Exploring mediation through major bleeding between direct oral anticoagulants and cardiovascular events (MB mediation in CV RWE)

First published: 22/05/2024

Last updated: 22/05/2024

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000168

Study ID

1000000168

DARWIN EU® study

No

Study countries

United States

Study description

This multi-database observational study will estimate the extent to which the effect of direct oral anticoagulants versus warfarin on cardiovascular outcomes is mediated through their differential impact on extracranial MB rates. This causal mediation analysis will utilize real-world data and novel advanced statistical techniques to model the mediation effects, controlling for confounding factors that could influence both bleeding risk and cardiovascular outcomes. Causal validity study diagnostics with have been applied during protocol development to support evidence reliability.

Study status

Ongoing

Research institutions and networks

Institutions

Johnson & Johnson

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Networks

Observational Health Data Sciences and Informatics (OHDSI) Network

First published: 01/02/2024

Last updated: 01/02/2024

Network

Contact details

Study institution contact

James Weaver jweave17@its.jnj.com

Study contact

jweave17@its.jnj.com

Primary lead investigator

Martijn Schuemie 0000-0002-0817-5361

Primary lead investigator

ORCID number:

0000-0002-0817-5361

Study timelines

Date when funding contract was signed

Planned: 17/05/2024

Actual: 17/05/2024

Study start date

Planned: 17/05/2024

Actual: 17/05/2024

Data analysis start date
Planned: 17/05/2024

Actual: 17/05/2024

Date of final study report
Planned: 31/07/2024

Sources of funding

- Pharmaceutical company and other private sector

Study protocol

Schuemie Yuan Weaver Barnathan - MB mediation in CV RWE.pdf (11.78 MB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Method development or testing

Data collection methods:

Secondary use of data

Study design:

Causal mediation cohort study. New-user comparative cohort design, comparing a target to a comparator cohort for risk of outcome in time-to-event data. A single mediator – extracranial major bleeding - is included in the Cox proportional hazards model.

Main study objective:

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. Estimating the indirect effect is the primary study objective.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

APIXABAN

DABIGATRAN ETEXILATE

RIVAROXABAN

Medicinal product name, other

Warfarin

Study drug International non-proprietary name (INN) or common name

APIXABAN

DABIGATRAN

DABIGATRAN ETEXILATE

EDOXABAN

RIVAROXABAN

Anatomical Therapeutic Chemical (ATC) code

(B01AE07) dabigatran etexilate

dabigatran etexilate

(B01AF01) rivaroxaban

rivaroxaban

(B01AF02) apixaban

apixaban

(B01AF03) edoxaban

edoxaban

Medical condition to be studied

Atrial fibrillation

Ischaemic stroke

Myocardial infarction

Additional medical condition(s)

Extracranial major bleeding

Population studied

Short description of the study population

The study will include patients who meet criteria for inclusion in the target cohorts (1. rivaroxaban intiators or 2. direct oral anticoagulants intitiators) and comparator cohort (warfarin intiators). 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 non-valvular atrial fibrillation observed between 365 days before until and including the index date. Full details of the target, comparator, mediator, and outcome definitions are reported in protocol sections 16.

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Estimated number of subjects

2.974.000

Study design details

Setting

The data will be drawn from five large secondary use observational databases from the United States (four administrative claims, one electronic health record). These data sources met data element requirements per empirical evaluation. 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 protocol sections 16.

Comparators

Warfarin initiators with non-valvular atrial fibrillation.

Outcomes

Cardiovascular events ischaemic stroke and acute myocardial infarction. Mediator condition extracranial major bleeding. Definitions are provided in protocol section 16.

Data analysis plan

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.

- 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.

Data management

Data sources

Data source(s), other

- Merative™ MarketScan® Commercial Claims and Encounters Database
- Merative™ MarketScan® Medicare Supplemental and Coordination of Benefits Database
- Optum® de-identified Electronic Health Record Dataset
- Optum’s de-identified Clinformatics® Data Mart Database
- IQVIA™ Adjudicated Health Plan Claims Data

Data sources (types)

Administrative healthcare records (e.g., claims)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

OMOP

CDM website

https://www.ohdsi.org/Data-standardization/

CDM version

5.4

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation moment

after extract-transform-load to a common data model

Data characterisation details

The DatabaseDiagnostics package (Blacketer, 2023) was used to select those databases that include the required data elements for the estimation questions. Protocol section 10.4.3.