# 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:** 23/05/2024

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

## Fundació Institut Català de Farmacologia (FICF)

Spain

**First published:** 29/03/2010

**Last updated:** 17/09/2019

Institution | 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:** 26/11/2024

**Network**

# Contact details

**Study institution 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

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**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.

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**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)

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**Special population of interest**

Hepatic impaired

Other

Renal impaired

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**Special population of interest, other**

Atrial fibrillation patients

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**Estimated number of subjects**

700000

## 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.

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**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)

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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...

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# 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