Comparing the risk of metoprolol-related adverse drug reactions between women and men with heart failure using effectiveness outcomes as a proxy: a population-based cohort study using CPRD

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Study Ongoing

Administrative details

EU PAS number

EUPAS105418

Study ID

105419

DARWIN EU® study

No

Study countries

☐ Netherlands

Study description

Women are approximately 1.5 times more likely than men to have adverse drug reactions (ADRs). Although sex differences in cardiovascular medicine are well known, clinical relevance of these differences remains mostly unproven. One of the relevant medications are beta-blockers, that represent a pillar in the pharmacological treatment of patients with chronic heart failure (CHF). Current guidelines advise the use of bisoprolol, metoprolol, nebivolol and carvedilol interchangeably in the treatment of CHF. Despite this, beta-blockers are not a homogeneous class, with differences in beta-1/beta-2-receptor selectivity as well as vasodilatory action. Moreover, different drugs behind each generation exhibits unique pharmacokinetic and pharmacodynamic characteristics, which can lead to differential responses to the treatment. However, it has been shown that women with HF are underrepresented in the randomized controlled trials (RCTs). Sex differences with respect to the ADRs are also insufficiently investigated. From 155 eligible HF trials identified in a systematic review, only 11 reported ADR data for women and men separately. Despite the sex-neutral approach of HF guidelines, findings from clinical practice suggest that a sex-specific recommendations should be addressed. This study aims to determine if sex appears to modify the safety of metoprolol and carvedilol in CHF by using data from general practitioner offices from across the UK. We will apply the Active Comparator, New User design to analyse effectiveness outcomes of metoprolol and carvedilol as a proxy of ADRs in women and men with HF.

Study status

Ongoing

Research institutions and networks

Institutions

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

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Institution | Educational Institution | ENCePP partner

Contact details

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Primary lead investigator

Olaf Klungel

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 15/04/2023

Actual: 15/04/2023

Study start date
Planned: 26/06/2023

Actual: 26/06/2023

Date of final study report
Planned: 15/10/2023

Sources of funding

- Other

More details on funding

University

Regulatory

Was the study required by a regulatory body?

No

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

Not applicable

Methodological aspects

Study type

Study type list

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Main study objective:

Do women with heart failure who use metoprolol have a higher risk of adverse drug reactions compared to women using carvedilol, and is this association different in their male counterparts?

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(C07AB02) metoprolol

metoprolol

(C07AG02) carvedilol

carvedilol

Medical condition to be studied

Cardiac failure

Population studied

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)

Estimated number of subjects

30000

Study design details

Outcomes

The outcomes of interest are all-cause and heart failure-specific mortality, hospitalisation for heart failure, and prescription discontinuation. To compare with the effectiveness findings, diagnoses of adverse events will be identified.

Data analysis plan

The analysis method used for this study will be the Active Comparator, New User (ACNU) design. ACNU study design seeks to emulate the design of a head-to-head randomized controlled trial. Specifically, ACNU study design is an effective way to avoid biases typically related to pharmacoepidemiologic studies, such as confounding by indication, healthy initiator bias and healthy adherer bias. Statistical analyses will include a main analysis (effectiveness outcomes), a secondary analysis (treatment discontinuation) and a tertiary analysis (actual ADR diagnoses). All analyses will be stratified by sex and age. Moreover, we will stratify our analysis based on whether or not hypertension is present, and a sensitivity analysis will include only patients diagnosed with heart failure with reduced ejection fraction.

Data management

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)

Clinical Practice Research Datalink

Data sources (types)

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