OHDSI Comparison of febuxostat and allopurinol in gout

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# List of abbreviations

CVD Cardiovascular disease

SCD Sudden Cardiac Death

CARES Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities

# Abstract

A previous prospective randomized study demonstrated that febuxostat was associated with increased cardiovascular mortality compared to allopurinol in patients with concomitant major cardiovascular disease (CVD). This difference in cardiovascular mortality was mainly driven by sudden cardiac death. Still, there is scarce evidence for risk of sudden cardiac death between febuxostat and allopurinol in real-world practice. We conduct observational study investigating sudden cardiac death risk of febuxostat and allopurinol in patients with gout. Furthermore, we compare the risk of acute myocardial infarction, stroke, heart failure, gout flare, and drug hypersensitivity between febuxostat and allopurinol.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | 26 September 2018 | SC You | Initial draft |

# Rationale and Background

Febuxostat is widely used urate-lowering agent because it is more effective than allopurinol to lower serum urate in patients with gout.1 Furthermore, febuxostat can be used without dosage adjustment in chronic kidney disease. The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) group was a prospective multicenter, double-blind randomized clinical trial, which assessed the cardiovascular risk of febuxostat compared with allopurinol in patients with gout and a history of CVD. This study concluded that febuxostat was associated with significantly higher overall and cardiovascular mortality compared to allopurinol, mostly driven by sudden cardiac death.2 . Still, there is scarce evidence for risk of sudden cardiac death between febuxostat and allopurinol in real-world practice.

# Research Questions and Objectives

## Research Questions

Primary research questions

* Is febuxostat associated with increased risk of sudden cardiac death compared to febuxostat in real-world practice? What is the event rate difference?

Secondary objectives:

* Is febuxostat associated with increased risk of cardiovascular disease compared to febuxostat in real-world practice? What is the event rate difference?
* Is febuxostat associated with increased risk of gout flare compared to febuxostat in real-world practice? What is the event rate difference?
* Is febuxostat associated with lower risk of drug hypersensitivity compared to febuxostat in real-world practice? What is the event rate difference?

## Objectives

The goal of this protocols is conducting comparative effectiveness research to establish evidences for benefits and harms of febuxostat and allopurinol.

**Primary objective**:

-Assess the adjusted hazard ratio and event rate difference for use of febuxostat vs allopurinol on risk of sudden cardiac death

**Secondary objectives**:

-Assess the adjusted hazard ratio and event rate difference for use of febuxostat vs allopurinol on risk of cardiovascular disease

-Assess the adjusted hazard ratio and event rate difference for use of febuxostat vs allopurinol on risk of gout flare

-Assess the adjusted hazard ratio and event rate difference for use of febuxostat vs allopurinol on risk of drug hypersensitivity

# Research methods

## Study Design

### Overview

This study will be a retrospective, observational cohort study. By ‘retrospective’ we mean the study will use data already collected at the start of the study. By ‘observational’ we mean no intervention will take place in the course of this study. By ‘cohort study’ we mean two cohorts, a treatment and comparator cohort, will be followed from index date (start of first exposure) to some end date, and assessed for the occurrence of the outcomes of interest.

The treatment cohort will be users of febuxostat. The comparator cohort will be new users of allopurinol. For both groups we restrict to people with gout, one of the main indications for the drugs of interest. The primary outcome of is sudden cardiac death. Proportional hazard models will be used to assess the hazard ratios between the two exposure cohorts.

Adjustment for baseline confounders will be done using propensity scores. First, a propensity model will be fitted and used to create propensity scores (PS). These PS will be used to match the treatment and comparator cohorts, and the proportional hazards outcome models will be conditioned on the matched sets of strata respectively.

