

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

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Study

Ongoing

## Administrative details

### EU PAS number

EUPAS1000000168

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### Study ID

1000000168

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### DARWIN EU® study

No

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### Study countries

 United States

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### 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.

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### **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

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Study contact

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### Primary lead investigator

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Primary lead investigator

### ORCID number:

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## Study timelines

### Date when funding contract was signed

Planned: 17/05/2024

Actual: 17/05/2024

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### Study start date

Planned: 17/05/2024

Actual: 17/05/2024

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**Data analysis start date**

Planned: 17/05/2024

Actual: 17/05/2024

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**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

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

Not applicable

## Methodological aspects

### Study type

### Study type list

**Study topic:**

Human medicinal product

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**Study type:**

Non-interventional study

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**Scope of the study:**

Effectiveness study (incl. comparative)

Method development or testing

**Data collection methods:**

Secondary use of data

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**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

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### **Medicinal product name, other**

Warfarin

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

APIXABAN

DABIGATRAN

DABIGATRAN ETEXILATE

EDOXABAN

RIVAROXABAN

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### **Anatomical Therapeutic Chemical (ATC) code**

(B01AE07) dabigatran etexilate

dabigatran etexilate

(B01AF01) rivaroxaban

rivaroxaban

(B01AF02) apixaban

apixaban

(B01AF03) edoxaban

edoxaban

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## **Medical condition to be studied**

Atrial fibrillation

Ischaemic stroke

Myocardial infarction

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## **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 initiators or 2. direct oral anticoagulants initiators) and comparator cohort (warfarin initiators). 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  $\geq 1$  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.

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## **Age groups**

- **Adult and elderly population ( $\geq 18$  years)**

- Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly ( $\geq 65$  years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)
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## **Estimated number of subjects**

2974000

# 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  $\geq 365$  days of prior database observation time. Full target and comparator cohort definitions are available in protocol sections 16.

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## **Comparators**

Warfarin initiators with non-valvular atrial fibrillation.

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## **Outcomes**

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

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## **Data analysis plan**

For each target-comparator-outcome triplet, two Cox models 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

### ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

## 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

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### **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

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#### **CDM website**

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

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#### **CDM version**

5.4

## Data quality specifications

### **Check conformance**

Yes

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### **Check completeness**

Yes

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### **Check stability**

Yes

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**Check logical consistency**

Yes

## Data characterisation

**Data characterisation conducted**

Yes

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**Data characterisation moment**

after extract-transform-load to a common data model

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**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.