

# DARWIN EU® - Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives

**First published:** 16/01/2025

**Last updated:** 13/02/2025

Study

Ongoing

## Administrative details

### EU PAS number

EUPAS1000000443

### Study ID

1000000443

### DARWIN EU® study

Yes

### Study countries

☐ Denmark

☐ Norway

☐ Spain

## Study description

Venous thromboembolism (VTE) refers to the formation of a blood clot in a deep vein and is a rare but potentially preventable cause of death in women of reproductive age. Multiple studies have showed that oral combined hormonal contraception is associated with an increased risk of VTE, especially high-dose combined oral contraception ( $\geq 50 \mu\text{g}$  ethinyl estradiol and progestins).[1]

Additionally, the use of non-steroidal anti-inflammatory drugs (NSAIDs) has also been linked to increased VTE risk. Meta-analyses and observational studies have suggested an increased risk of VTE among NSAIDs users.[2,3]

Recently, a nationwide study from Denmark found that NSAIDs use is associated with increased VTE risk in women 15-49 years old, especially among those with concomitant use of high/medium risk hormonal contraception. [4]

This study was fraught with limitations, particularly as the study design did not satisfactorily account for confounding.

More data on the association of venous thromboembolism with NSAIDs in women of reproductive age has been requested by medicines regulators to see if such associations are seen in other databases, including data on women using hormonal contraception.

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## Study status

Ongoing

## Research institutions and networks

### Institutions

## Department of Medical Informatics - Health Data Science, Erasmus Medical Center (ErasmusMC)

☐ Netherlands

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**Last updated:** 02/05/2024

**Institution**

**Educational Institution**

**ENCePP partner**

## Networks

### Data Analysis and Real World Interrogation Network (DARWIN EU®)

☐ Belgium

☐ Croatia

☐ Denmark

☐ Estonia

☐ Finland

☐ France

☐ Germany

☐ Greece

☐ Hungary

☐ Italy

☐ Netherlands

☐ Norway

☐ Portugal

- ☐ Spain
- ☐ Sweden
- ☐ United Kingdom

**First published:** 01/02/2024

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Network

## Contact details

### Study institution contact

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Study contact

[study@darwin-eu.org](mailto:study@darwin-eu.org)

### Primary lead investigator

Xintong Li

Primary lead investigator

## Study timelines

### Date when funding contract was signed

Planned: 26/06/2024

Actual: 26/06/2024

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### Study start date

Planned: 08/01/2025

Actual: 08/01/2025

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### **Date of final study report**

Planned: 20/06/2025

## Sources of funding

- EMA

## Study protocol

[DARWIN EU\\_Protocol\\_P3-C3-008\\_NSAIDS\\_V4.pdf](#)(958.48 KB)

## Regulatory

### **Was the study required by a regulatory body?**

Yes

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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:**

Drug utilisation

Safety study (incl. comparative)

**Data collection methods:**

Secondary use of data

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**Study design:**

Drug/Vaccine Safety Studies

Patient-level DUS

**Main study objective:**

1. To characterise the use of NSAIDs among women aged 15-49.
2. To measure the association of any NSAID use and the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.
3. To measure the association of ibuprofen, diclofenac and naproxen use on the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.

## Study Design

**Non-interventional study design**

Cohort

## Study drug and medical condition

**Name of medicine, other**

Anti-inflammatory and antirheumatic products, non-steroids (NSAIDS) Defined by all M01A group except M01AX05, M01AX12, M01AX25 and M01AX26

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**Medical condition to be studied**

Venous thrombosis

## Population studied

**Short description of the study population**

Objective 1: Drug utilisation of NSAIDs.

The study population will be women aged 15-49 who initiate oral NSAIDs of ibuprofen, diclofenac and naproxen on or after 2014 while using hormonal contraceptives, defined using a 90-day washout window. We will require at least 365 days of data availability before NSAIDs use.

Objective 2 and 3: Incidence of VTE

The source population will be women of reproductive age using hormonal contraceptives or therapies. We will not limited to medication with contraceptive as indication, but also medications as a combination of estrogen and progestin for other indications. For example, the DIANE®-35, which contains ethinylestradiol and cyproterone acetate, is a treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age, will be included in this study.

The study population will include women aged 15-49, using hormonal contraceptives, and with no history of venous or arterial thromboembolism, cancer (except non-melanoma skin cancer), thrombophilia, hysterectomy, bilateral oophorectomy, sterilisation or infertility treatment.

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## **Age groups**

Adults (18 to < 46 years)

# Data management

## Data sources

### **Data source(s)**

Clinical Practice Research Datalink (CPRD) GOLD

Danish Health Data Registries

The Information System for Research in Primary Care (SIDIAP)

Norwegian Linked Health registry at University of Oslo

## 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**

<https://ohdsi.github.io/CommonDataModel/index.html>

## Data quality specifications

**Check conformance**

Unknown

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**Check completeness**

Unknown

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**Check stability**

Unknown

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**Check logical consistency**

Unknown

## Data characterisation

**Data characterisation conducted**

Unknown