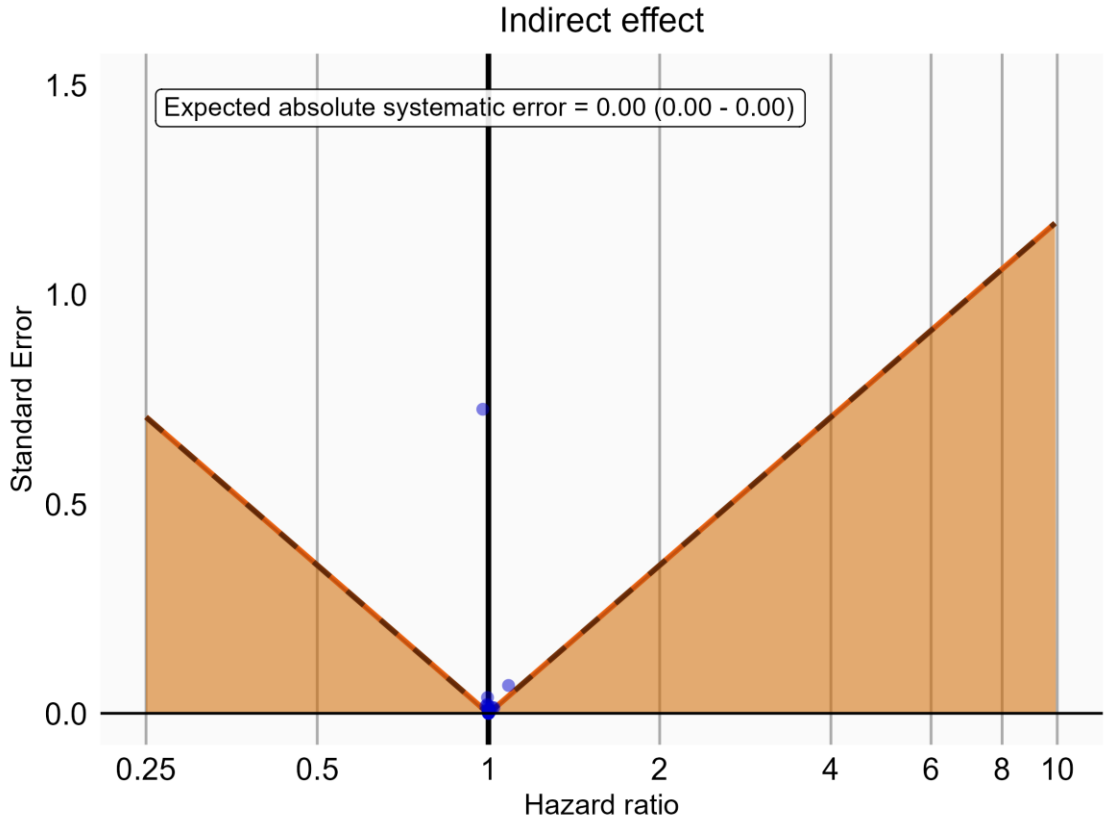
Negative control estimates of the indirect effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in Clinformatics®.



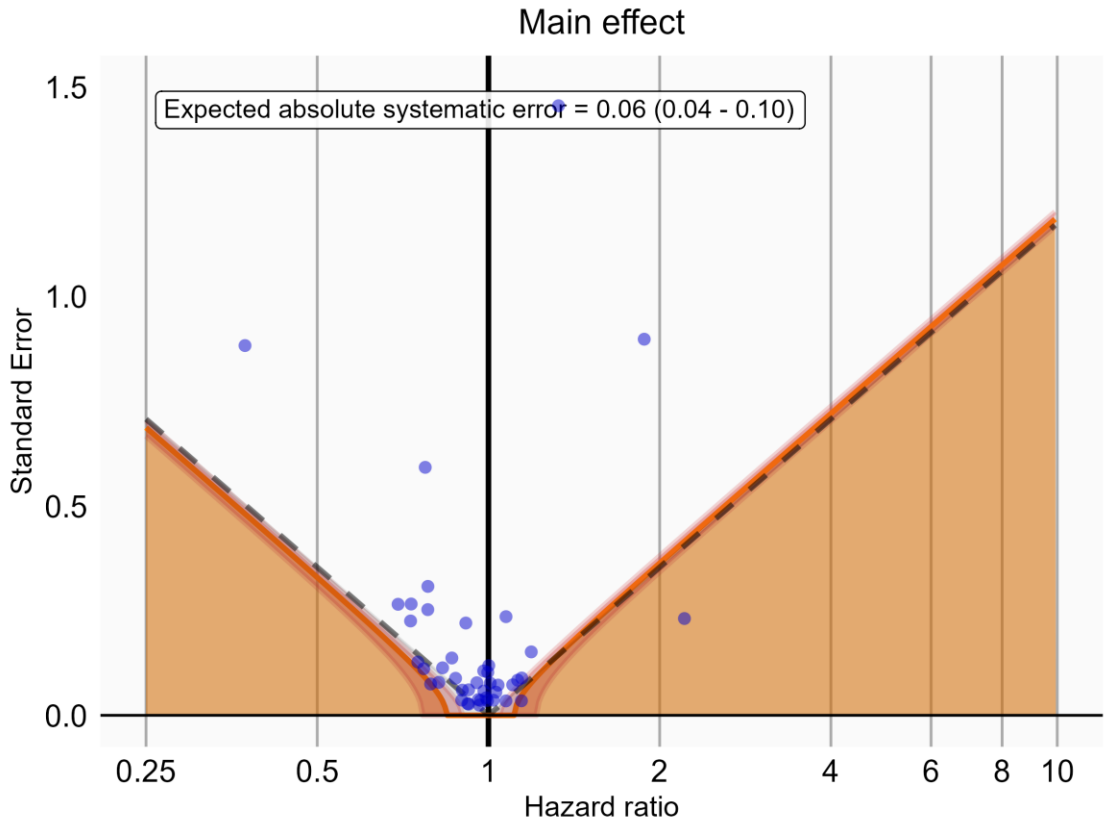
Negative control estimates of the main effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in Clinformatics®.



Negative control estimates of the direct effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in Clinformatics®.

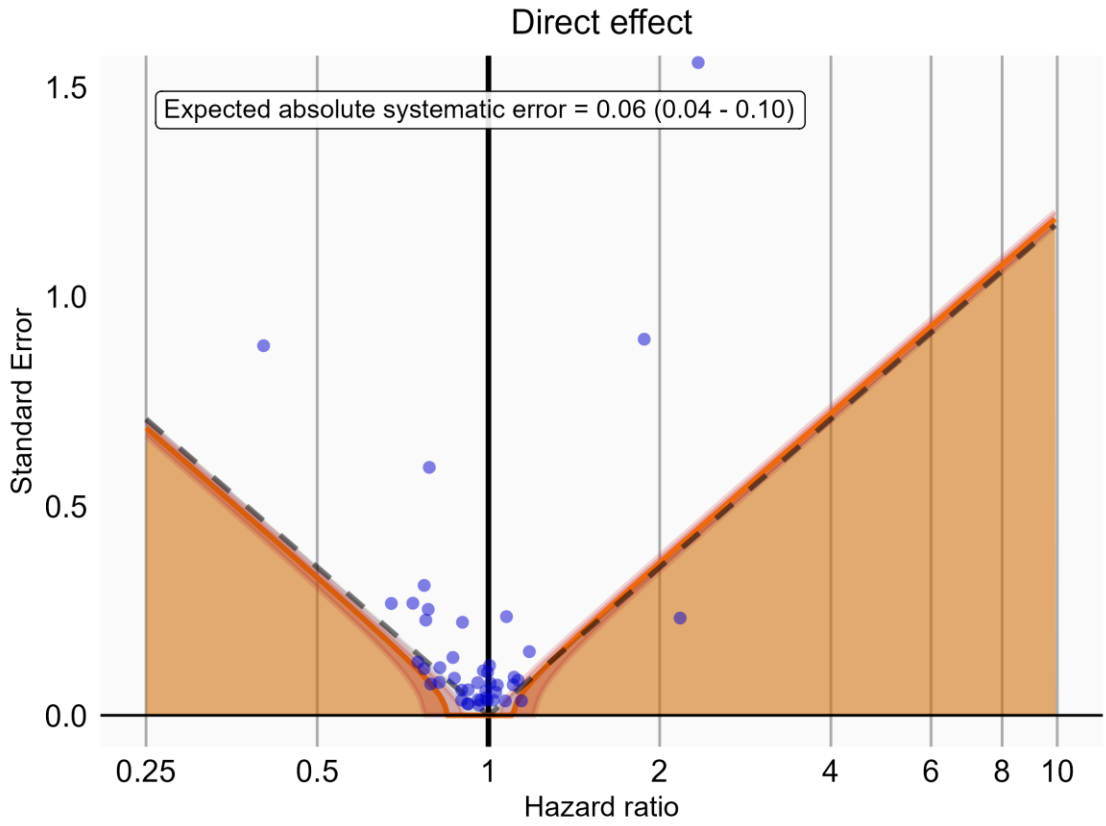


Negative control estimates of the indirect effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in Clinformatics®.



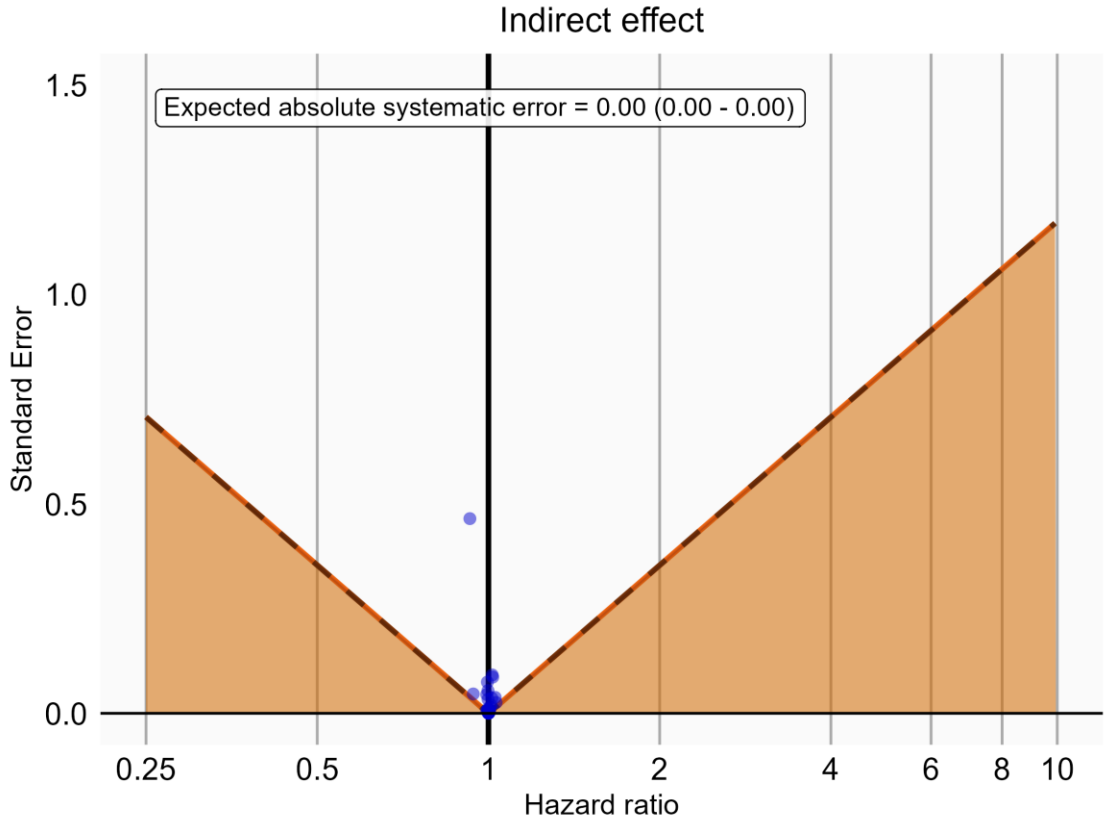
1202

1203 *Negative control estimates of the main effect comparing Rivaroxaban to Warfarin using*
1204 *mediator Extracranial Major bleeding IP-ER in Clinformatics®.*

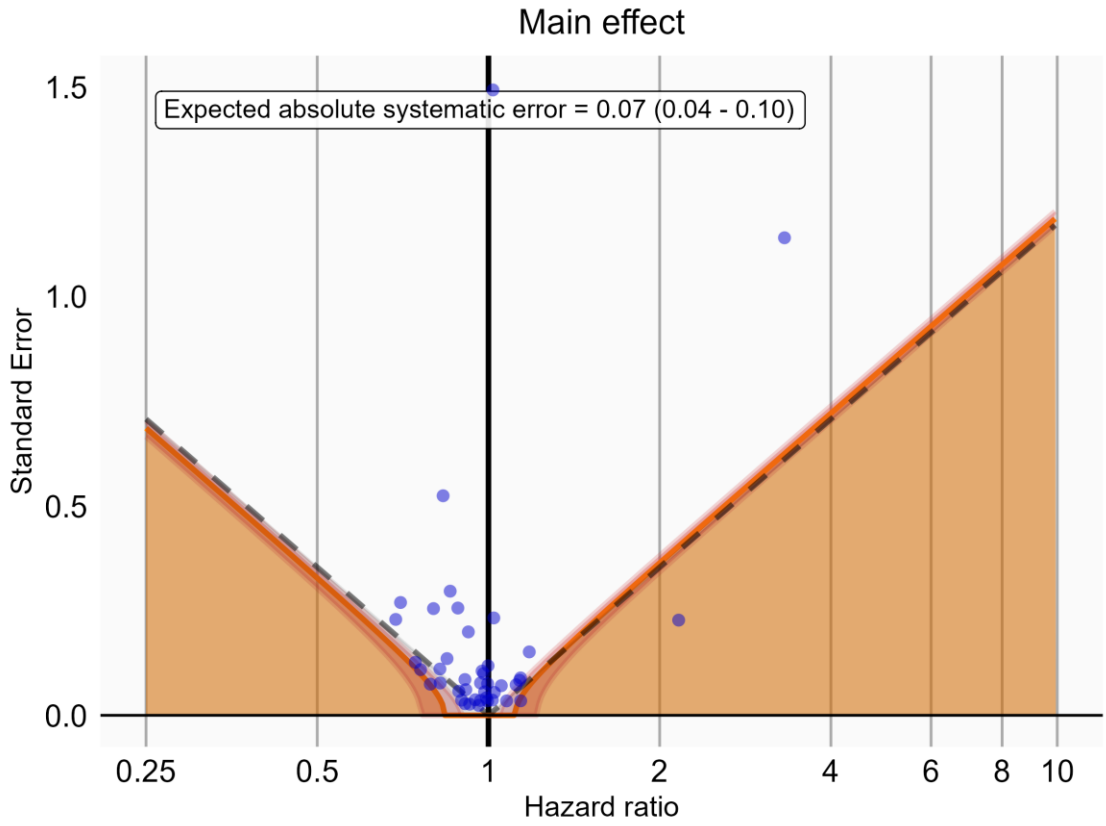


1205

1206 *Negative control estimates of the direct effect comparing Rivaroxaban to Warfarin using*
1207 *mediator Extracranial Major bleeding IP-ER in Clinformatics®.*

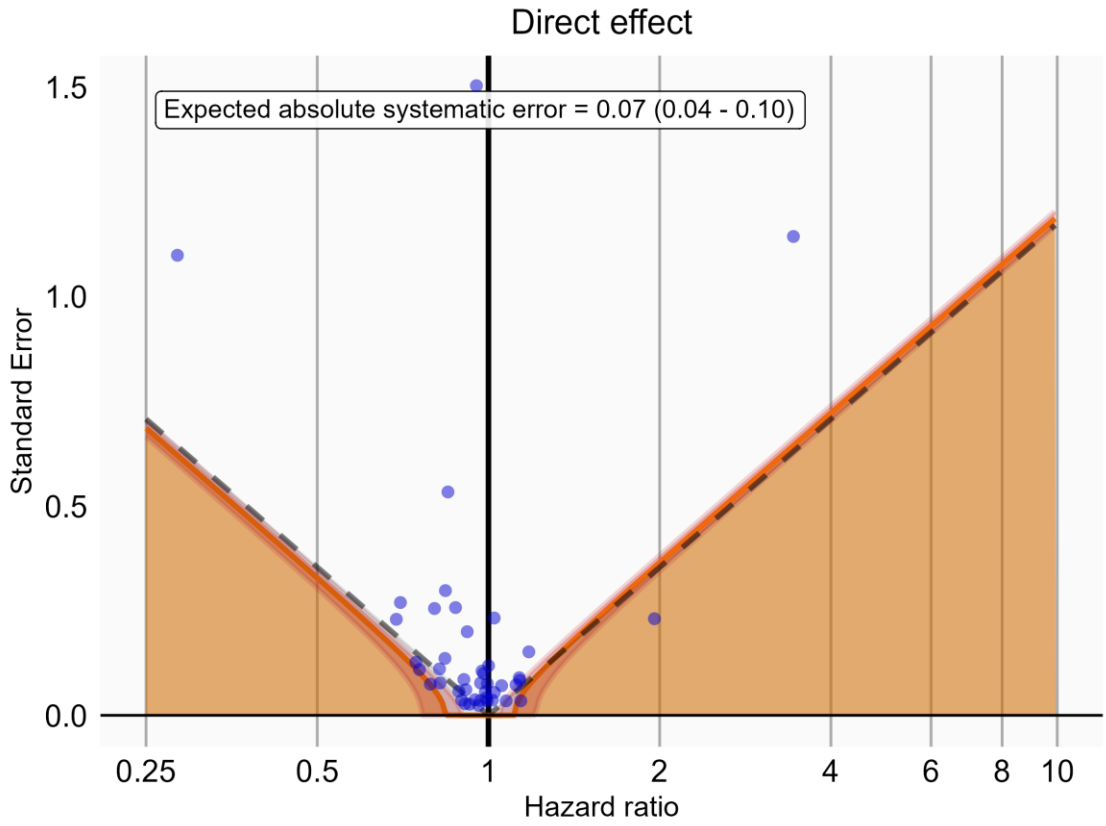


Negative control estimates of the indirect effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP-ER in Clinformatics®.

