Comparative effectiveness of triple therapy with Bisoprolol, Perindopril, Amlodipine, versus dual therapy in hypertensive patients: an observational retrospective cohort study

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Study Planned

Administrative details

EU PAS number

EUPAS1000000374

Study ID

1000000374

DARWIN EU® study

No

Study countries

☐ United Kingdom

Study description

This study aims to determine the effectiveness on blood pressure reduction of the triple combination of Perindopril+ Amlodipine+ Bisoprolol (used concomitantly as combination), compared to the respective dual therapy components in real life conditions.

Adult hypertensive patients on two-drug combination therapy (two drugs among Perindopril, Amlodipine and Bisoprolol) and who are not controlled by the dual therapy (with systolic blood pressure (SBP) ≥140mmHg) will be included. Patients who will initiate the third drug and be on the Bisoprolol + Perindopril+ Amlodipine triple therapy will be compared to those who will remain on dual therapy.

The primary outcome will be the difference in change in SBP from baseline to week 8 between the two treatment groups, estimated with a Mixed Model of Repeated Measures. Diastolic blood pressure change at 8 weeks, blood pressure control at 8 weeks and rates of adverse events will be compared between the two treatment groups. Treatment patterns including adherence to index therapy and healthcare resource use will be also described for the triple therapy users. The rates of cardiovascular events including myocardial infarction, stroke, heart failure and chronic kidney disease as well as cardiovascular death will be also investigated as an exploratory objective.

These data will be used to generate evidence for the fixed-dose combination (FDC) of perindopril, amlodipine and bisoprolol, currently under development by Servier that may reduce pill burden in hypertensive patients.

Study status

Planned

Research institutions and networks

Institutions

Institut de Recherches Internationales Servier

First published: 01/02/2024

Last updated: 01/02/2024

Institution

OXON Epidemiology

☐ Spain

☐ United Kingdom

First published: 06/12/2010

Last updated: 15/03/2024

Institution | Laboratory/Research/Testing facility | Non-Pharmaceutical company | ENCePP partner

Contact details

Study institution contact

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Primary lead investigator

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Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 02/01/2023

Study start date
Planned: 25/11/2024

Data analysis start date
Planned: 17/02/2025

Date of final study report
Planned: 21/08/2025

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Institut de Recherches Internationales Servier

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 topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

Retrospective observational cohort study. Patients will be identified in CPRD between January 2005 and September 2019 and followed until March 2020.

Main study objective:

The overall objective of the study is to study the effectiveness on blood pressure reduction of Bisoprolol (Biso), Perindopril (Per), Amlodipine (Amlo) and used concomitantly as free combination, compared to respective dual combination(s) of these 3 drugs in real life conditions, in order to confirm the contribution of all the active substances to the desired therapeutic effect on BP.

Primary objective: To compare the systolic blood pressure (SBP) change at 8 weeks between patients who started the combination of Biso/Per/Amlo (triple therapy) to those treated with the free or fixed combination of two drugs out of the three molecules (dual therapy) in hypertensive uncontrolled patients.
Secondary objectives
- To compare the diastolic blood pressure (DBP) change at 8 weeks between the patients who started the triple therapy to patients treated with the dual therapy.
- To compare the blood pressure control rate at 8 weeks between the patients who started the triple therapy to patients treated with the dual therapy.
- To estimate and compare incidence of adverse events (AEs) during follow-up between patients who started the triple therapy to those treated with the dual therapy.
- To describe treatment patterns of the three drugs taken concomitantly during follow-up and the adherence to treatment.
- To describe healthcare resource use in patients who started the triple therapy
Exploratory objective
- To estimate and compare incidence of cardiovascular events including cardiovascular death during follow-up

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Name of medicine, other

Perindopril, Amlodipine, Bisoprolol

Study drug International non-proprietary name (INN) or common name

AMLODIPINE

PERINDOPRIL ARGININE

Medical condition to be studied

Hypertension

Population studied

Short description of the study population

Adult hypertensive patients uncontrolled on two-drug combination therapy identified in CPRD :

- Aged 18 years or over
- With at least one diagnosis record of primary hypertension
- Who have been prescribed concomitantly with two drugs (in free or fixed combination) among Bisoprolol, Perindopril, and Amlodipine at a stable dose for at least 4 weeks
- With uncontrolled blood pressure defined as SBP ≥140mmHg using the most recent BP record in the 2 weeks before or at index date
- With no other antihypertensive treatment received in the 4 weeks before index date
- Who have no prescription of the third drug (the component that is not part of

the dual therapy) within 365 days before index date
- Who have been registered for at least one year in CPRD
- With Hospital Episode Statistics (HES) and ONS linkage available

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Age groups

Adult and elderly population (≥18 years)

Study design details

Setting

The source population for this study will be all patients identified in CPRD who meet inclusion and exclusion criteria , during the study inclusion period - January 2005 to September 2019. The latest data available at the time of application will be used to maximize the sample size, taking into account the latest linked data.

Comparators

This study will compare the uncontrolled hypertensive patients on triple therapy to those on dual therapy.
- The treatment group will be the triple therapy group i.e., patients on dual therapy who start the third mono-component among the three targeted drugs (Biso, Per and Amlo) during the inclusion period of the study. This group will include patients on either Per+Amlo who add Biso, or Per+Biso who add Amlo, or Amlo+Biso who add Per.
- The control group will be the dual therapy group and will include patients on either Per+Amlo or Per+Biso or Amlo+Biso

Comparison of triple therapy users to dual therapy users will be done by creating exposure sets based on index date and dual-therapy components and

then matching using propensity score (PS) method to minimize the effect of confounding factors.

Outcomes

Primary outcome

The primary outcome will be change in SBP between ID and 8 weeks. We will identify an index value defined as the most recent SBP recorded in the two weeks preceding or at the ID, used for patient eligibility.

Post index measurements will be all SBP records reported (on distinct dates) within the time window of interest, from 4 weeks to 24 weeks after the ID and the change from index to week 8 will be estimated with a Mixed Model of Repeated Measures (MMRM) and compared between treatment groups.

Secondary effectiveness outcomes

Change in DBP between ID and 8 weeks:

The change in DBP between index and post-index DBP values will be calculated and compared between treatment groups. The same period assessment used for SBP will be applied for DBP.

Secondary safety outcome

The AEs to be studied are relevant safety events retrieved from the summary of product characteristics of each drug of interest (Biso, Per, Amlo); and from post-marketing safety data reported in the safety database among patient cases where bisoprolol, perindopril and amlodipine were co-administered.

Data analysis plan

Exposure sets will be created by index date and dual-therapy components and patients will be matched using propensity score to ensure comparability between treatment groups in these exposure sets. Missing outcomes due to

change in treatment during outcome assessment period will be handled using Baseline Mean Carried Forward imputation method.
The primary outcome will be estimated on the matched cohort and with a Mixed Model of Repeated Measures.

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), other

Clinical Practice Research Datalink (CPRD) AURUM

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