Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: non-interventional study of patients taking Direct Oral Anticoagulants in the EU

First published: 23/11/2016

Last updated: 23/05/2024

Study Finalised

Administrative details

EU PAS number

EUPAS16014

Study ID

46296

DARWIN EU® study

No

Study countries

Denmark

France

Germany

Netherlands

Spain

Study description

This study is using longitudinal data collected in 8 electronic health care databases from six EU countries to characterize the risk of major bleeding in Direct Oral Anticoagulant (DOAC) users in a real-world setting to help establish the effectiveness of existing and future risk minimization measures. The research undertaken will focus on targeted clinical and demographic subgroups for which variations in plasma concentrations might affect the safety of the products.

Study status

Finalised

Research institutions and networks

Institutions

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**

Fundació Institut Català de Farmacologia (FICF)

Spain

First published: 29/03/2010

Last updated: 17/09/2019

Institution | Outdated | Educational Institution | Hospital/Clinic/Other health care facility | Not-for-profit | ENCePP partner

Pharmacoepidemiology Research Collaboration (PRC), University of Copenhagen

Denmark

First published: 18/04/2017

Last updated: 24/03/2023

Institution | Educational Institution | ENCePP partner

Aarhus University

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Medical Devices, AEMPS)

Spain

First published: 01/02/2024

Last updated: 04/09/2024

Institution | **EU Institution/Body/Agency** | **Not-for-profit** | **Regulatory Authority** | **ENCePP partner**

Networks

EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network

Netherlands

First published: 01/02/2024

Last updated: 24/09/2025

Network

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Helga Gardarsdottir

Primary lead investigator

Study timelines

Date when funding contract was signed

Actual: 01/09/2016

Study start date

Actual: 01/01/2008

Date of interim report, if expected

Actual: 12/02/2018

Date of final study report

Actual: 05/10/2018

Study protocol

20161101_DOAC_bleedingProtocol_Forreview.pdf (1.03 MB)

20180601_AMENDED_PROTOCOL_DOAC_bleeding_EUPAS16014_version 3.0.pdf (605.7 KB)

Regulatory

Was the study required by a regulatory body?

Yes

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

Not applicable

Other study registration identification numbers and links

EMA/2015/27/PH

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Drug utilisation

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Main study objective:

Obj 1. The risk of major bleeding associated with use of DOACs when compared to other oral anticoagulants. Obj 2. The utilization of DOACs in the EU for treatment of NVAF. Obj 3. Prescribers' compliance with recommendations included in sections 4.1 and 4.3-4.5 of the SmPC of each DOAC

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medical condition to be studied

Atrial fibrillation

Population studied

Short description of the study population

The study population consists of all new (D)OAC users aged ≥18 years and at least one year (365 days) register in the database with a recorded diagnosis of NVAF.

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Special population of interest

Hepatic impaired

Other

Renal impaired

Special population of interest, other

Atrial fibrillation patients

Estimated number of subjects

700.000

Study design details

Outcomes

The risk of major bleeding, such as gastrointestinal bleeding, intracranial bleeding and haemorrhagic stroke, associated with use of DOACs AND Descriptive analysis of patient characteristics of new DOAC users, the number of patients switching to another antithrombotic agent and treatment duration. Prescriber compliance with recommendations included in SmPC section 4.1, 4.3, 4.4, and 4, Stroke, including ischaemic stroke and haemorrhagic stroke, and all-cause mortality.

Data analysis plan

Descriptive studies: The analysis will be descriptive using information on the index date. Stratified by database, individual DOACs, age group, gender, study period 2008-2015, calendar year: 2008, 2009, 2010, 2011, 2012, 2013, 2014 and 2015, Indication, Renal functionCohort study: Crude incidence rates of outcomes per 1,000 person years will be estimated, stratified by sex and age groups. Cox proportional hazard regression analysis will be applied to estimate effects (adjusted hazard ratios, HR) of (D)OAC treatment.

Documents

Study results

EUPAS16014 DOAC study abstracts FINAL 20190206.pdf (83.57 KB)

EUPAS16014 DOAC study abstracts FINAL completed 20210730.pdf (133.4 KB)

Final study report on Zenodo

Study, other information

20170703_Abstract_EUPAS16104.pdf (27.11 KB)

Study publications

van den Ham HA, Souverein PC, Klungel OH, Platt RW, Ernst P, Dell'Aniello S, Sc…

Ibáñez L, Sabaté M, Vidal X, et al.Incidence of direct oral anticoagulant use i…

Souverein PC, HA van den Ham, Huerta C, et al. Comparing risk of major bleeding…

Rottenkolber M, Schmiedl S et al. Prescribers' compliance with summary of produ…

Sabaté M, Vidal X, Ballarin E, Rottenkolber M, Schmiedl S, Grave B, Huerta C, M…

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.

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

180611_DOI_all.pdf (9.49 MB)

DOI_all.pdf (5.64 MB)

Composition of steering group and observers

20161123_Composition.pdf (19.15 KB)

NoSteeringGroup.pdf (9.6 KB)

Signed code of conduct

empty_file_1.pdf (11.35 KB)

Signed code of conduct checklist

empty_file_1.pdf (11.35 KB)

Signed checklist for study protocols

empty_file_1.pdf (11.35 KB)

Data sources

Data source(s)

Clinical Practice Research Datalink

Danish registries (access/analysis)

The Information System for Research in Primary Care (SIDIAP)

BIFAP - Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (Pharmacoepidemiological Research Database for Public Health Systems)

Data sources (types)

Administrative healthcare records (e.g., claims)

Disease registry

Drug dispensing/prescription data

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No