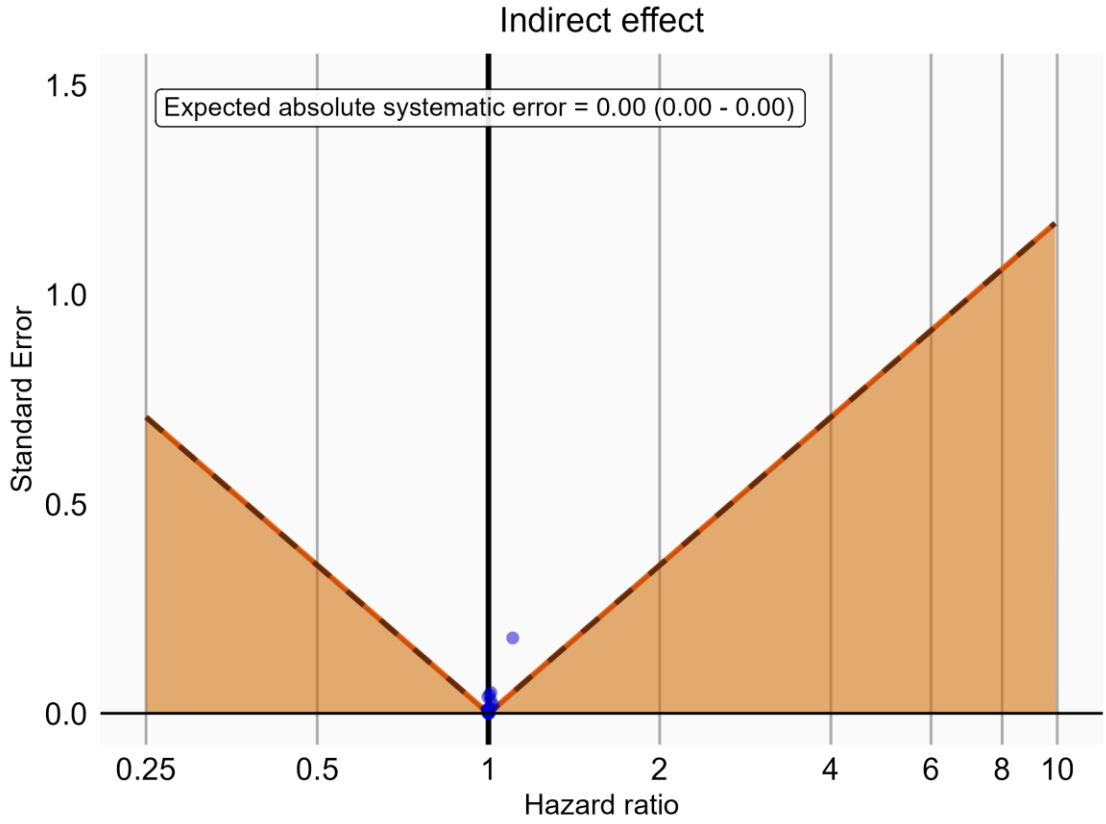


1211

1212 *Negative control estimates of the main effect comparing Rivaroxaban to Warfarin using*
1213 *mediator Extracranial Major bleeding IP in Clinformatics®.*

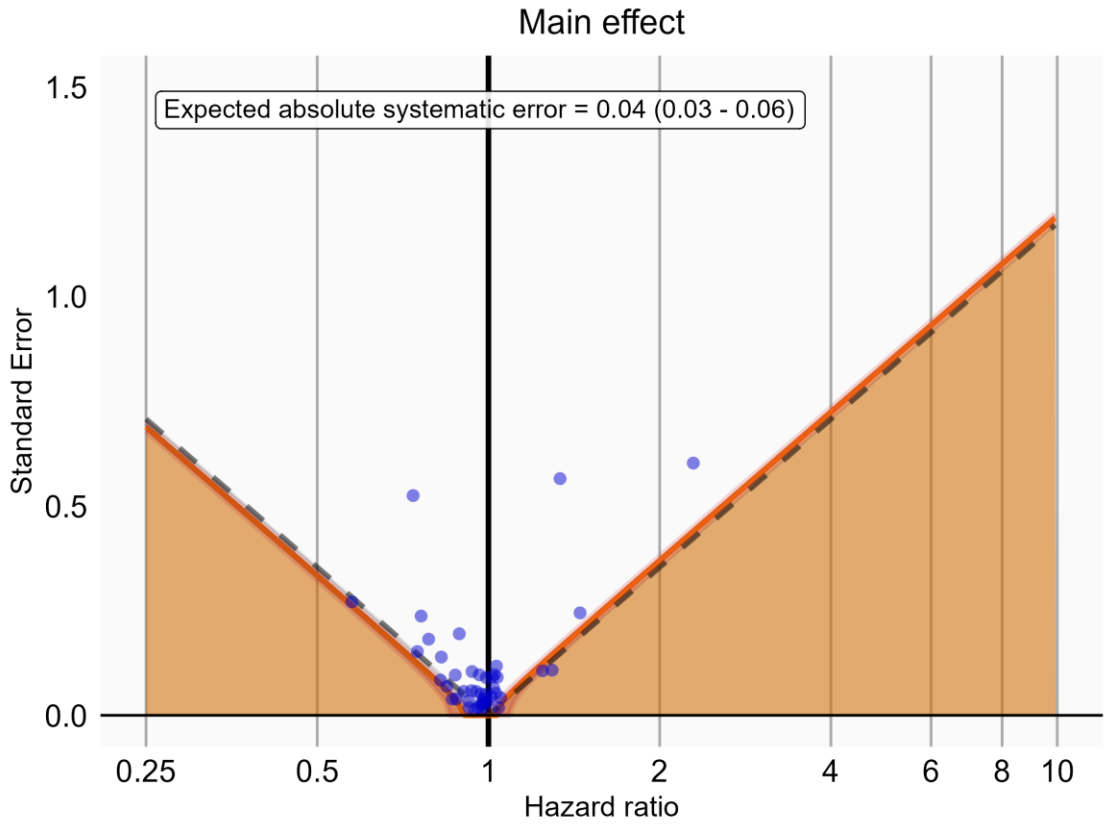


Negative control estimates of the direct effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in Clinformatics®.

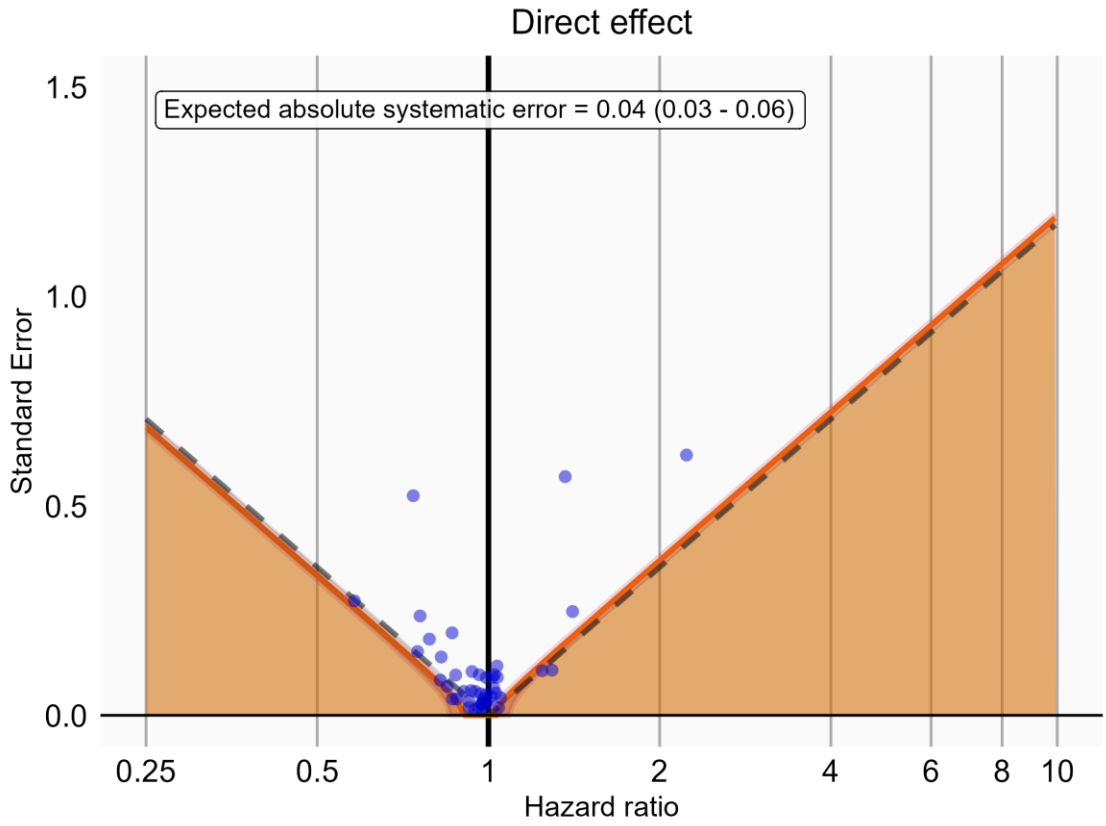


Negative control estimates of the indirect effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in Clinformatics®.

18.5.3. Optum® EHR

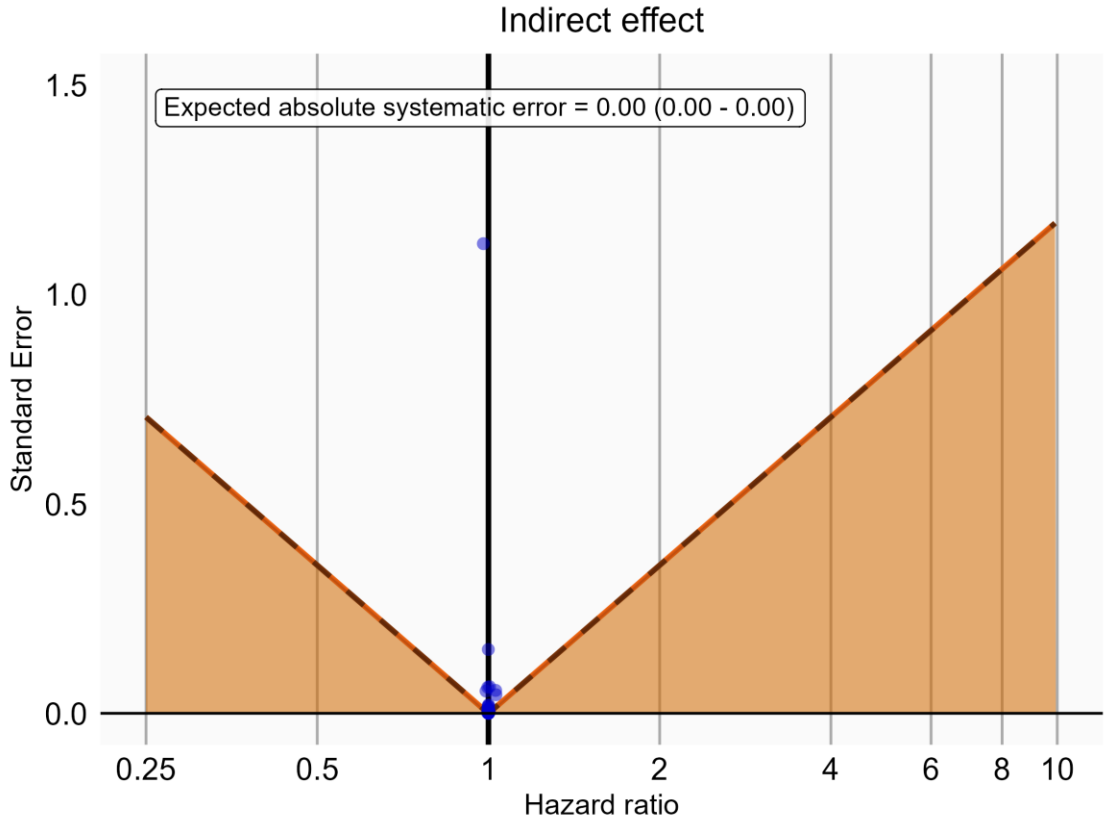


Negative control estimates of the main effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in Optum® EHR.



