Asymptomatic hyperuricemia: to treat or not to treat. A target trial emulation to assess major cardiorenal outcomes (HYPER-TTE-HARV)

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000000386

Study ID

1000000386

DARWIN EU® study

No

Study countries

Spain

United States

Study description

Hyperuricemia is defined as a serum uric acid level >6.8 mg/dl. Most of the uric acid is produced endogenously while the remaining accounts for the metabolism of dietary purines and sugars. Uric acid is mainly excreted by the kidneys and fewer by the intestines. However, certain aspects of the pathophysiology of uric acid are still not clearly understood. In particular, whether elevated uric acid plays a role in the development of cardiovascular risk factors, such as diabetes or hypertension, or the initiation and progression of chronic kidney disease, are still subjects of debate. Cross-sectional studies showed an association between hyperuricemia and chronic kidney disease, but such study design fails to establish the direction of causality. In longitudinal studies, hyperuricemia was associated with an increased risk of incident chronic kidney disease rather than with a risk for progression to end-stage renal disease. Despite this, recent guidelines advocate for not to treat asymptomatic hyperuricemia as many patients do not present related symptoms as gout flares, and urate-lowering drugs are not absent of serious risks. Three large randomized clinical trials found no benefit of allopurinol in slowing kidney disease progression or prevention of cardiovascular events among asymptomatic subjects, but they included patients with normal uric acid levels so that precluded to test our hypothesis. When it comes to real-world, some physicians decide to prescribe urate-lowering drugs for asymptomatic hyperuricemia while others do not. Observational studies provide information on the effectiveness of treatments when randomized trials are not possible. However, making causal inferences are challenging due to lack of randomization and wrong study designs. To overcome this, the target trial emulation provides the framework to avoid bias by designing the hypothetical randomized experiment to answer the specific question of interest using real-world data and appropriate methods

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Study status

Ongoing

Research institutions and networks

Institutions

Universidad de Alcalá

Harvard T.H. Chan School of Public Health

Contact details

Study institution contact

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Primary lead investigator

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 31/12/2024

Study start date

Planned: 19/09/2024

Actual: 19/09/2024

Data analysis start date
Planned: 06/02/2025

Date of final study report
Planned: 31/07/2025

Sources of funding

- Non-EU institutional research programme

More details on funding

The Real Colegio Complutense at Harvard has awarded the principal investigator with a faculty fellowship for research stays at CAUSALab (Harvard T.H. Chan School of Public Health)

Study protocol

BIFAP_study_protocol_V2_Clean.pdf (391.2 KB)

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 topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Hypothesis generation (including signal detection)

Method development or testing

Data collection methods:

Secondary use of data

Study design:

A retrospective cohort study following the components of a target trial emulation

Main study objective:

To evaluate whether to treat asymptomatic hyperuricemia with urate-lowering drugs would reduce the incidence of cardiorenal outcomes, in particular, chronic kidney disease, ischemic stroke, and acute myocardial infarction.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

FEBUXOSTAT

Medicinal product name, other

Allopurinol

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

ALLOPURINOL

FEBUXOSTAT

Anatomical Therapeutic Chemical (ATC) code

(M04AA01) allopurinol

allopurinol

(M04AA03) febuxostat

febuxostat

Medical condition to be studied

Hyperuricaemia

Additional medical condition(s)

Asymptomatic hyperuricaemia

Population studied

Short description of the study population

Subjects with age >18 and of any sex, with incident asymptomatic hyperuricemia. Those with history of symptomatic hyperuricemia, cancer and cardiorenal events (acute myocardial infarction, ischemic stroke, and kidney disease), with less than 1 previous year of follow-up registered in the database,

or contraindications to receive urate-lowering drugs will be excluded.

Age groups

- **Adult and elderly population (≥18 years)**

Estimated number of subjects

250000

Study design details

Setting

From 2003 to 2019, a retrospective cohort will be constructed following the components of the target trial that articulates the causal question, as specified below. All subjects fulfilling the inclusion criteria below will be included:
1) Subjects with age >18 (some urate-lowering drugs are not indicated below this age), and of any sex.
2) Incident asymptomatic hyperuricemia, defined as a first record of serum uric acid >6.8 mg/dl and without prior records of gout, gout flares, gout arthritis, colchicine use or a similar suggestive term.
3) No previous history of: cancer (except non-melanoma skin cancer) within the last 3 years, acute myocardial infarction, ischemic stroke, and kidney disease (estimated glomerular filtration rate -eGFR-, albuminuria or proteinuria outside the normal range and/or a diagnosis of chronic or acute kidney disease, dialysis, or kidney transplantation).
4) A minimum registry of 1-year with their primary care physician in the database with the standards of quality registration applied by the staff of BIFAP. The assessment of the number of previous visits to primary care will help to relax the expectation that subjects will keep active in the health system throughout the study period.

The use of urate-lowering drugs will be compared with the non-use.

Comparators

New use of urate-lowering drugs (allopurinol/febuxostat)

Non-use of urate-lowering drugs

Outcomes

Incident cardiorenal events as acute myocardial infarction, ischemic stroke and chronic kidney disease.

Data analysis plan

We will estimate the observational analogs of the intention-to-treat and per-protocol effects. Intention-to-treat needs to adjust for baseline confounders, that is, imbalanced prognostic factors at baseline. The adjustment may be performed either propensity score matching or weighting (inverse probability weighting), or standardization, among others. Due to the characteristics of the database, factors to adjust are those predictors of prescription. Per-protocol analysis needs to adjust for pre- and post-baseline non-adherence to treatments, in addition to those adjustments of intention-to-treat analysis. In per-protocol analysis, the deviation from the initial strategy assigned will result in censorship. As this may introduce post-baseline selection bias, adjustment for predictors of adherence must be performed. Risk curves under each treatment strategy will be constructed. Risks ratios and risk differences at different timepoints will be obtained and compared under different treatment strategies. A Cox proportional hazards model may be also fitted to estimate averaged hazard ratios. Subgroup analysis will be also performed by age, gender, or cardiovascular risk factors. The set of potential confounders will be selected by expert criteria and after the construction and analysis of directed acyclic graphs. The sequence of trials with the cloning-censoring-weighting approach will be applied. If computational constraints occur, a random sample of non-

exposed subjects will be selected.

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)

BIFAP - Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (Pharmacoepidemiological Research Database for Public Health Systems)

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

No

Check logical consistency

No

Data characterisation

Data characterisation conducted

No