DARWIN EU® - Assessing the feasibility of conducting a causal study on the potential association between beta-blockers and breast cancer

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000001013

Study ID

1000001013

DARWIN EU® study

Yes

Study countries

Denmark

Norway

Spain

Sweden

United Kingdom

Study description

Hypertension is highly prevalent in adult women and commonly requires long-term use of antihypertensive medications. Long-term use of antihypertensive medications raises concerns about potential adverse effects, including cancer risk.

Beta-blockers have been used for decades to treat hypertension. Beyond cardiovascular effects, beta-adrenergic signalling may influence cancer-related processes, which could affect breast cancer development. However, prior observational evidence is inconsistent, likely due to confounding by indication and design differences. B1-selective beta-1 agents differ from non-selective agents, yet many studies have evaluated beta-blockers as a single class.

This feasibility study assesses whether selected data sources in the DARWIN EU® Data Network can support robust causal research on a comparative safety of beta-blockers in relation to incident breast cancer.

Study status

Ongoing

Research institutions and networks

Institutions

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

Netherlands

First published: 03/11/2022

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

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Network

Contact details

Study institution contact

Natasha Yefimenko study@darwin-eu.org

Study contact

study@darwin-eu.org

Primary lead investigator

Yuqing Hu

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 15/12/2025

Actual: 15/12/2025

Study start date

Planned: 21/05/2026

Actual: 21/05/2026

Date of final study report

Planned: 30/10/2026

Sources of funding

- EMA

Study protocol

DARWIN EU_Protocol_P4-C1-024_Beta blockers & Breast cancer_V4.0.pdf (1.98 MB)

Regulatory

Was the study required by a regulatory body?

Yes

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

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Drug utilisation

Data collection methods:

Secondary use of data

Study design:

A cohort study will be conducted using routinely collected health data from 5 data sources from 5 countries across Europe and in 3 European Union (EU) member states.

Main study objective:

1. To describe baseline demographic, clinical characteristics, the potential indications, as well as previous and baseline antihypertensive medication use in female individuals newly initiating the following distinct antihypertensive classes: B1-selective beta-blockers, non-selective beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), non-dihydropyridines calcium channel blockers (CCBs), dihydropyridines CCBs.
2. To describe the number, proportion, and time-to-event distribution of the following events among female individuals newly initiating B1-selective beta-blockers, non-selective beta-blockers, ACE inhibitors, ARBs, non-dihydropyridines CCBs, dihydropyridines CCBs during 5 and 10 years of follow-up: 1) all cause death, 2) loss to follow-up, and 3) discontinuation of index treatment.
3. To estimate the yearly incidence of primary breast cancer in the general adult (≥18 years) female population overall and by age group (18–40, 41–50, >50 years).
4. Based on the size of each cohort, assess whether the study size provides adequate precision to support a causal analysis.

Study Design

Non-interventional study design

Cohort

Population studied

Short description of the study population

Study population:

Objectives 1, 2, and 4: Newly initiating an index treatment during the study period (At least 1 prescription/dispensation of an index treatment; when both are available, prescription data will be prioritised).

Inclusion criteria

• Female individuals aged ≥18 years

• ≥365 days of prior observation

• Hypertension diagnosis on or before the index date[JN1.1]

Exclusion criteria

• Breast cancer diagnosis (including in situ breast cancer) or bilateral preventive mastectomy any time before the index date.

Washout: Infinite washout [-inf, -1] will be applied for prior use of the index treatment class. For any beta-blocker cohorts, washout will be applied across all beta-blockers. For any CCBs cohorts, washout will be applied across all CCBs

For objective 3, a different cohort (general female population) will be defined:

Inclusion criteria

• Female individuals aged ≥18 years

• ≥365 days of prior observation

Exclusion criteria

• Breast cancer diagnosis (including in situ) or bilateral preventive mastectomy any time before index date.

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Study design details

Setting

This study will be conducted using routinely collected data from five primary/secondary care data sources in the DARWIN EU® network of data partners from five European countries (Table 1 and ANNEX I). All data were a priori mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM). Information on data sources included and a rationale for their inclusion in terms of ability to capture the relevant data is described in ANNEX II.

Outcomes

Objective 1:

Not applicable.

Objective 2:

• Discontinuation of index treatment: discontinuation will be defined as a gap of >90 days without a subsequent prescription/dispensation of index treatment. The date of discontinuation will be the last prescription/dispensation + days of supply, where available. More detailed information about days of supply data

and how the end of each prescription is estimated in each data source can be found in Annex II.

• All-cause death

• Loss to follow-up: defined as the end of an individual’s observation period in the data source, which

may reflect deregistration, disenrollment, or emigration.

Objective 3:

The outcome will be defined as the occurrence of incident breast cancer recorded in the data sources. Breast cancer codes are available in SNOMED and ICDO3. The preliminary concept sets used for the identification of outcomes are described in Annex IV. These codes will be refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by clinical experts and the review of phenotypes after their execution in the participating data sources.[7]

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)

Danish Health Data Registries

Norwegian Linked Health registry at University of Oslo

Health Impact - Swedish Population Evidence Enabling Data-linkage

Clinical Practice Research Datalink (CPRD) GOLD

Data sources (types)

Electronic healthcare records (EHR)

Population registry

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

OMOP

CDM website

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

CDM version

https://ohdsi.github.io/CommonDataModel/

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No