TARGET-EU: Rivaroxaban and risk of major gastrointestinal bleeding in elderly patients with non-valvular atrial fibrillation

First published: 29/05/2026

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Study Planned

Administrative details

EU PAS number

EUPAS1000001001

Study ID

1000001001

DARWIN EU® study

No

Study countries

Denmark

Netherlands

Spain

Study description

This case study is part of the broader TARGET-EU project (EUPAS1000000539), which aims to advance the regulatory use of real-world data through the application of target trial emulation and estimand methodologies.

Background: Non-valvular atrial fibrillation (NVAF) is a common arrhythmia associated with significant morbidity and mortality. Direct oral anticoagulants (DOACs) are recommended over vitamin K antagonists in NVAF patients. Evidence suggests clinically important differences in bleeding risk between DOACs, particularly in high-risk populations such as the elderly, who are often underrepresented in randomised controlled trials.

Objectives: The primary objective is to estimate the effect of initiating rivaroxaban versus apixaban on time to a first major gastrointestinal (GI) bleeding event among adults aged 75 years or older with non-valvular atrial fibrillation.

Methods: We will conduct an active comparator new-user cohort study using linked electronic health records from Denmark (Danish national registers) and Spain (SIDIAP). Eligible individuals are adults aged 75 years or older who initiated rivaroxaban or apixaban between 2013 and 2023. In the primary analysis, a while-on-treatment strategy is used for treatment-related intercurrent events (discontinuation and switching), and a while-alive strategy is applied to non-GI bleeding death. Inverse probability of treatment weighting (IPTW) is used to estimate treatment effects. The primary analysis uses a Cox proportional hazards model, with supplemental analyses using an accelerated failure time model to estimate restricted mean survival time at 1 and 2 years. Sensitivity analyses will assess the impact of departures from key assumptions, including censoring-at-random (via inverse probability of censoring weighting) and outcome misclassification (via probabilistic bias analysis).

Study status

Planned

Research institutions and networks

Institutions

Electronic Health Records (EHR) Research Group, London School of Hygiene & Tropical Medicine (LSHTM)

United Kingdom

First published: 19/04/2010

Last updated: 30/10/2024

Institution | **Educational Institution** | **ENCePP partner**

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

First published: 01/03/2010

Last updated: 27/05/2026

Institution | **Educational Institution** | **ENCePP partner**

Clinical Pharmacology, Vall d'Hebron Institut de Recerca (VHIR)

Spain

First published: 18/05/2021

Last updated: 20/05/2021

Institution | Outdated | Hospital/Clinic/Other health care facility | ENCePP partner

University Medical Center Utrecht (UMCU)

Netherlands

First published: 24/11/2021

Last updated: 22/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, IDIAPJGol

Spain

First published: 05/10/2012

Last updated: 23/05/2025

Institution | Educational Institution | Laboratory/Research/Testing facility | Not-for-profit | ENCePP partner

Teamit Institute

Spain

First published: 12/03/2024

Last updated: 12/03/2024

Institution | Other | ENCePP partner

University of Copenhagen (UCPH)

Contact details

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Primary lead investigator

Patrick Souverein

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 10/09/2024

Study start date
Planned: 09/03/2026

Date of final study report
Planned: 10/06/2026

Study protocol

Emulation_Protocol_CS4_REV5_clean.pdf (829.11 KB)

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:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

This study will emulate a hypothetical target trial using a retrospective, active-comparator, new-user cohort design based on routinely collected electronic health records.

Main study objective:

The overall aim is to assess whether rivaroxaban is associated with a different risk of major gastrointestinal bleeding compared with apixaban in adults aged 75 years or older with non-valvular atrial fibrillation.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

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

RIVAROXABAN

APIXABAN

Anatomical Therapeutic Chemical (ATC) code

(B01AF01) rivaroxaban

rivaroxaban

(B01AF02) apixaban

apixaban

Medical condition to be studied

Atrial fibrillation

Population studied

Short description of the study population

The study population will consist of adults aged 75 years or older with non-valvular atrial fibrillation (NVAF) who initiate treatment with either rivaroxaban or apixaban during the study period. Cohort entry (index date) is defined as the date of the first prescription of either treatment.