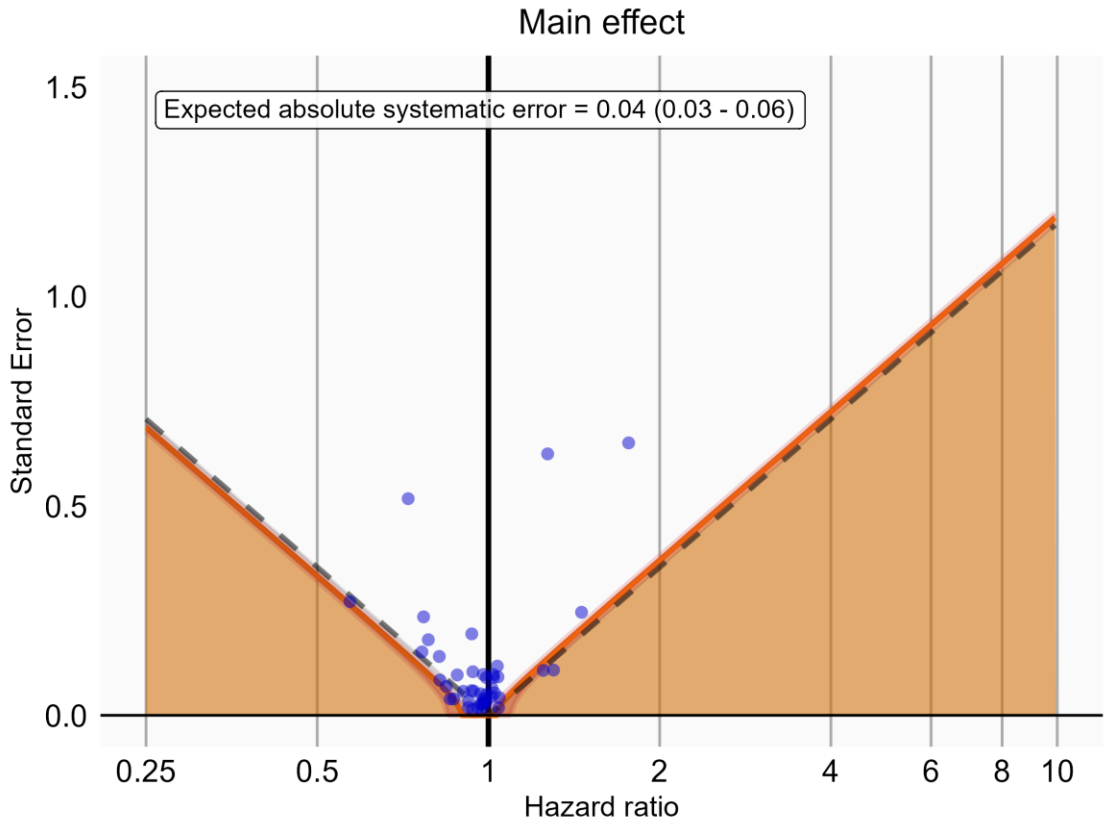
1224

1225 *Negative control estimates of the direct effect comparing DOACs to Warfarin using mediator*
1226 *Extracranial Major bleeding IP-ER in Optum® EHR.*



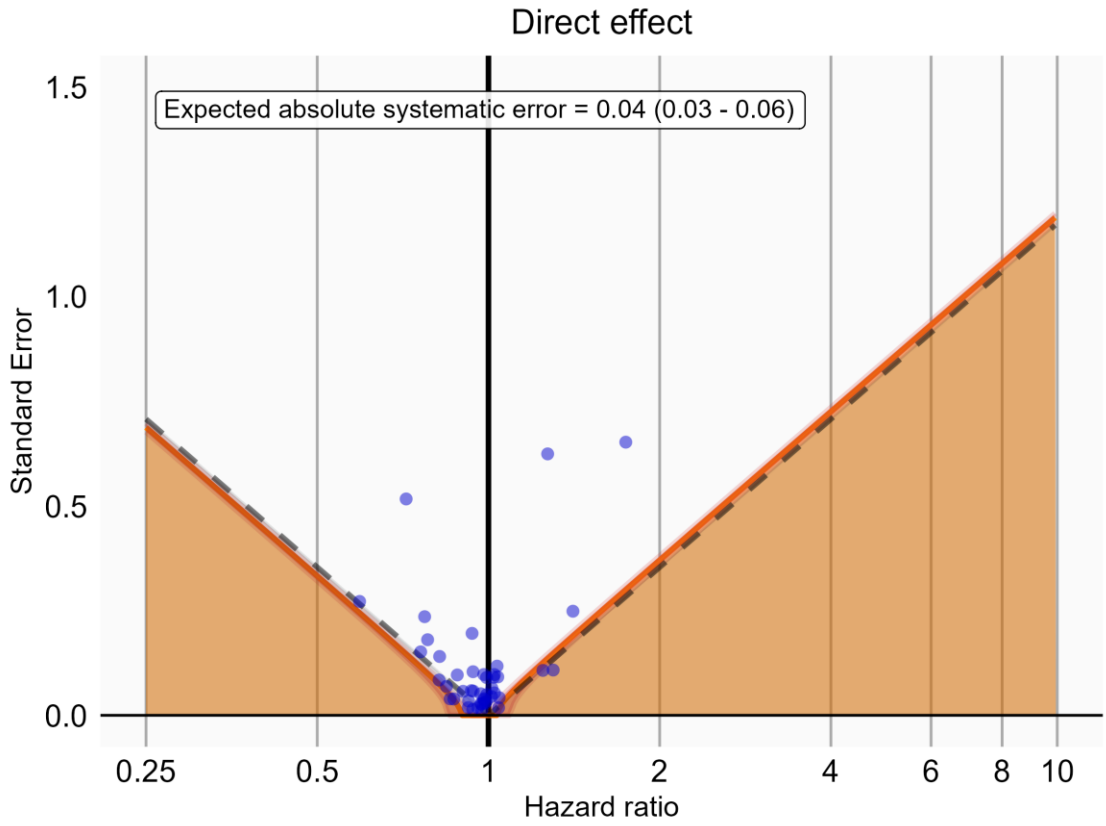
1227

1228 *Negative control estimates of the indirect effect comparing DOACs to Warfarin using mediator*
1229 *Extracranial Major bleeding IP-ER in Optum® EHR.*

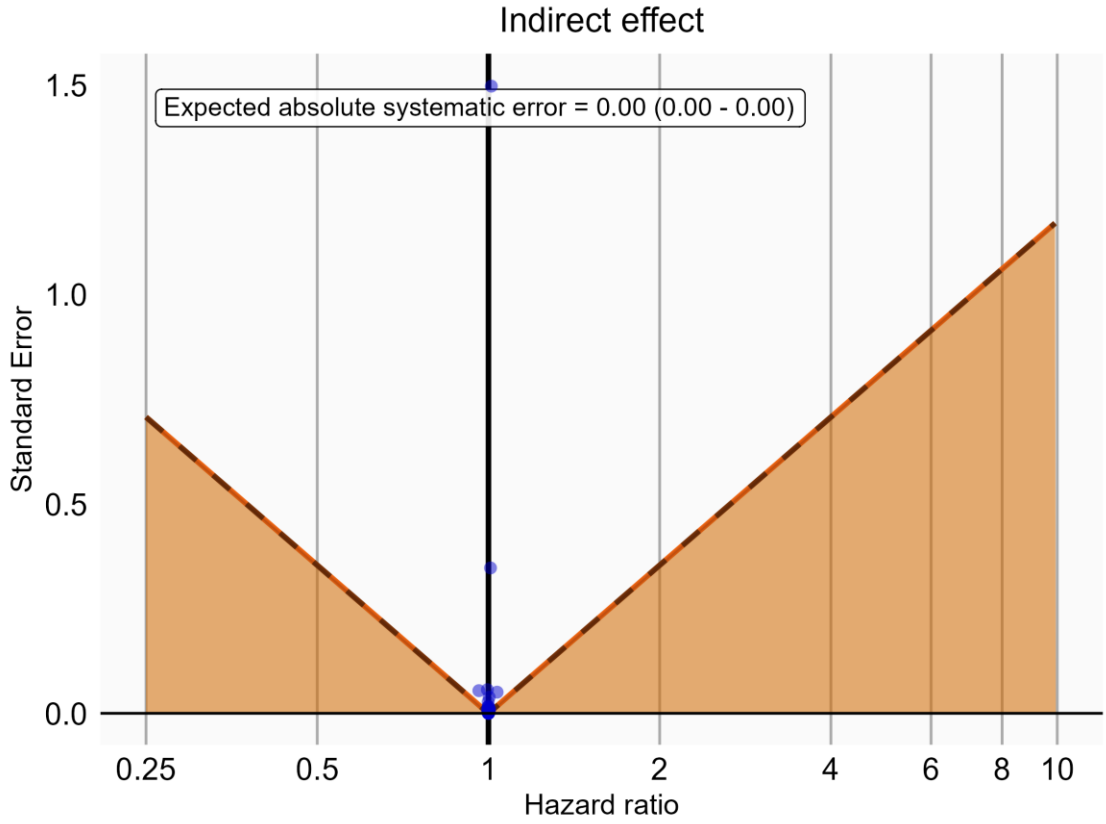


1230

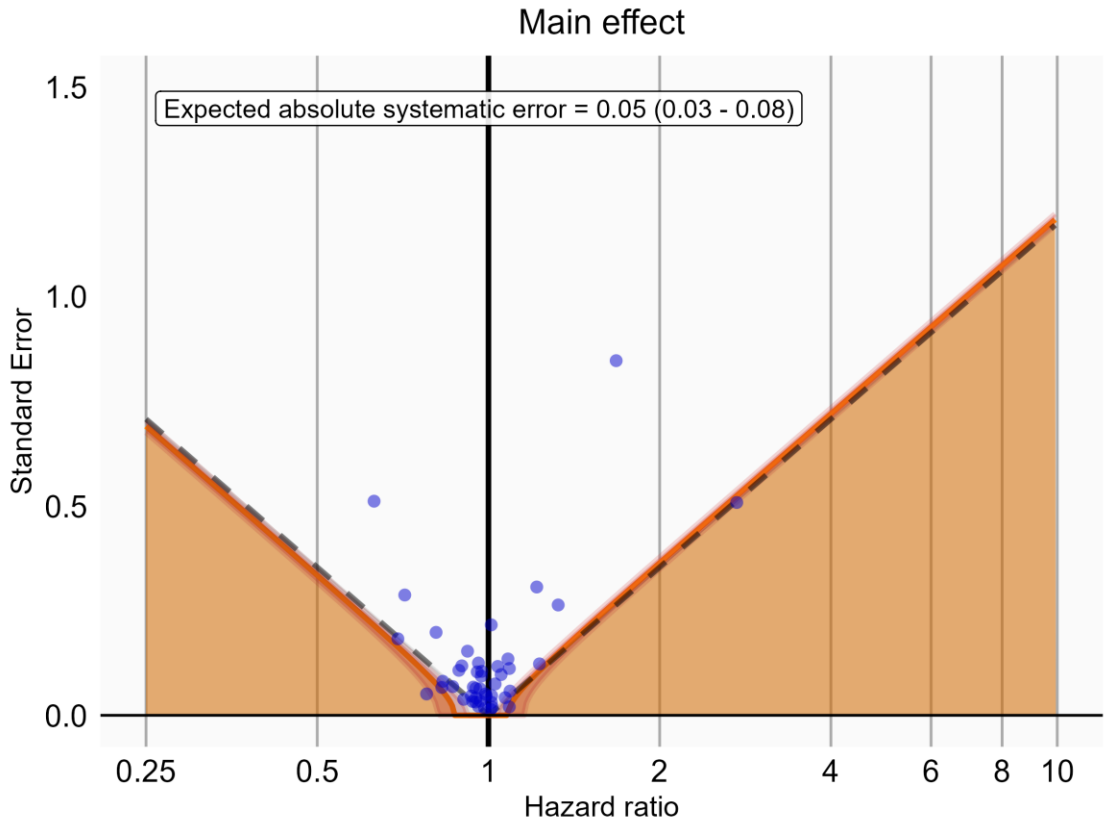
1231 *Negative control estimates of the main effect comparing DOACs to Warfarin using mediator*
1232 *Extracranial Major bleeding IP in Optum® EHR.*



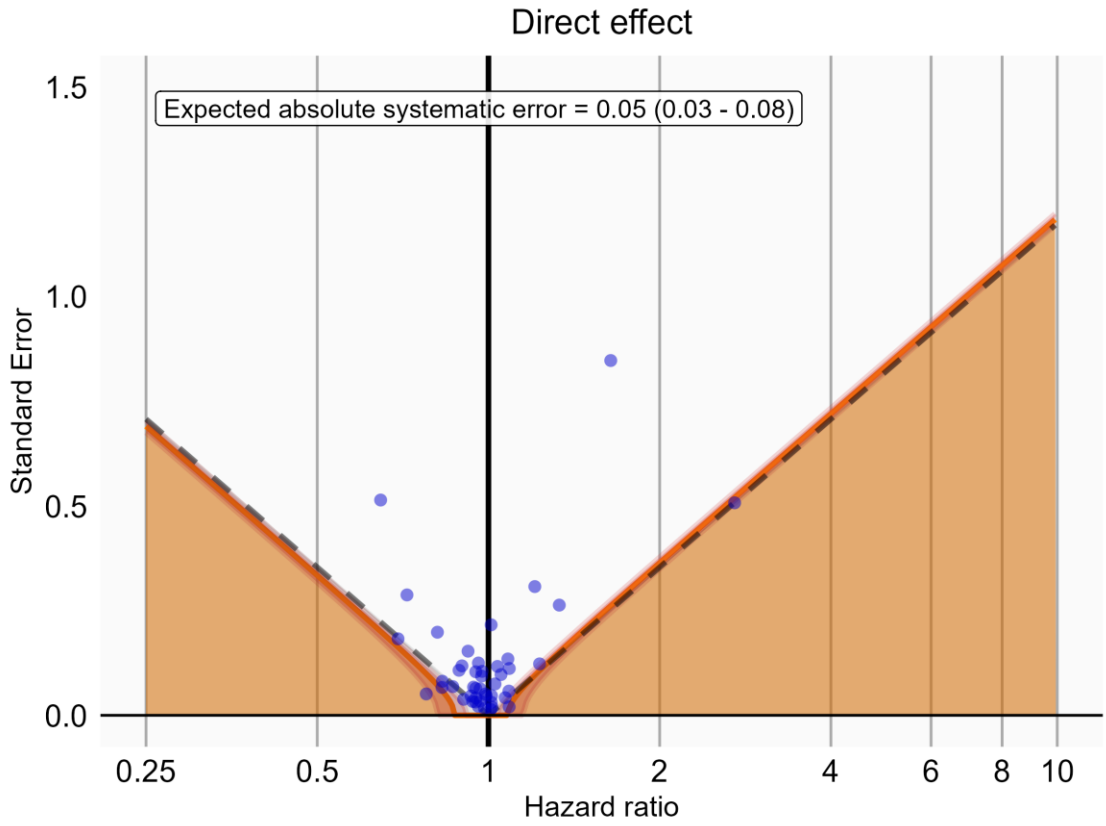
Negative control estimates of the direct effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in Optum® EHR.



Negative control estimates of the indirect effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in Optum® EHR.

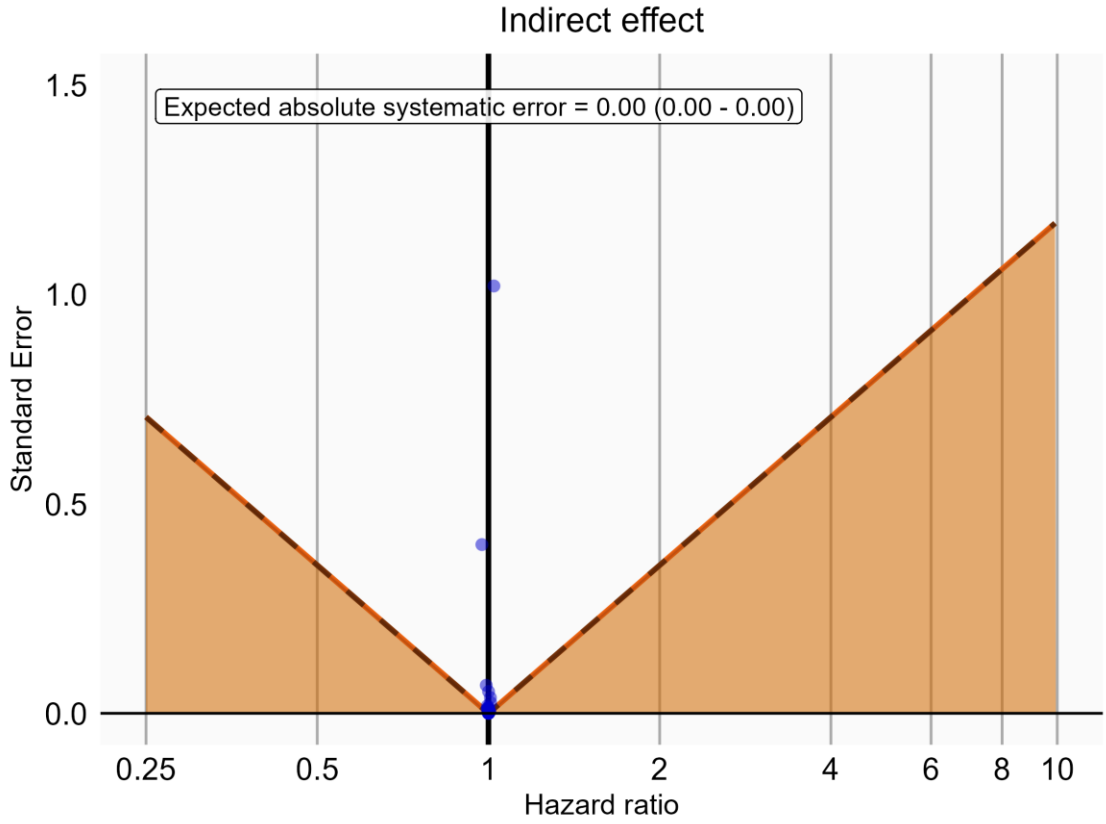


Negative control estimates of the main effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP-ER in Optum® EHR.

