

Risk of cardiac valve disorders associated with the use of biphosphonates (Cardiac valve disorders and biphosphonate use)

First published: 06/06/2012

Last updated: 02/07/2024

Study

Finalised

Administrative details

EU PAS number

EUPAS2616

Study ID

20749

DARWIN EU® study

No

Study countries

☐ Italy

☐ Netherlands

☐ United Kingdom

Study description

A signal of disproportionate reporting concerning the risk of cardiac valve calcification leading to cardiac valve insufficiency associated with the use of bisphosphonates was found in EudraVigilance. A similar association between bisphosphonate use and valvular and vascular calcification in women has also been previously described in a cohort study conducted in the United States (MESA study). The primary objective of this signal strengthening study is to confirm or refute the presence of a possible risk of cardiac valve disorders (all types of disorders, confirmed by cardiac imaging) in patients treated with bisphosphonates using EU longitudinal healthcare data from the EU-ADR Alliance. This signal strengthening study will determine the need for, and feasibility of conducting a traditional hypothesis testing study. Signal strengthening will be performed using the most recently updated demographic, clinical, and prescription data from six databases in three EU member states (Italy, Netherlands, the United Kingdom), pooled using a distributed network approach by generation of common input data followed by local aggregation through custom-built software, Jerboa©. Potential cases of cardiac valve disorders in the database network will be identified using database-specific coding algorithms. Exposure to bisphosphonates will be assessed with drug prescription/dispensing data using the World Health Organisation's (WHO) Anatomical Therapeutic Chemical (ATC) classification system. Several signal detection/strengthening methods will be employed to assess the association of cardiac valve disorder and use of bisphosphonates

Study status

Finalised

Research institutions and networks

Institutions

Erasmus Medical Centre Rotterdam

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Primary Care Research Institute Jordi Gol

The PHARMO Institute for Drug Outcomes Research (PHARMO Institute)

☐ Netherlands

First published: 07/01/2022

Last updated: 24/07/2024

Institution

Laboratory/Research/Testing facility

ENCePP partner

Networks

EU-ADR Alliance

First published: 01/02/2024

Last updated: 01/02/2024

Network

Contact details

Study institution contact

Miriam Sturkenboom mcjm.sturkenboom@gmail.com

Study contact

mcjm.sturkenboom@gmail.com

Primary lead investigator

Miriam Sturkenboom

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 02/12/2011

Actual: 02/12/2011

Study start date

Planned: 11/06/2012

Actual: 18/06/2012

Data analysis start date

Planned: 18/06/2012

Actual: 22/06/2012

Date of interim report, if expected

Planned: 02/07/2012

Actual: 16/07/2013

Date of final study report

Planned: 02/08/2012

Actual: 08/01/2014

Sources of funding

- EMA

Study protocol

[D1.b. Final Protocol signal strengthening \(BI\)_23May2012.pdf](#)(1.23 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:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:

Secondary use of data

Main study objective:

The primary objective of this study is to confirm, or refute, the existence of a statistical association of cardiac valve disorders (all types of disorders, confirmed by echocardiography, cardiac catheterisation, or other imaging modality) and use of bisphosphonate (for all indications), and eventually to identify effect modifiers.

Study Design

Non-interventional study design

Case-control

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(M05BA) Bisphosphonates

Bisphosphonates

Medical condition to be studied

Cardiac valve disease

Population studied

Short description of the study population

Patients treated with bisphosphonates who are registered in the databases participating in the study. All the subjects of any age with at least one year of data available in the database were included in the study.

Age groups

Term newborn infants (0 – 27 days)

Infants and toddlers (28 days – 23 months)

Children (2 to < 12 years)

Adolescents (12 to < 18 years)

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)

Estimated number of subjects

27000000

Study design details

Outcomes

Occurrence of any cardiac valve disorder

Data analysis plan

Through data mining techniques any association of individual bisphosphonates and each outcome definition will be explored and quantified. Various statistical methods have previously been evaluated for this purpose and in this study a combination of the best performing methods, enumerated below, will be applied to data pooled from all six databases.

a. Incidence Rate Ratio (IRR) is calculated as the ratio between incidence rate during exposure to the drug compared to a background incidence rate. A Mantel-Haenszel test is used to test the differences between the incidence rates, typically correcting for age and sex.

b. Longitudinal Gamma Poisson Shrinker (LGPS) is an adaptation of the GPS method, developed for use in spontaneous reporting databases, to longitudinal data. It applies Bayesian shrinkage to the IRR.

c. Automated Matched Case Control Method. For every potential case identified, a predefined number of controls will be matched to the same age, sex, index date.

Documents

Study results

[Executive Summary.pdf](#) (369.17 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.

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

[ENCePPDoIForms_merged.pdf](#)(427.67 KB)

Composition of steering group and observers

[Participants_Cardiac valve disorders and biphosphonate use.pdf](#)(188.04 KB)

Signed code of conduct

[CoC Declaration 2616.pdf](#)(375.52 KB)

Signed code of conduct checklist

[CoC Checklist 2616.pdf](#)(150.28 KB)

Signed checklist for study protocols

[Study Protocols Checklist 2616.pdf](#)(241.69 KB)

Data sources

Data source(s)

THIN® (The Health Improvement Network®)

Drug claims information system

Health Search/IQVIA Health Longitudinal Patient Database

Integrated Primary Care Information (IPCI)

Data sources (types)

Administrative healthcare records (e.g., claims)

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

Unknown