To be eligible, individuals must have a diagnosis of atrial fibrillation within a 30-day window around the index date and be aged 75 years or older at cohort entry.

Several exclusion criteria will be applied: individuals must have at least 365 days of recorded medical history prior to the index date; those with a documented diagnosis of valvular atrial fibrillation at any time before the index date will be excluded; and individuals with any prior use of a DOAC or vitamin K antagonist in the year preceding cohort entry will be excluded to implement a new-user design.

Age groups

- Adults (75 to < 85 years)
- Adults (85 years and over)

Study design details

Setting

This study is conducted using routinely collected electronic health records from 2013 to 2023, reflecting the period of routine clinical use of direct oral anticoagulants in older adults. The study is set in hospital and outpatient settings (Danish registers) and primary care with hospital linkage (SIDIAP), providing population-based coverage of real-world clinical care in Denmark and Spain.

Comparators

The comparator group consists of patients who initiate apixaban at any dose, formulation, or regimen. The use of an active comparator is the most appropriate approach as it aligns with real-world clinical practice, addresses confounding by indication, and allows the safety of rivaroxaban to be benchmarked against a commonly prescribed alternative for NVAF. Both treatments are used for the same indication, and treatment episodes may last for up to two years.

Outcomes

The primary endpoint is time to first occurrence of major gastrointestinal bleeding, identified through hospital admissions, primary care records, or death records using ICD-10 diagnostic codes. The definition of major bleeding follows the International Society on Thrombosis and Haemostasis (ISTH) criteria, operationalised in real-world data using relevant diagnostic codes.

Data analysis plan

Analyses are conducted within a target trial emulation framework to estimate the comparative effect of rivaroxaban versus apixaban on risk of major gastrointestinal bleeding.

For Estimand 1 (primary), the causal effect summary measure is the hazard ratio for time to first major GI bleeding, estimated using an inverse probability

of treatment weighted (IPTW) Cox proportional hazards model. The Cox model will be fitted separately within each data source (Danish registers and SIDIAP), and the resulting hazard ratios pooled using a random-effects meta-analysis; potential sources of heterogeneity will be described qualitatively.
Two supplemental estimands are also defined: Estimand 2 applies a while-on-treatment strategy using restricted mean survival time (RMST) at 1 and 2 years; Estimand 3 applies a hypothetical strategy for treatment discontinuation and switching. Sensitivity analyses include inverse probability of censoring weighting (IPCW), tipping point analysis, and probabilistic bias analysis for outcome misclassification

Documents

Study, other information

CS4_Feasibility Assessment (1).pdf (451.74 KB)

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)

The Information System for Research in Primary Care (SIDIAP)

Data source(s), other

Danish Health Care Registries

Data sources (types)

Population registry

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

ConcepTION CDM

CDM website

https://www.imi-conception.eu/

CDM release frequency

6 months

CDM version

V 2.2

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation details

The feasibility assessment for this case study, (appendix of the study protocol), was conducted as part of the broader TARGET-EU feasibility assessment (EUPAS1000000791). Data source suitability was evaluated using a structured framework based on the EMA data quality framework, assessing system characteristics, data quality, and fitness for the research question.

Both Danish national registers and SIDIAP were deemed feasible for studying rivaroxaban versus apixaban on major GI bleeding in adults aged 75 and older with NVAF, with sufficient sample size and exposure prevalence. The Danish registers offer nationwide, population-based coverage with high reliability of demographic and hospital data, but exact treatment duration must be estimated from prescription records. SIDIAP provides broad primary care

coverage of the Catalan population (~78%) with hospital linkage, but cause of death is not directly captured in the data source and treatment duration must also be estimated.