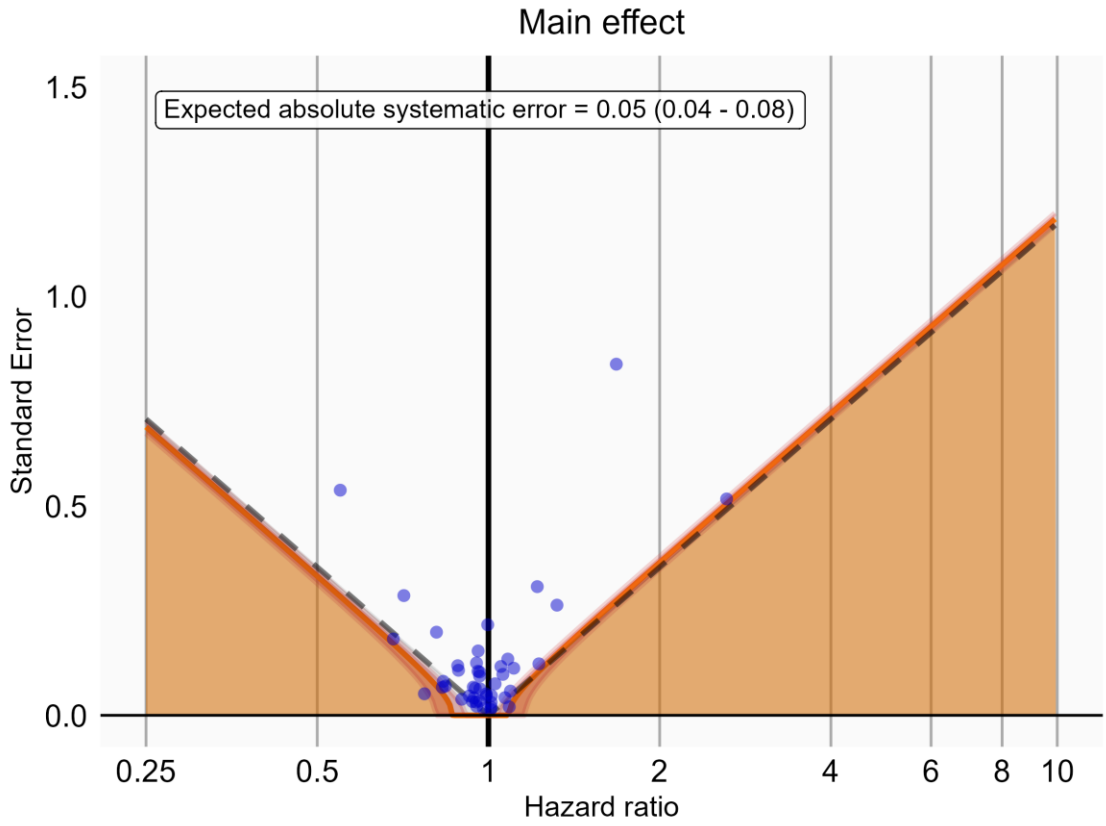


1242

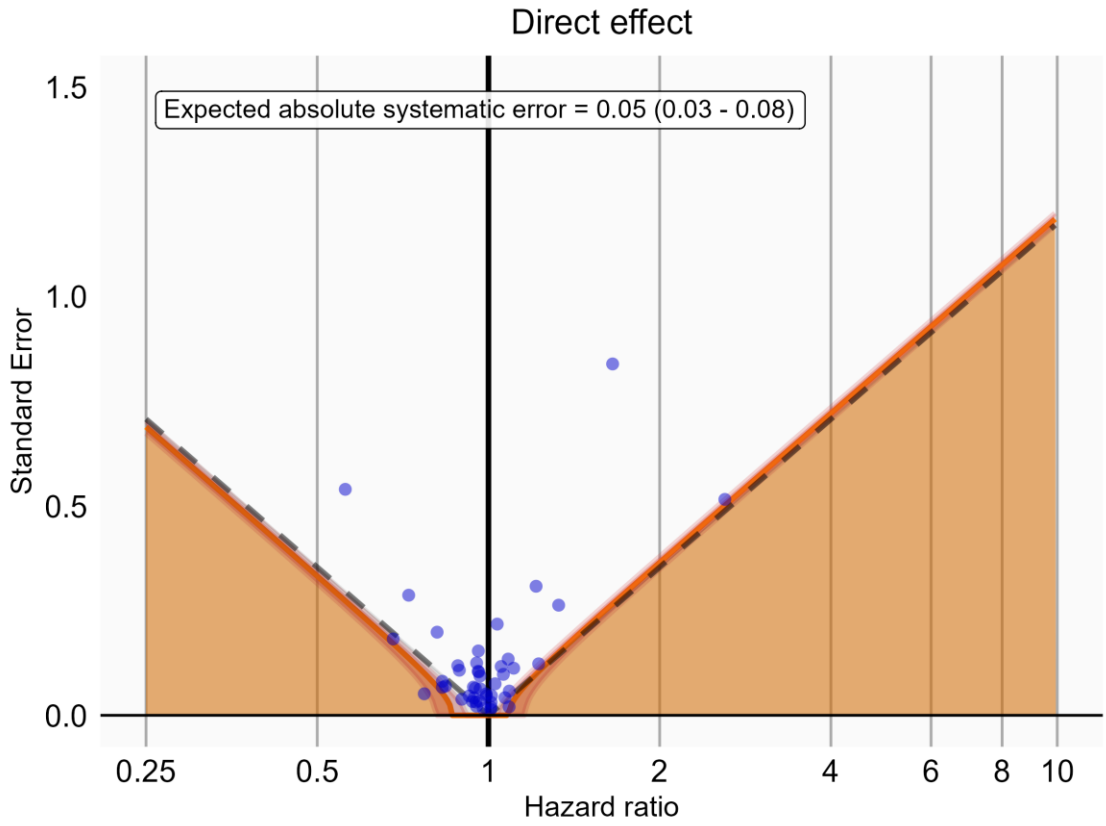
1243 *Negative control estimates of the direct effect comparing Rivaroxaban to Warfarin using*
1244 *mediator Extracranial Major bleeding IP-ER in Optum® EHR.*



Negative control estimates of the indirect effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP-ER in Optum® EHR.



Negative control estimates of the main effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in Optum® EHR.



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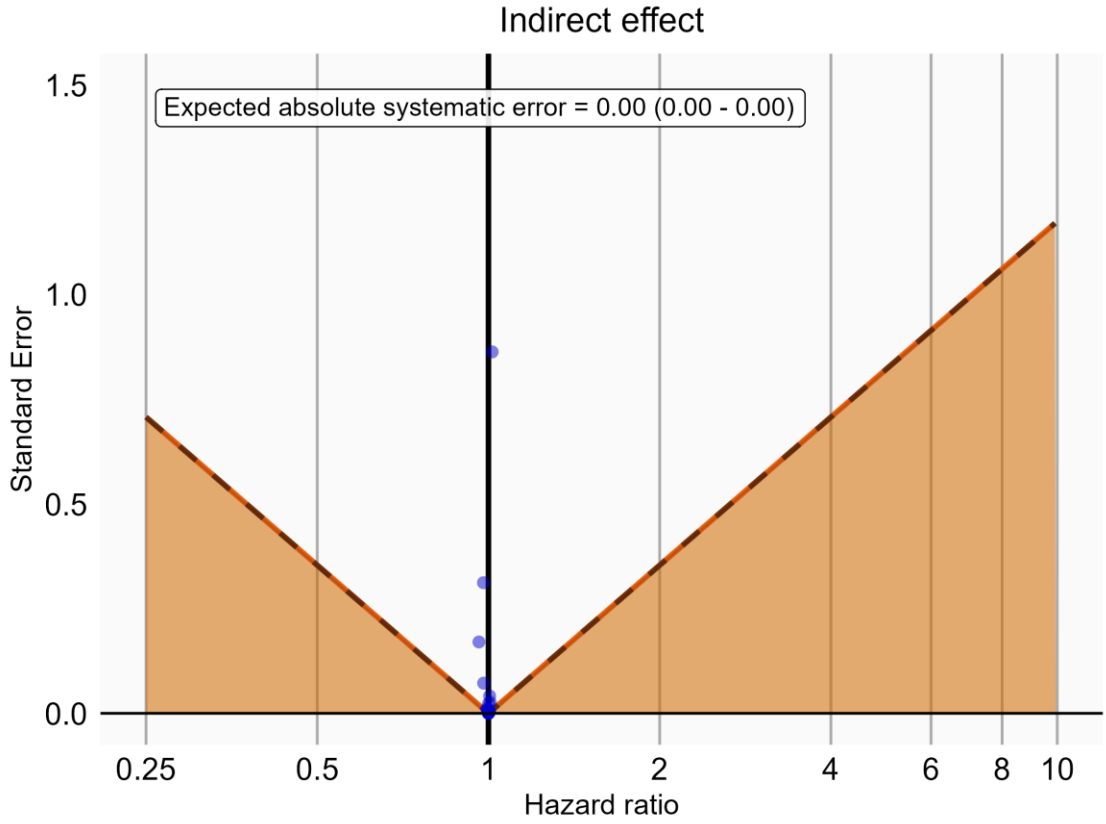

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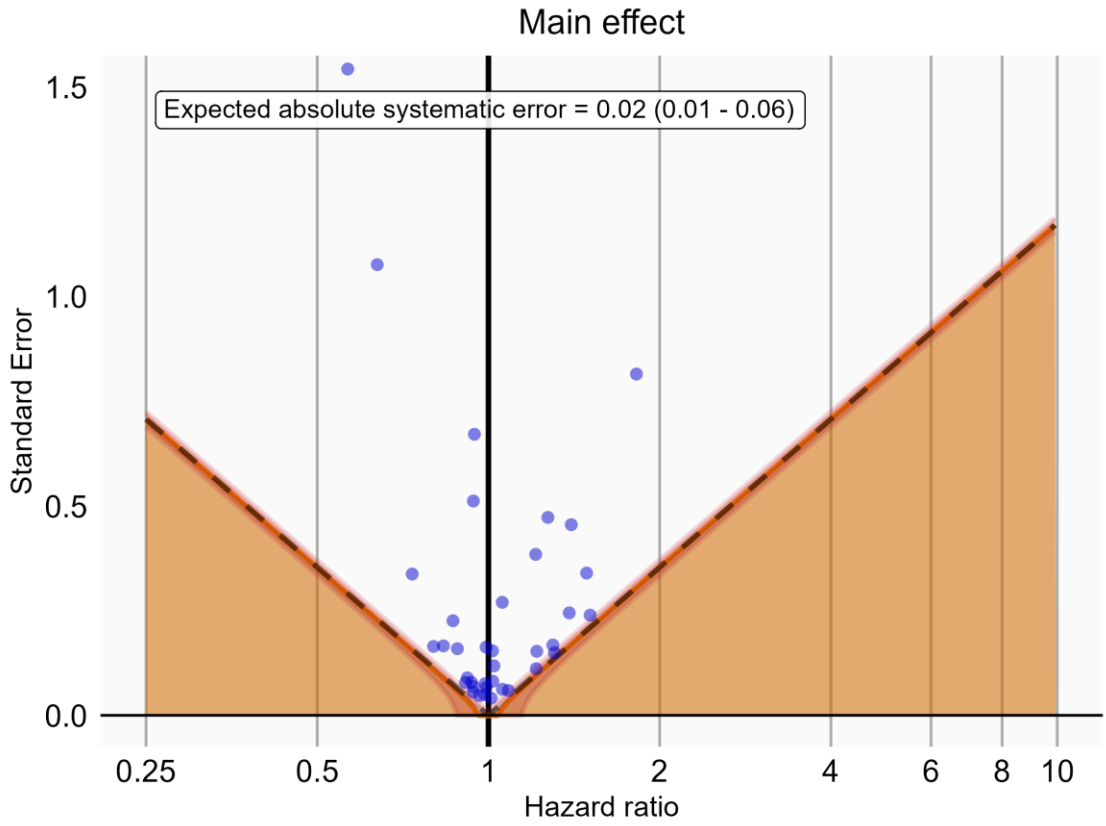
18.5.4. PharMetrics



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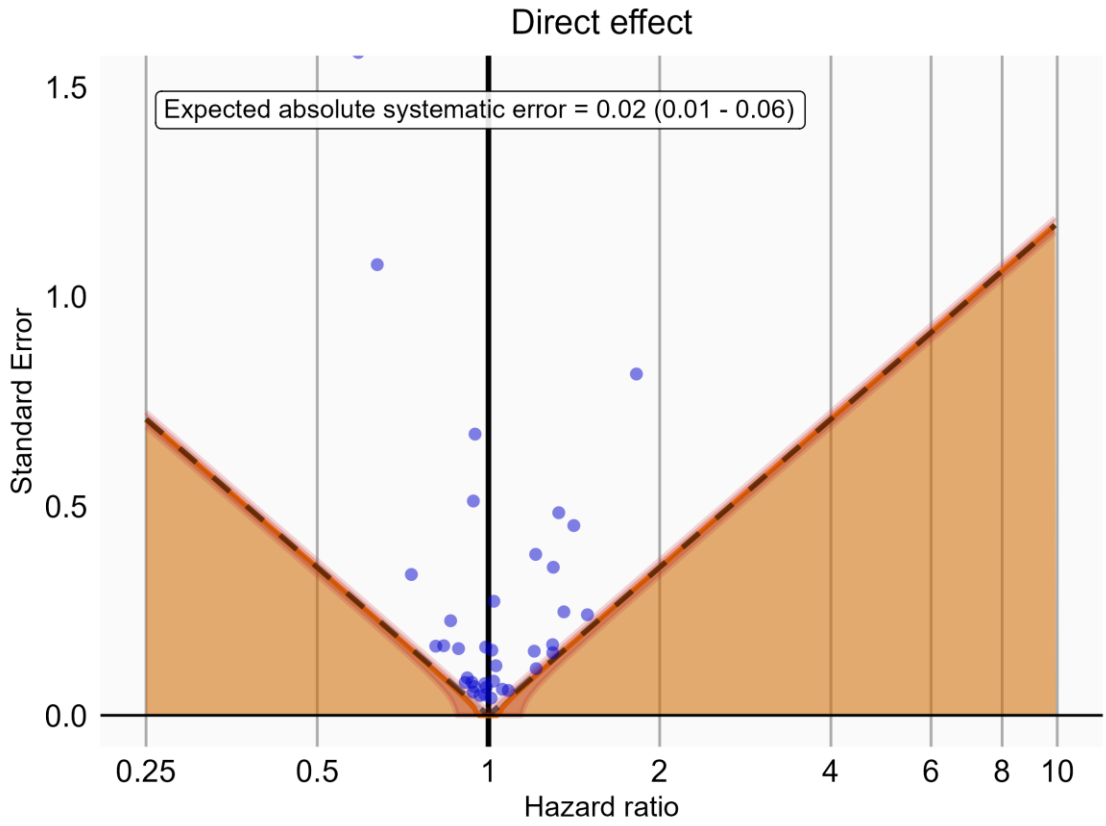
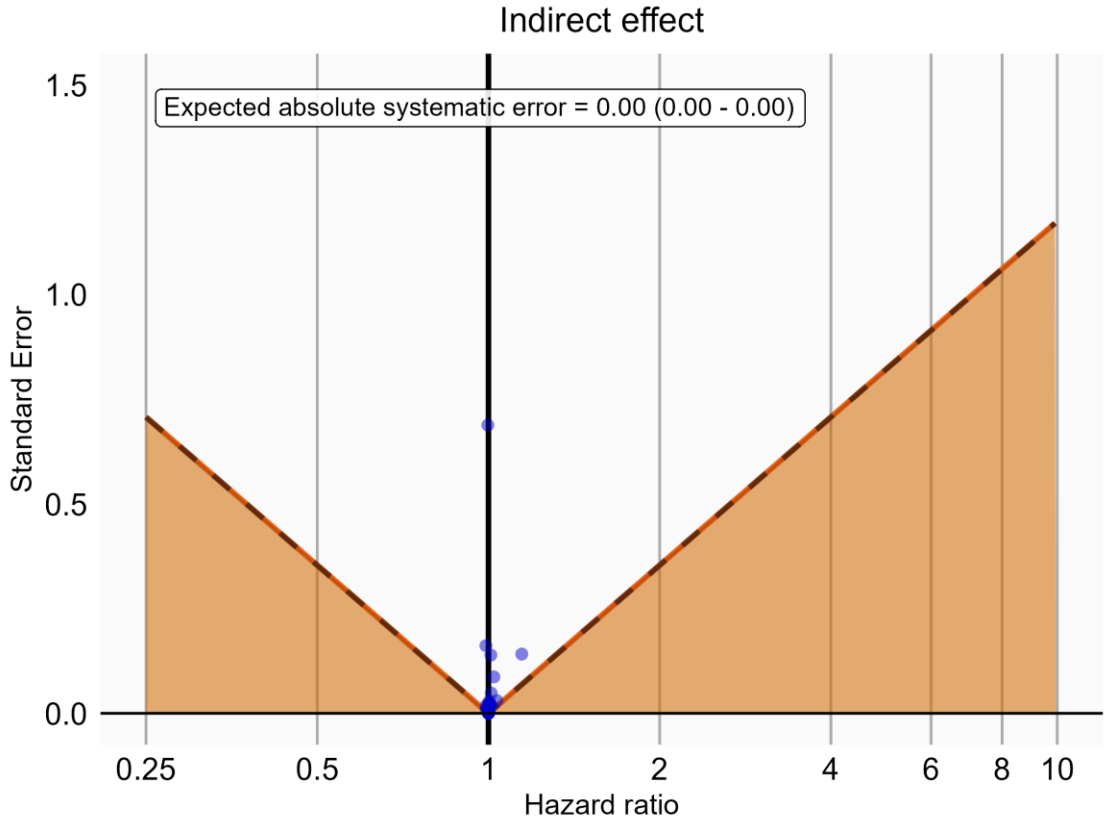


1261

1262 *Negative control estimates of the direct effect comparing DOACs to Warfarin using mediator*
1263 *Extracranial Major bleeding IP-ER in PharMetrics.*



1264

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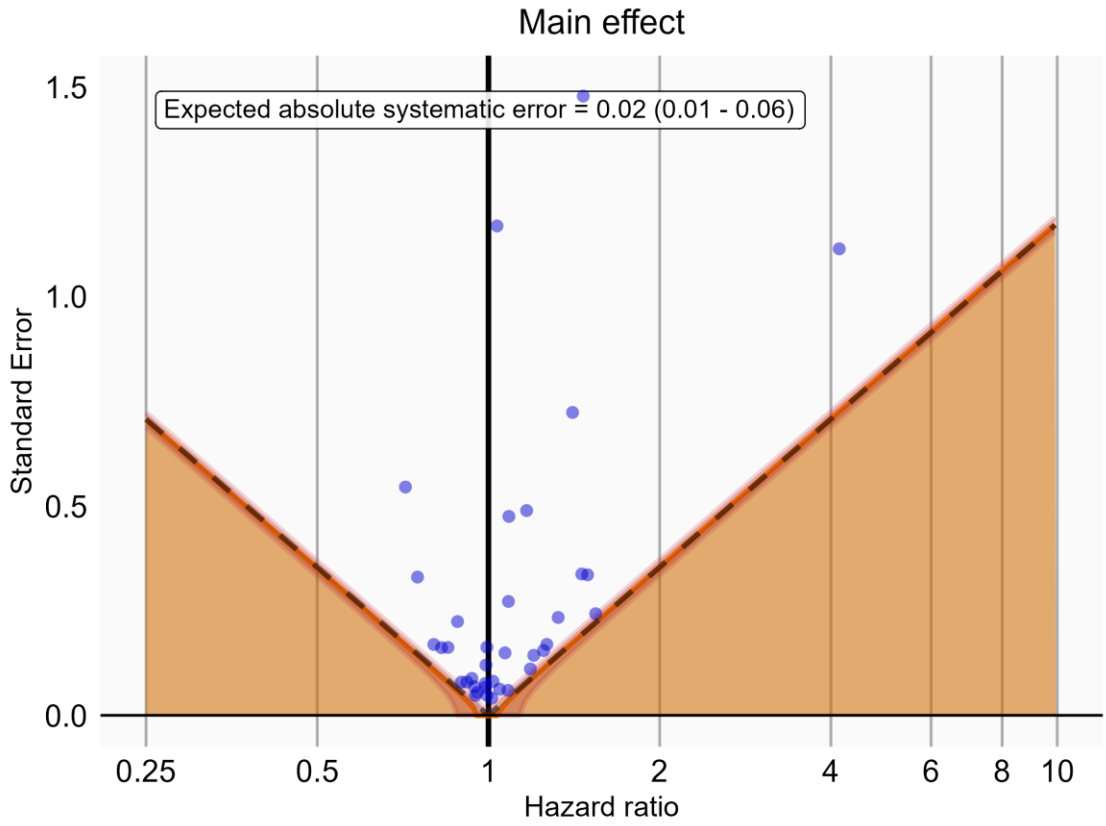
1266 *Extracranial Major bleeding IP-ER in PharMetrics.*



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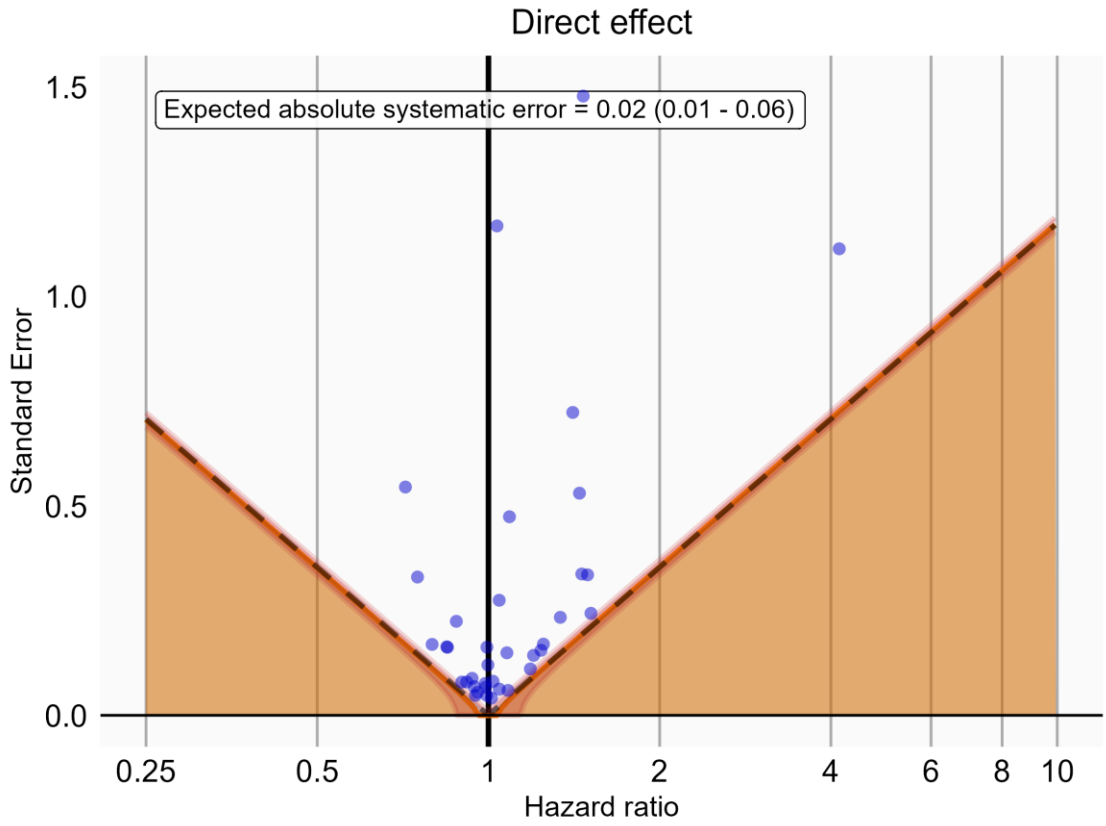

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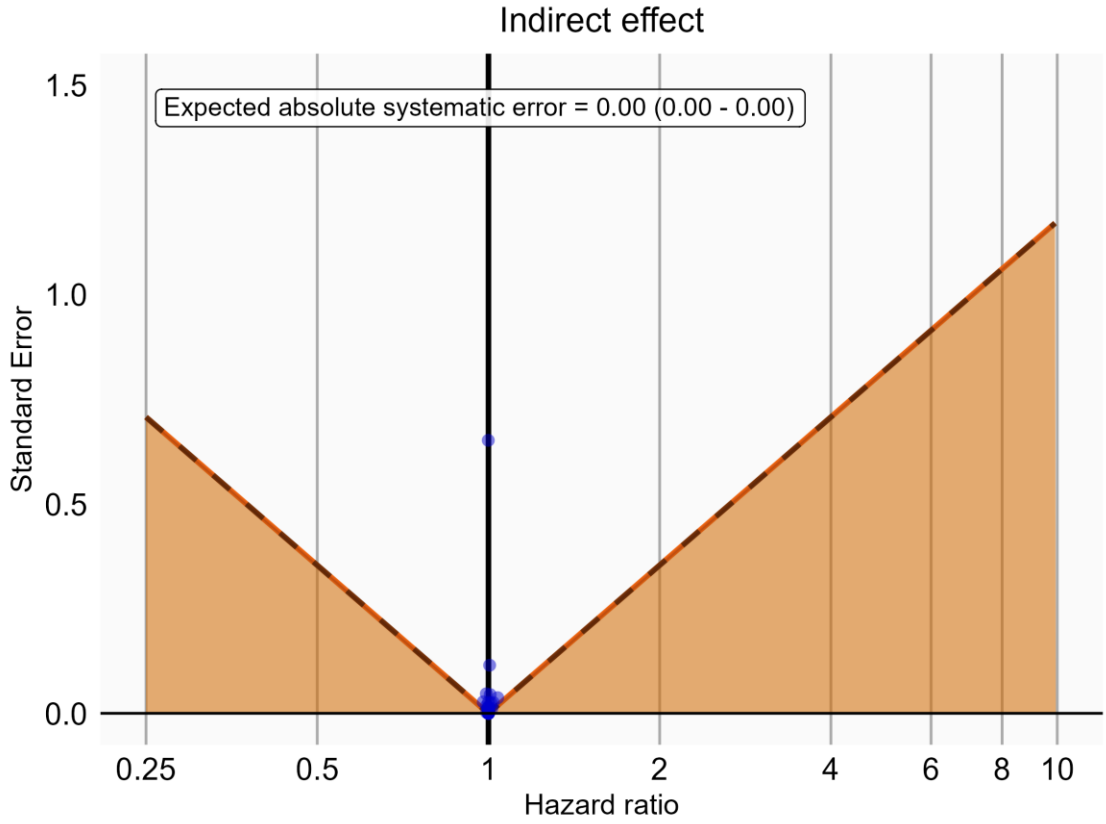
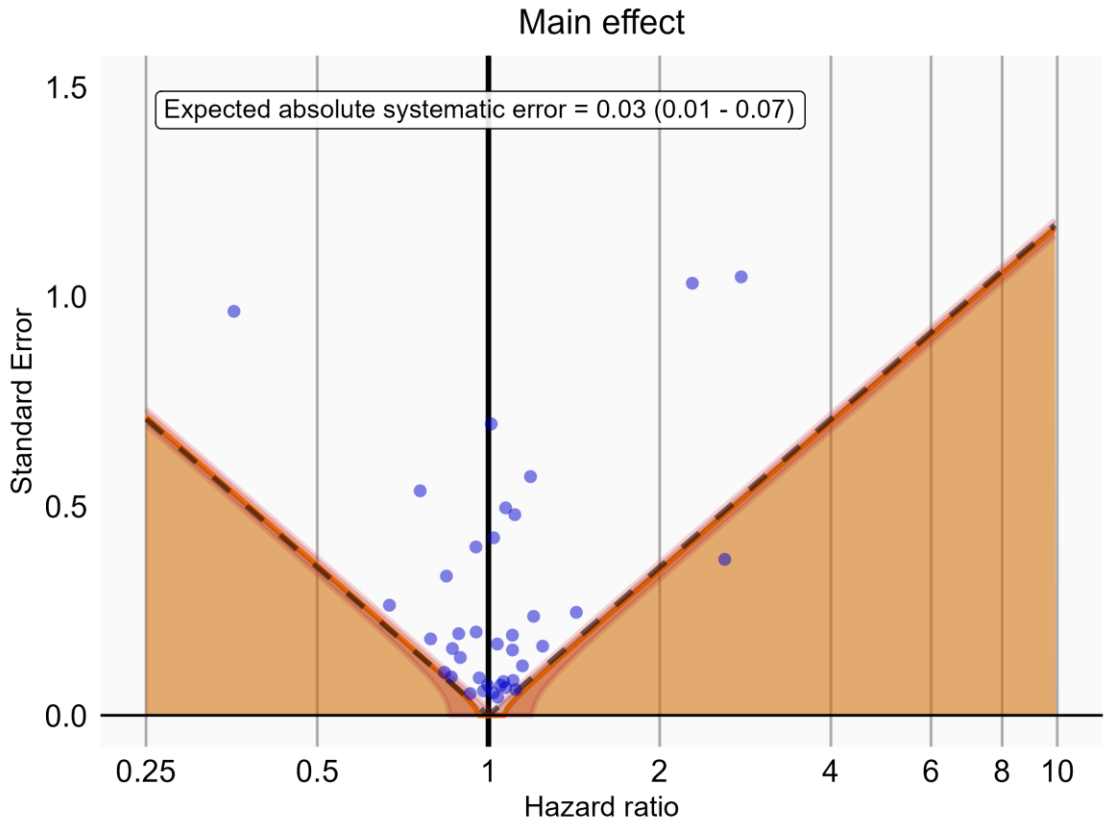


Negative control estimates of the indirect effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in PharMetrics.



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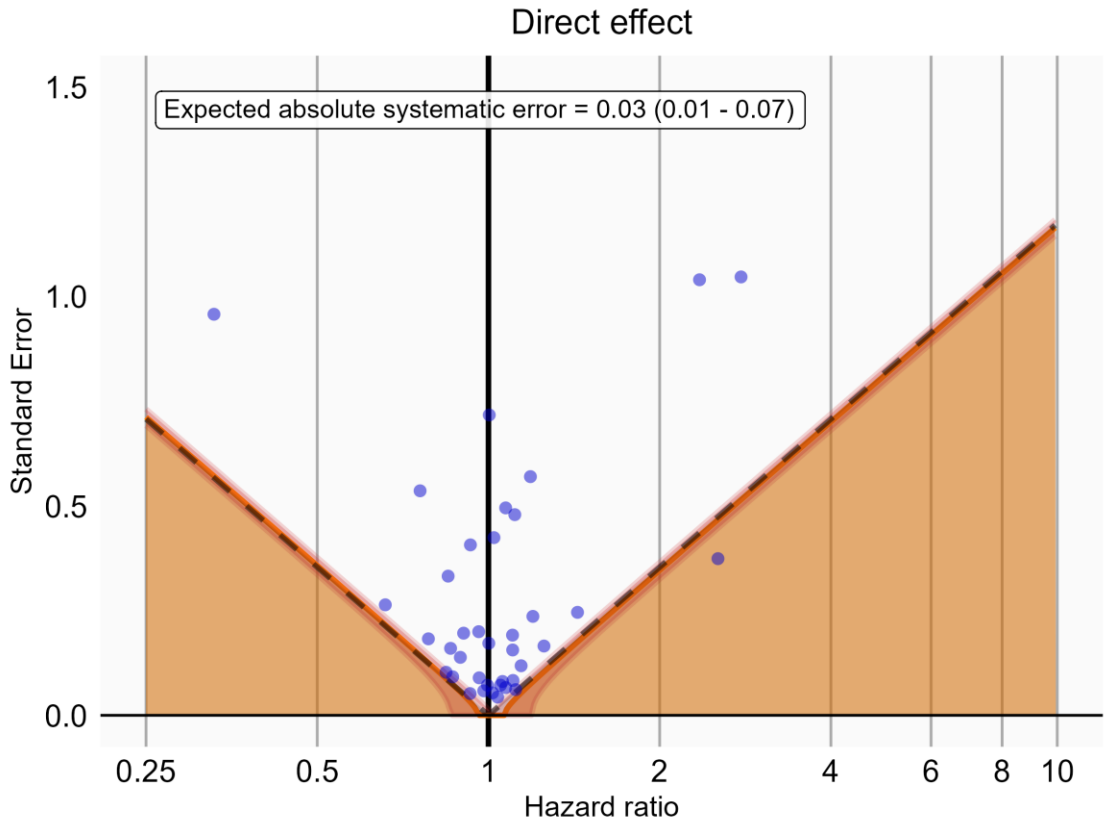

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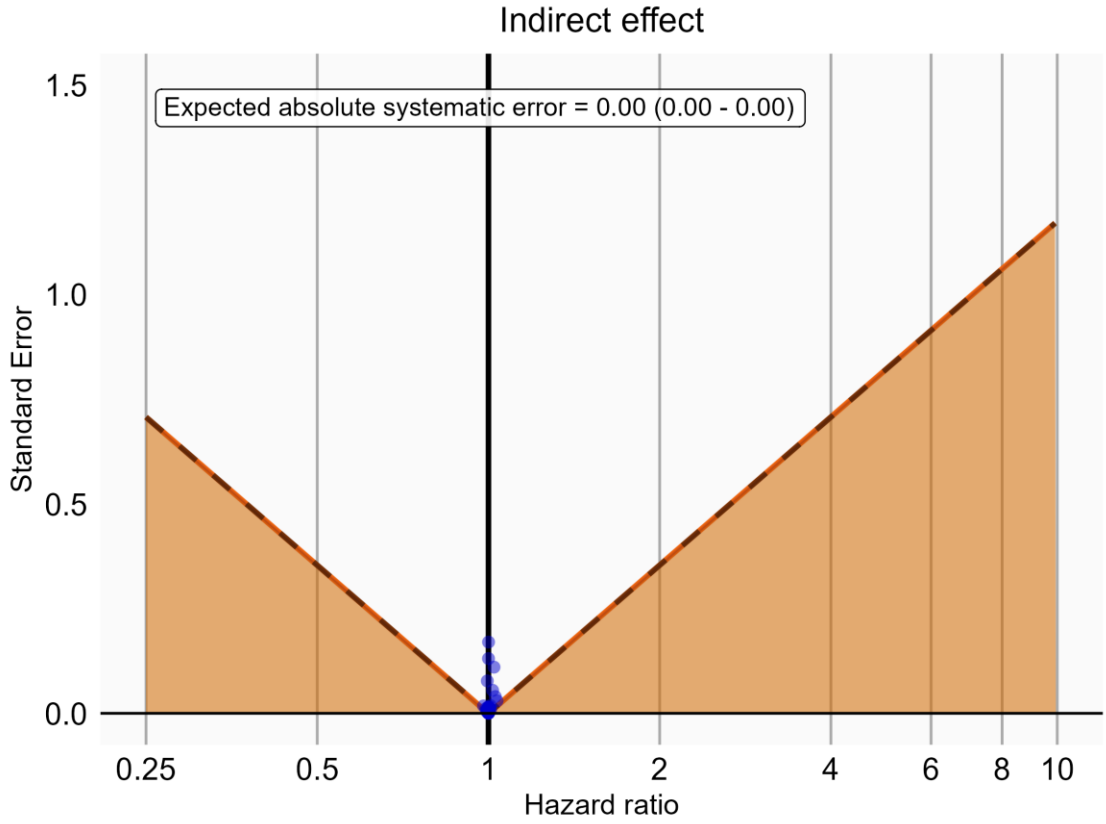
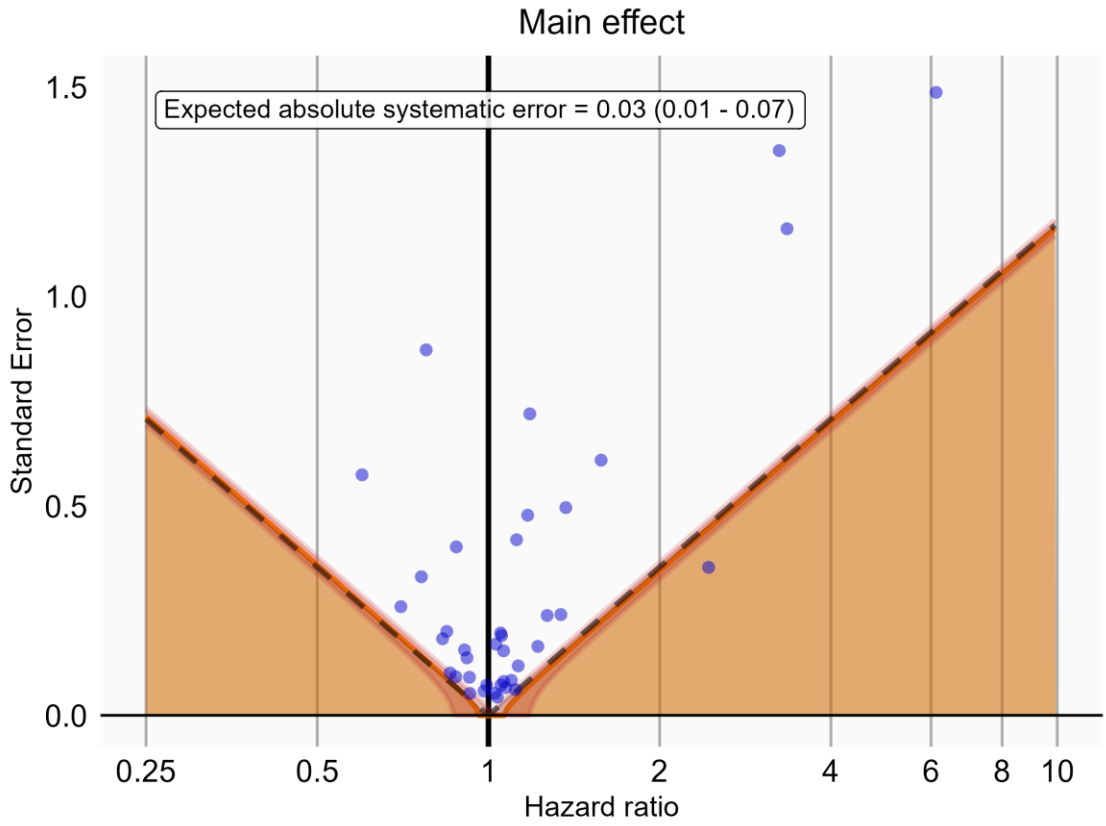


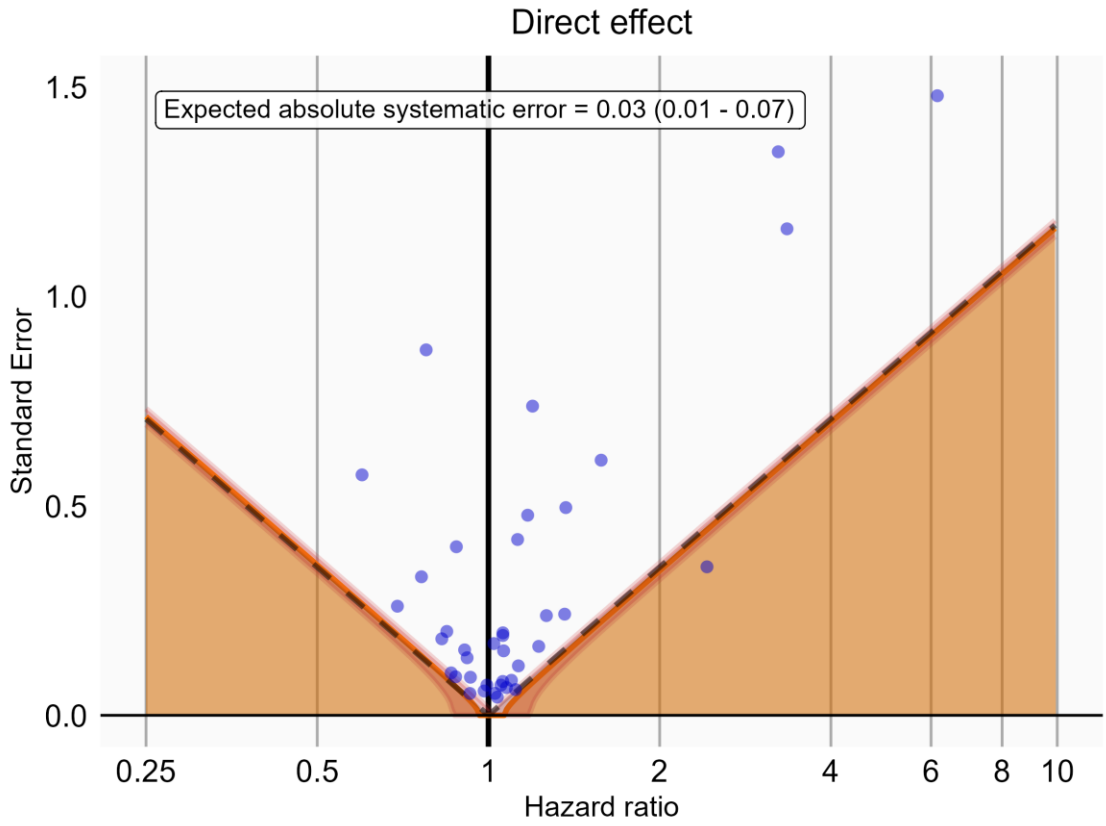
1282

1283 *Negative control estimates of the indirect effect comparing Rivaroxaban to Warfarin using*
1284 *mediator Extracranial Major bleeding IP-ER in PharMetrics.*



1285

1286 *Negative control estimates of the main effect comparing Rivaroxaban to Warfarin using*
1287 *mediator Extracranial Major bleeding IP in PharMetrics.*



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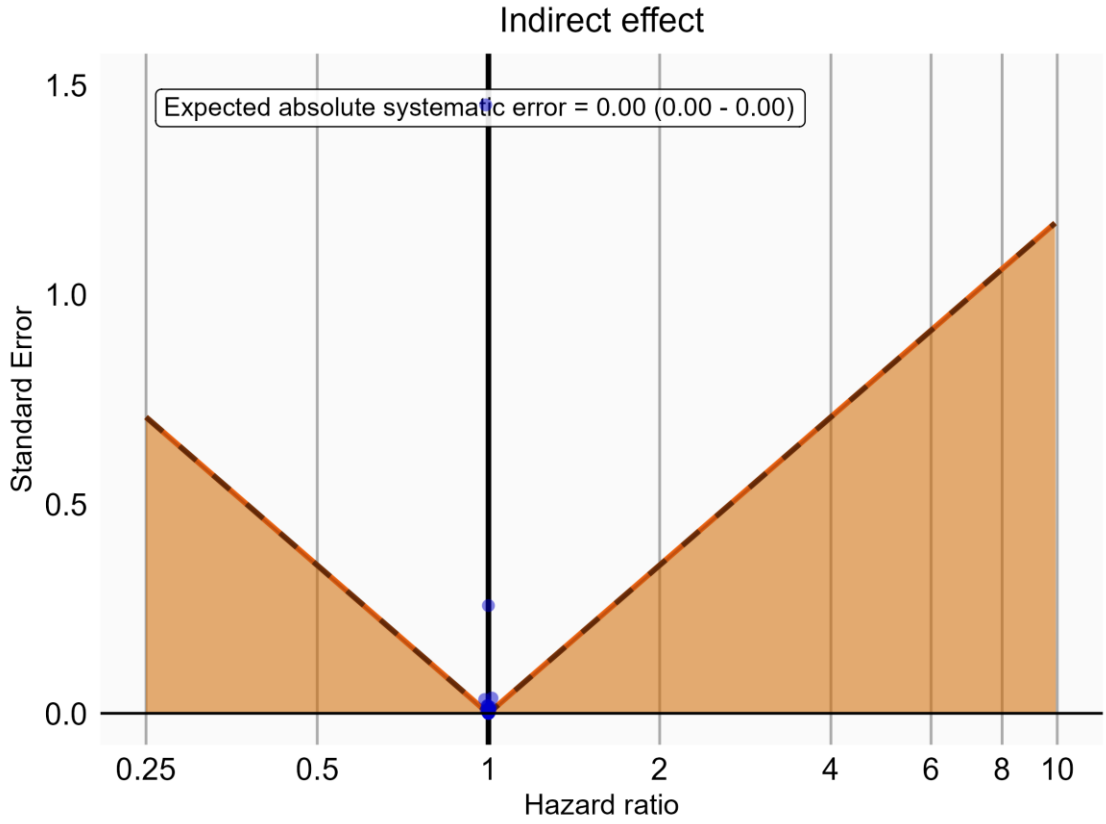
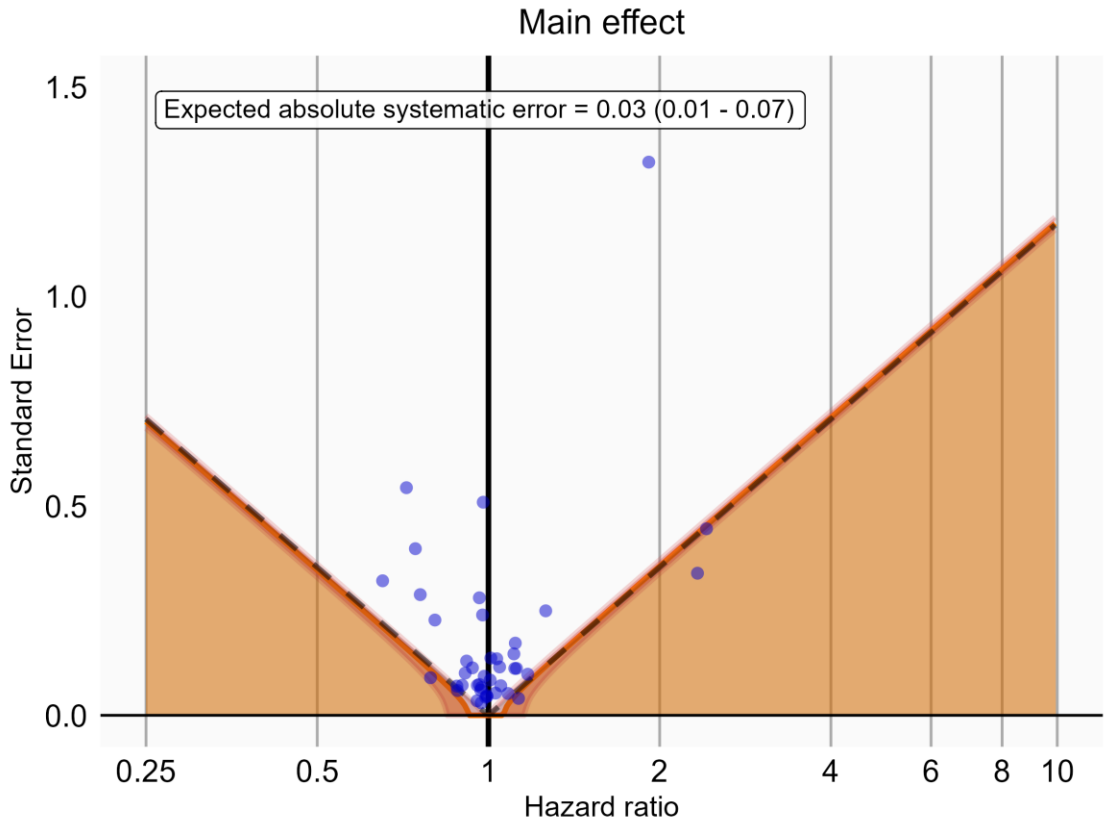
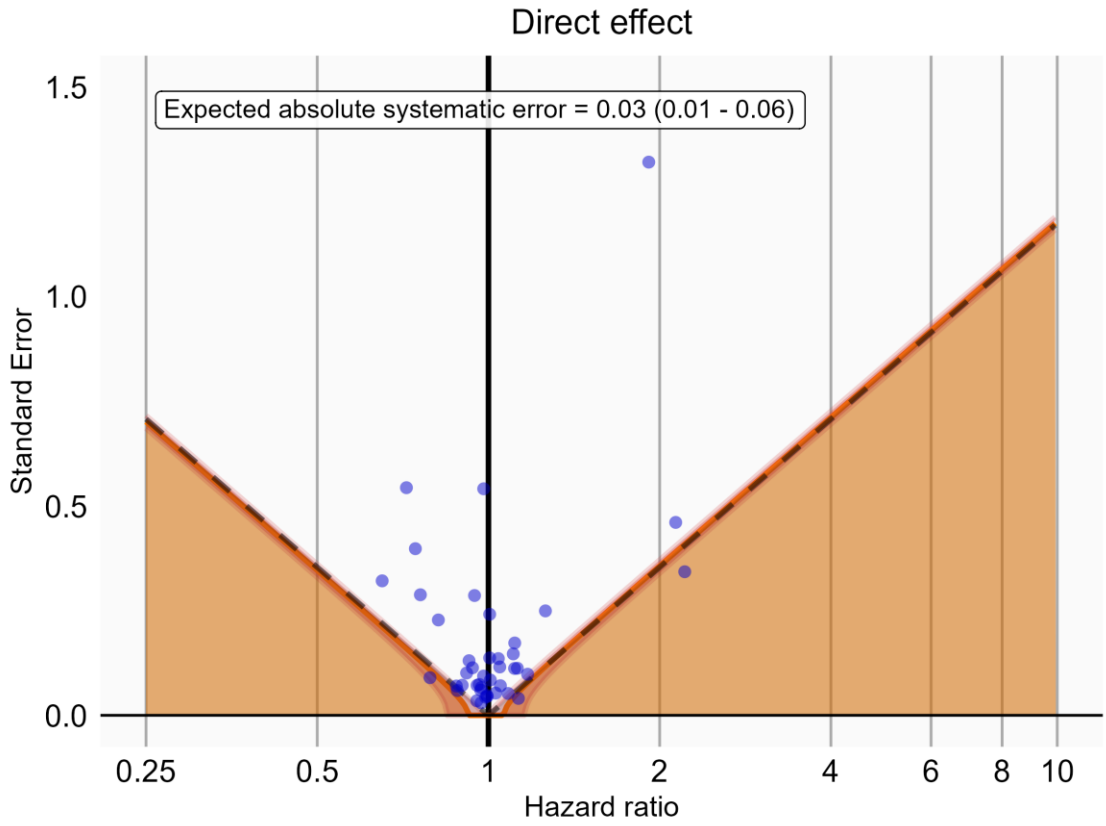


Negative control estimates of the indirect effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in PharMetrics.

18.5.5. MDCR



Negative control estimates of the main effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP-ER in MDCR.



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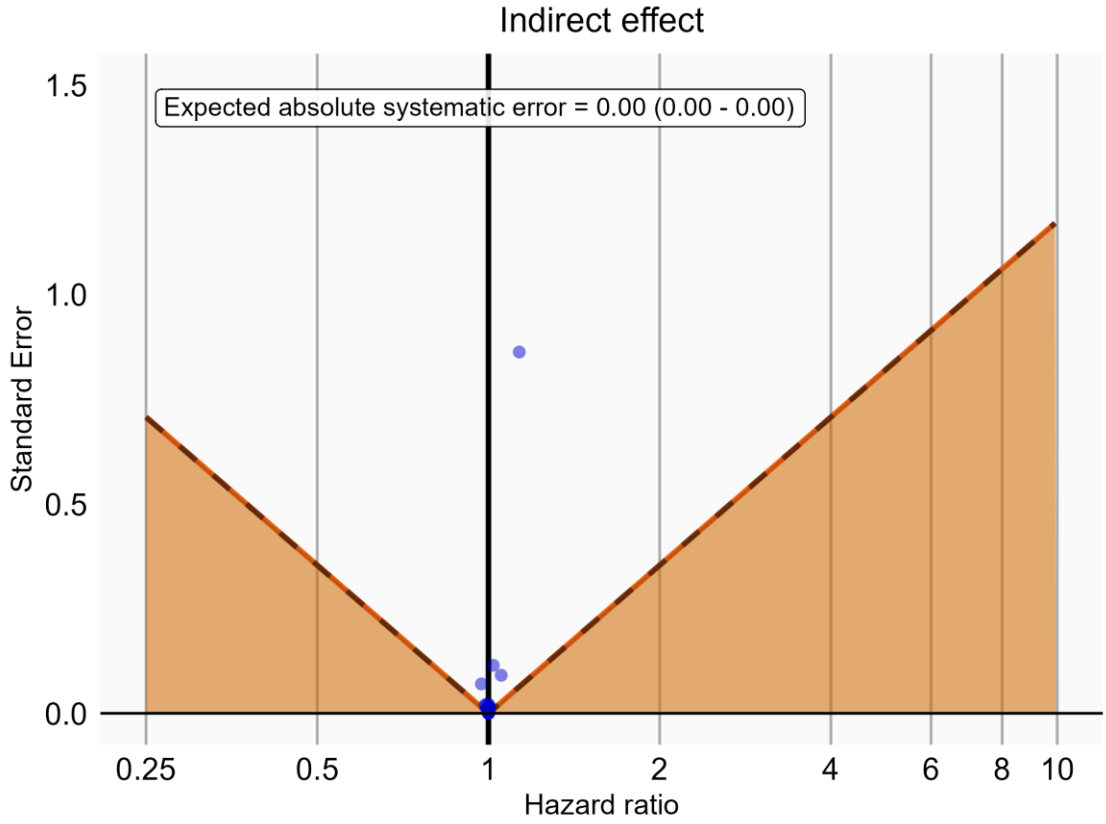

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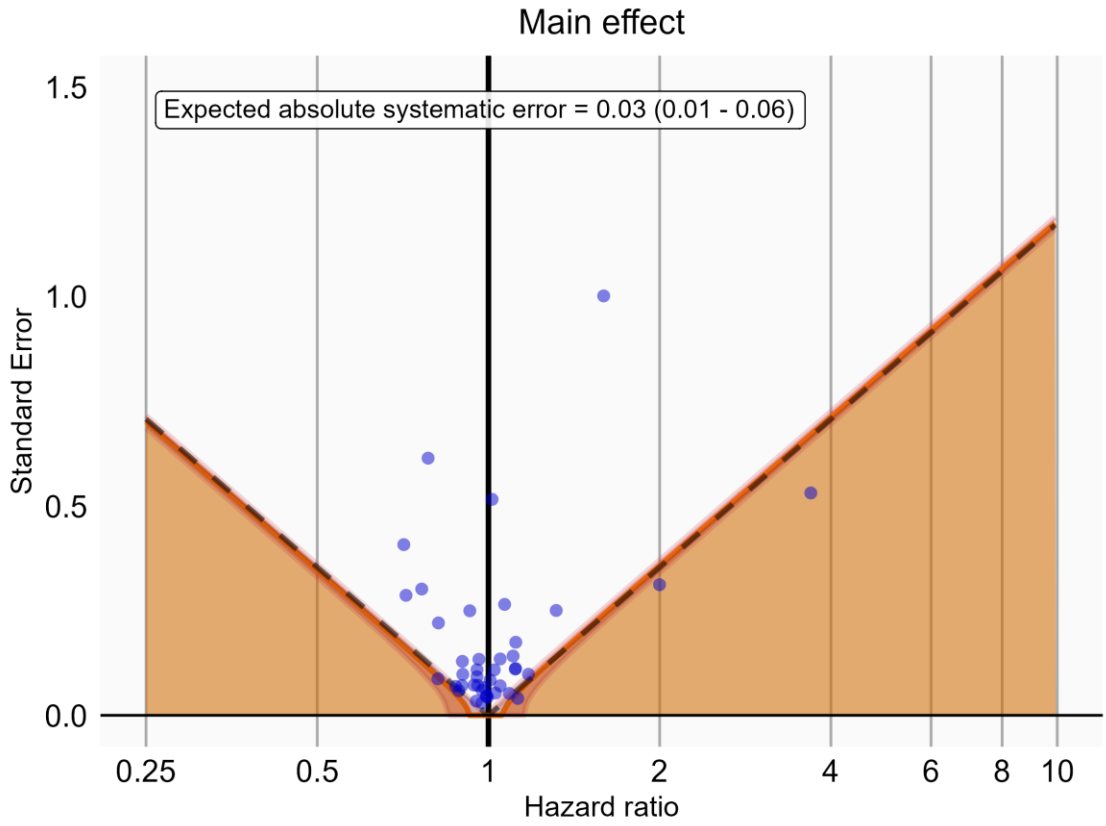
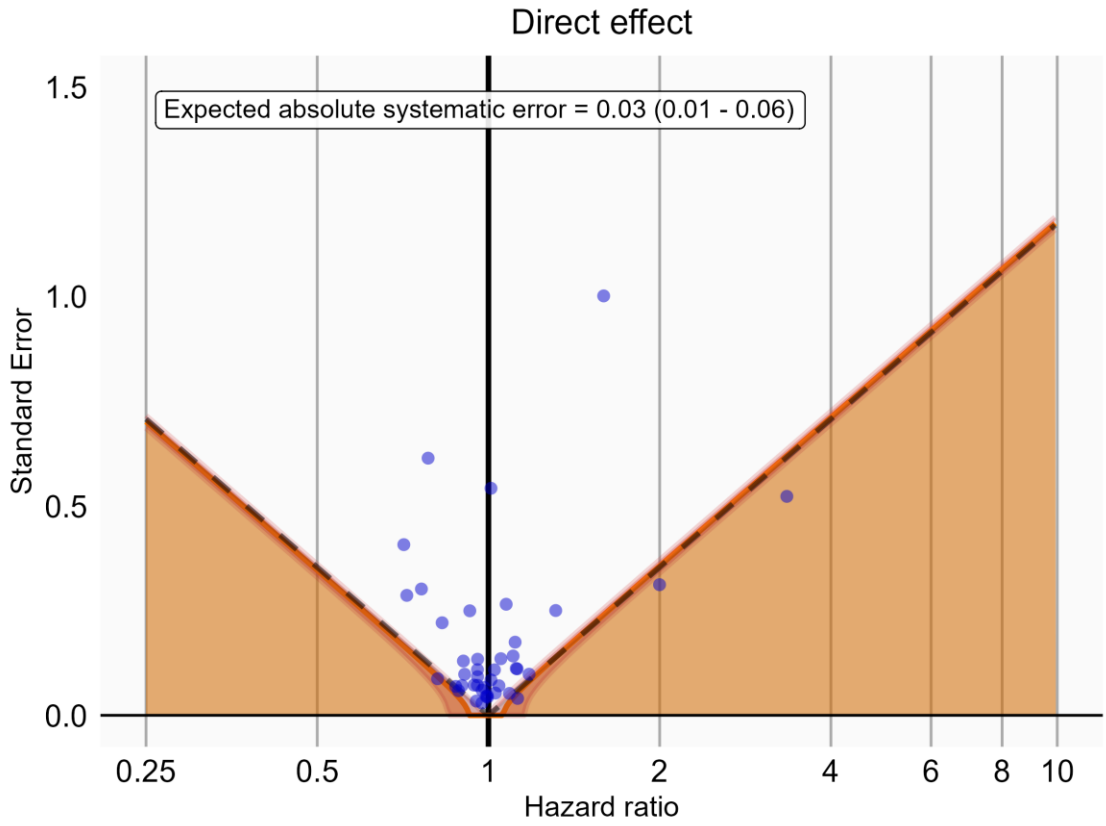


1304

1305 *Negative control estimates of the main effect comparing DOACs to Warfarin using mediator*
1306 *Extracranial Major bleeding IP in MDCR.*



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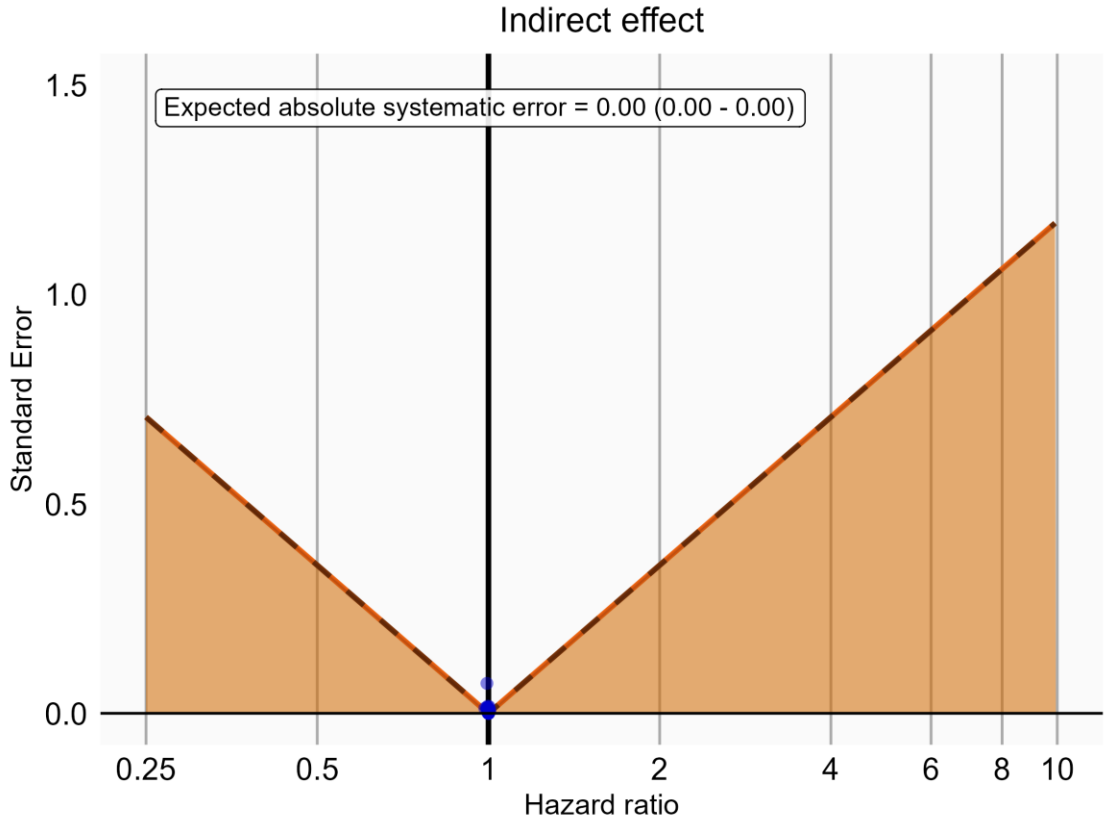
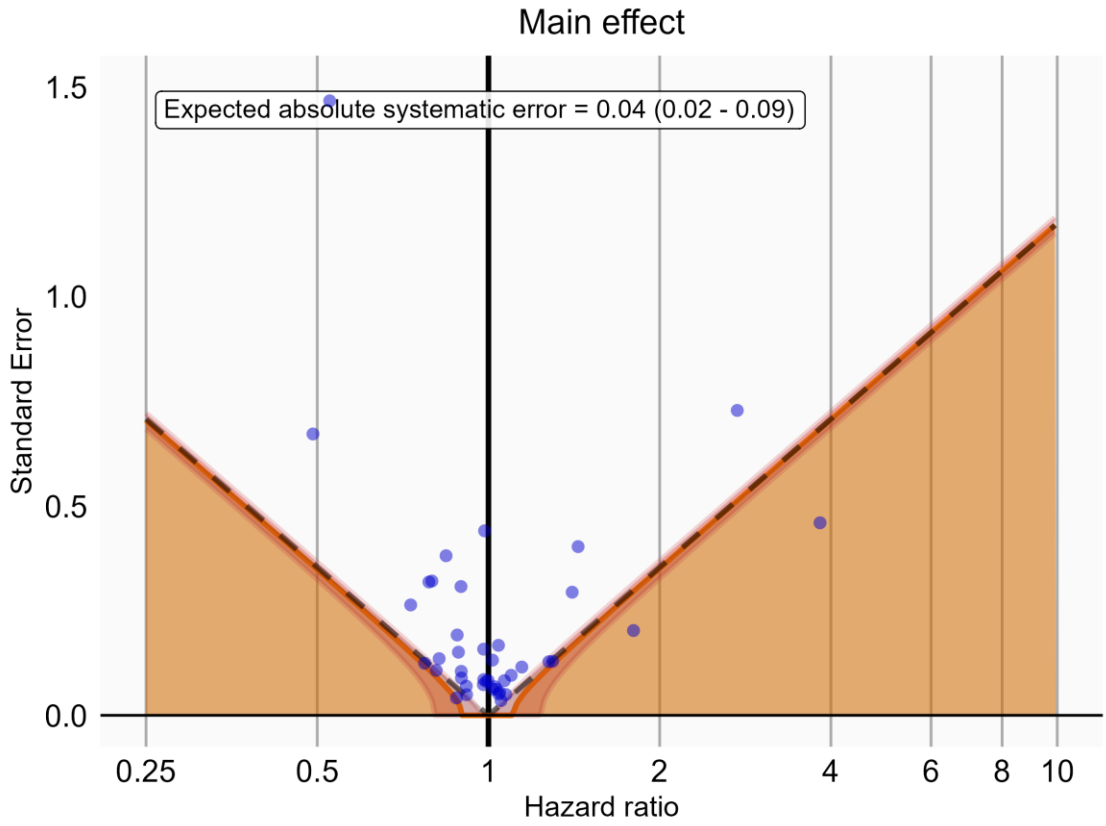


Negative control estimates of the indirect effect comparing DOACs to Warfarin using mediator Extracranial Major bleeding IP in MDCR.



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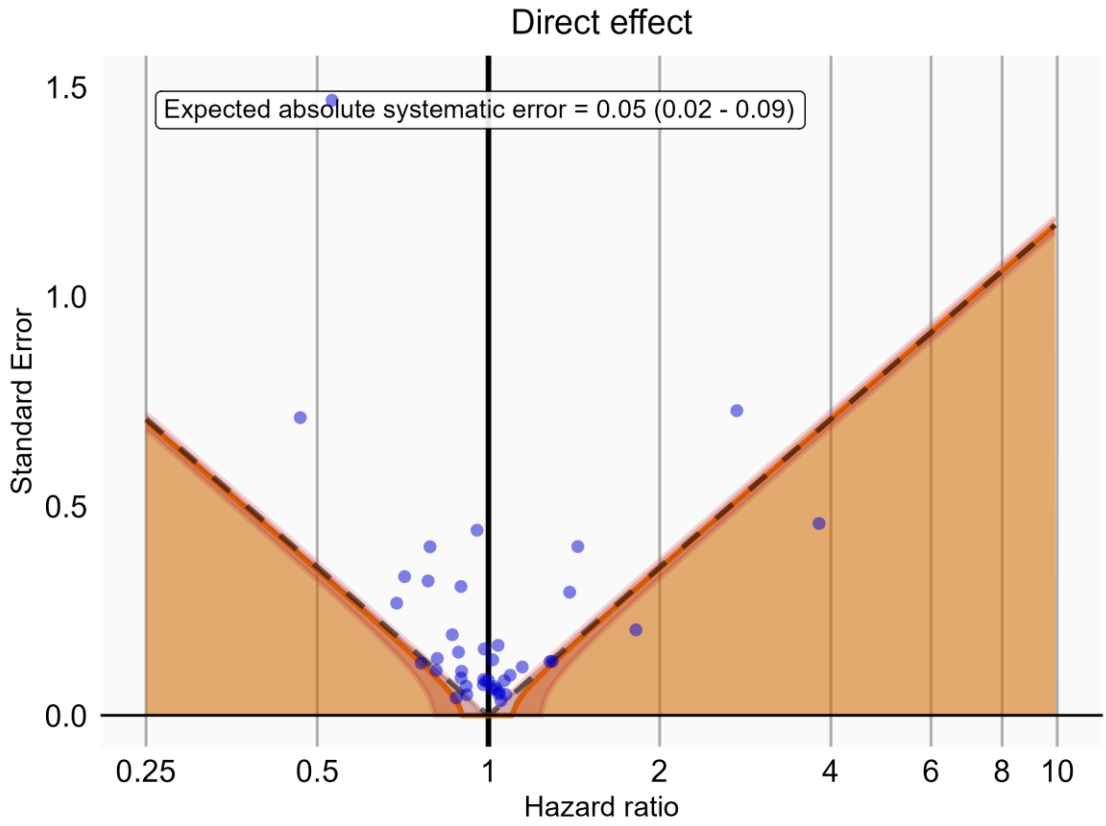
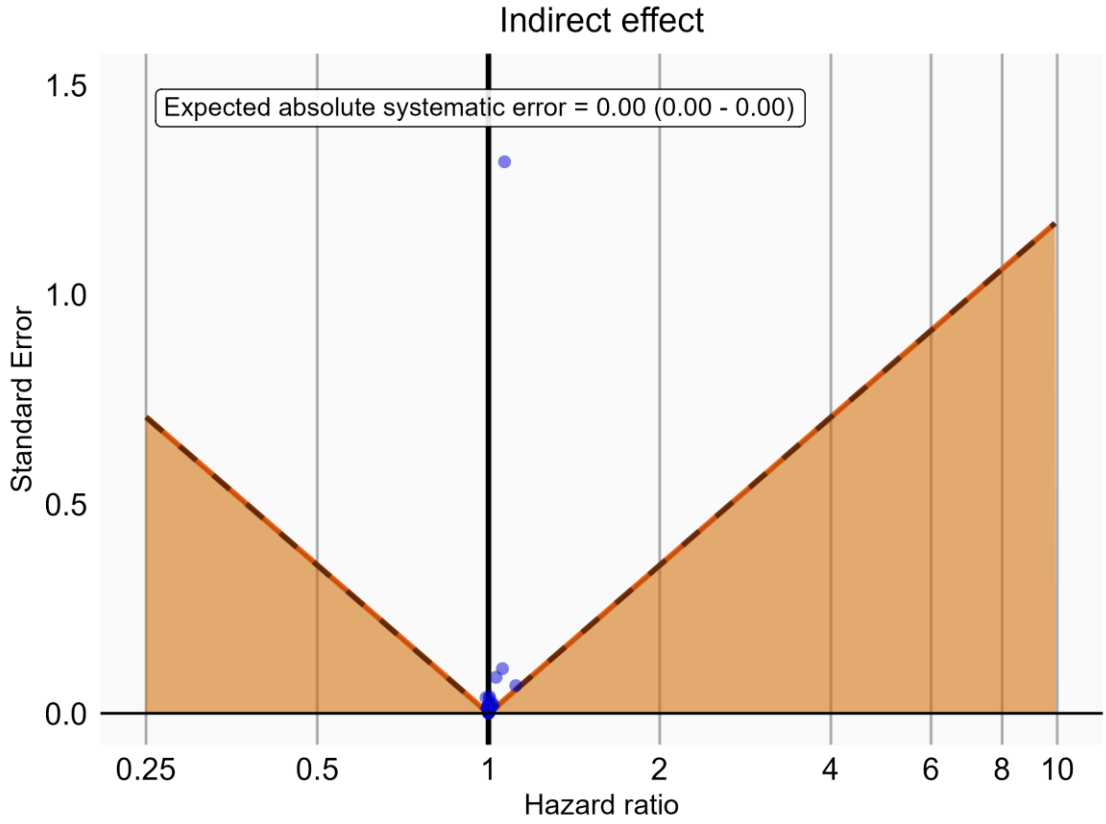


1316

1317 *Negative control estimates of the direct effect comparing Rivaroxaban to Warfarin using*
1318 *mediator Extracranial Major bleeding IP-ER in MDCR.*



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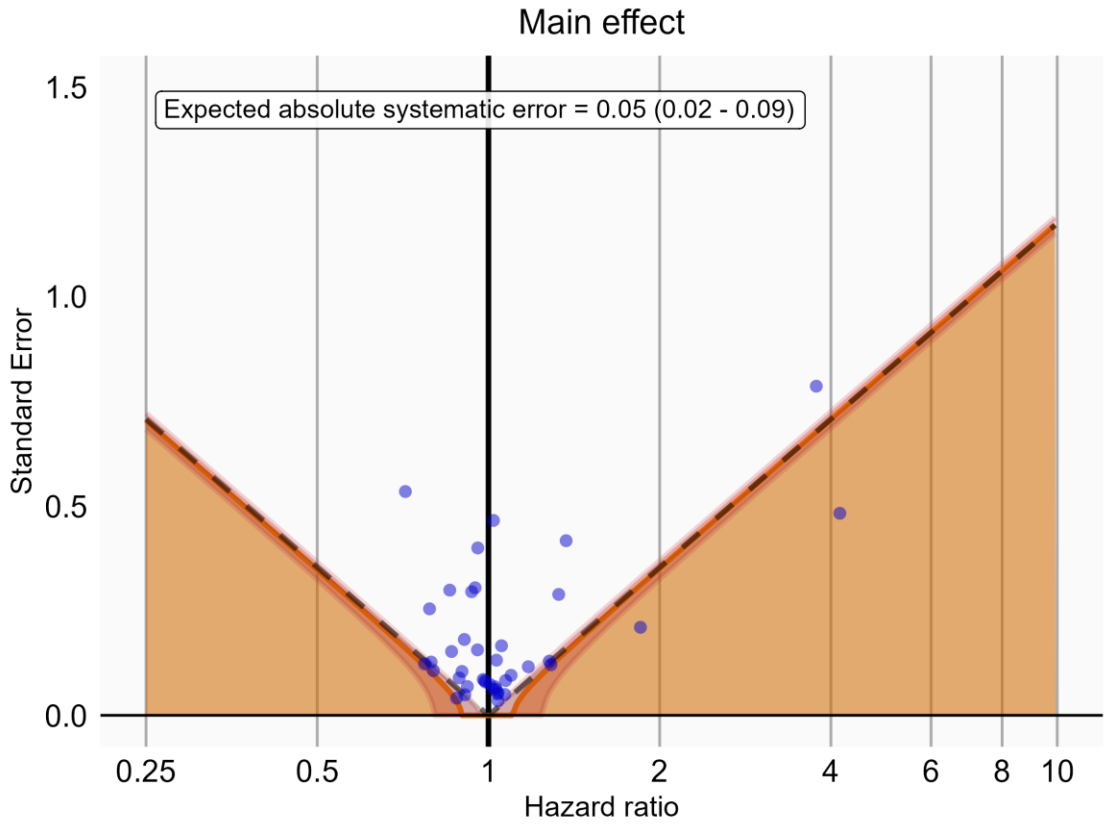

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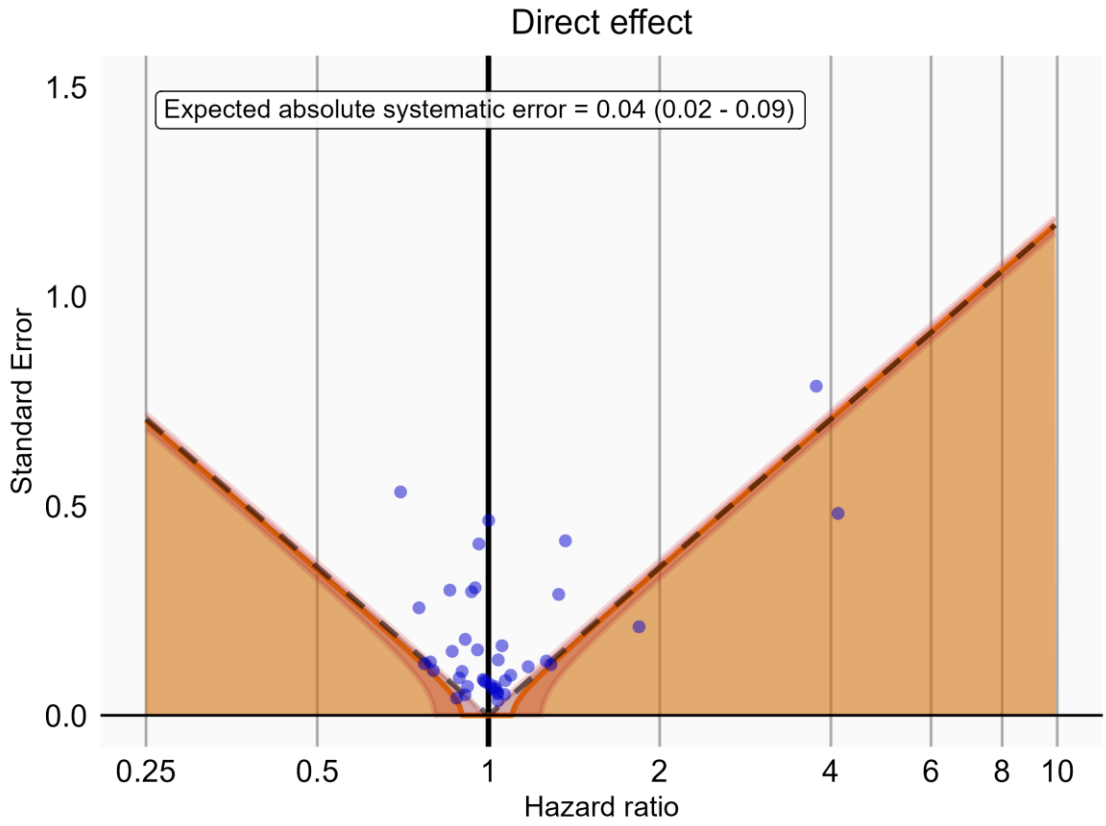

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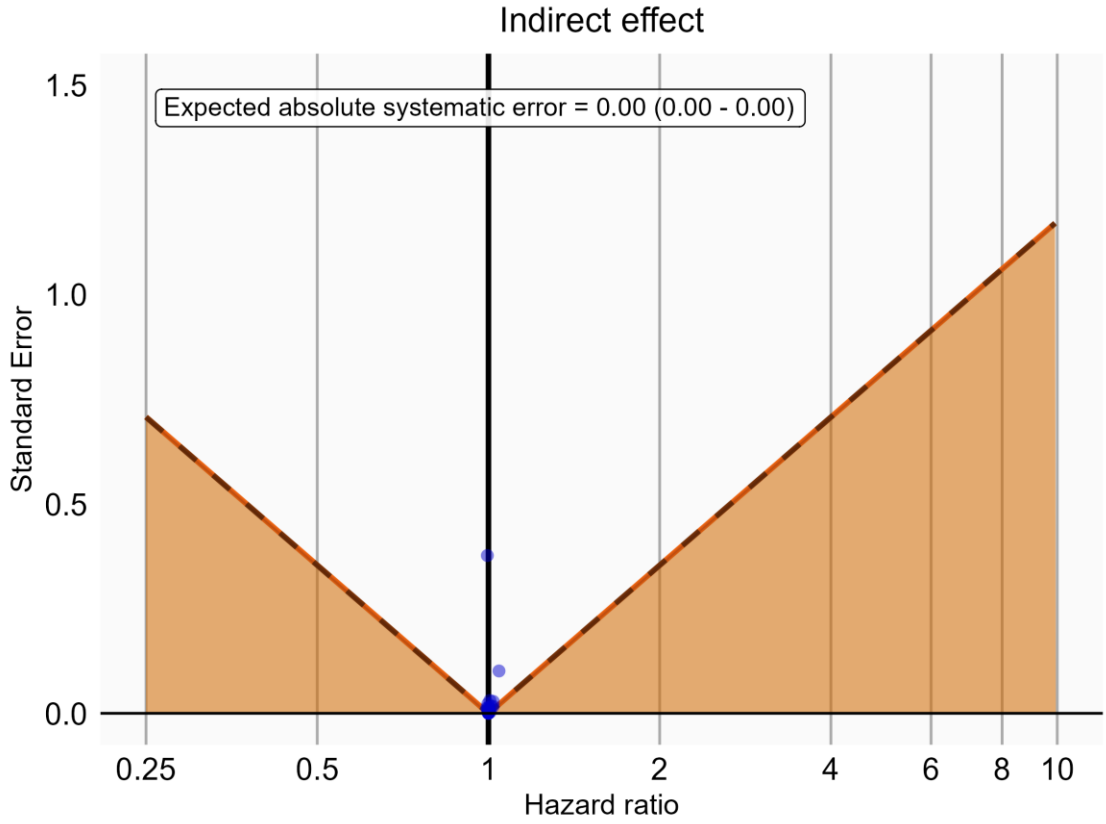

Negative control estimates of the indirect effect comparing Rivaroxaban to Warfarin using mediator Extracranial Major bleeding IP in MDCR.

SPONSOR'S RESPONSIBLE PARTY SIGNATURE AND PARTICIPATING PHYSICIAN AGREEMENT [IF APPLICABLE]

- **For a PASS protocol** (see TV-SOP-04710)**,** the final version of the protocol must be signed (typically in the EDMS) by the QPPV or other appropriate PV reviewer following approval by the appropriate regulatory authority before project initiation. The signature of the appropriate PV reviewer should be included (or referenced when signed in the EDMS) in the Marketing Authorization Holder(s) section at the start of the protocol.
- **For a non-PASS protocol,** the final version of the protocol should be signed by the project owner or other responsible party following internal approval before project initiation.
- This agreement page may be amended or deleted when an alternate signature process is utilized, based on project and/or operating company requirements.
- The Coordinating Study Physician section below is applicable only to country-specific coordinating physicians within the EU and should be deleted if not applicable.

Sponsor's Responsible Party (Main Author):

Name (typed or printed): _____

Institution: Janssen Research & Development, LLC.

Signature: _____ Date: _____

Participating Physician Agreement: [delete when not required]

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Coordinating Physician: [delete when not required]

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal Participating Physician:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Note: If the address or telephone number of the participating physician changes during the study, written notification will be provided to the sponsor; a protocol amendment will not be required.

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