### Study population

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the first exposure to febuxostat or allopurinol)

* Exposure to febuxostat or allopurinol more than 30 days
* At least 365 days of observation time prior to the index date
* A diagnose of gout disorder on within 30 months prior to the index date
* No diagnosis of the myeloproliferative disorder or primary malignant neoplasm of bone marrow preceding the index date
* No diagnosis of the xanthinuria preceding the index date
* Without other uricosuric drug within preceding 1 year

### Additional analysis details

The propensity model will be fitted using a regularized logistic regression with a LaPlace prior. The regularization hyperparameter will be selected by optimizing the likelihood in a 10-fold cross-validation.

Variable-ratio propensity score matching will be performed using greedy matching3. A caliper of 0.25 times the standard deviation of the propensity score distribution will be used. The outcome model will be fitted using a Cox regression conditioned on the matched sets, with only the treatment variable as predictor.

### Analysis variations

The following variations of the analysis will be performed:

Primary analysis:

* Using a PS model to match treated and comparator. The outcome model will be condition on the matched sets.

Secondary analyses:

* No PS model, a simple outcome model with only the treatment as predictor.
* Using a PS model and perform 1-on-1 matching. The outcome model will be condition on the matched sets, but will only contain the treatment as predictor. This is included to allow plotting of the Kaplan-Meier curve, which is not possible when using variable ratio matching.
* Variable ratio matching on the PS. The outcome model will include all covariates that were also included in the propensity model, and will be fitted using a L1 regularized conditional Cox regression with prior. The regularization hyperparameter will be selected be selected by optimizing the likelihood in a 10-fold cross-validation. No regularization will be applied to the coefficient corresponding to the treatment variable (i.e. those representing the hazard ratio of interest).
* All analyses will be repeated using an intent-to-treat risk window definition, which starts on treatment initiation, and ends when observation ends.
* All analyses will be repeated using subpopulation, who had more than 3 years of drug continuation

## Variables

### Exposures

#### Febuxostat

Initial Event Cohort

People having any of the following: 

* a drug era of febuxostat8
  + with era length > 30

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Rules

Inclusion Criteria #1: has prior gout within 3 months

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of Gout9

starting between 90 days Before and 0 days After event index date

Inclusion Criteria #2: No myeloproliferative disorder or Primary malignant neoplasm of bone marrow

Having all of the following criteria:

* at most 0 occurrences of a condition occurrence of myeloproliferative disorder12

starting between all days Before and 0 days After event index date

Inclusion Criteria #3: No previous xanthinuria

Having all of the following criteria:

* at most 0 occurrences of a condition occurrence of Xanthiuria22

starting between all days Before and 0 days After event index date

Inclusion Criteria #4: Without previous allopurinol or probenecid within 1 year

Having all of the following criteria:

* at most 0 occurrences of a drug exposure of Allopurinol and probenecid3

starting between 365 days Before and 0 days After event index date

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of febuxostat8

* allowing 30 days between exposures
* adding 0 days after exposure end

Censoring Events:

Exit Cohort based on the following: 

* a drug exposure of Allopurinol2

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

#### Allopurinol

Initial Event Cohort

People having any of the following: 

* a drug era of Allopurinol2
  + with era length > 30

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Rules

Inclusion Criteria #1: has prior gout within 3 months

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of Gout9

starting between 90 days Before and 0 days After event index date

Inclusion Criteria #2: No myeloproliferative disorder or Primary malignant neoplasm of bone marrow

Having all of the following criteria:

* at most 0 occurrences of a condition occurrence of myeloproliferative disorder12

starting between all days Before and 0 days After event index date

Inclusion Criteria #3: No previous xanthinuria

Having all of the following criteria:

* at most 0 occurrences of a condition occurrence of Xanthiuria22

starting between all days Before and 0 days After event index date

Inclusion Criteria #4: Without previous febuxostat or probenecid within 1 year

Having all of the following criteria:

* at most 0 occurrences of a drug exposure of Febuxostat and probenecid8

starting between 365 days Before and 0 days After event index date

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of Allopurinol2

* allowing 30 days between exposures
* adding 0 days after exposure end

Censoring Events:

Exit Cohort based on the following:   
a drug exposure of febuxostat7

### Outcomes

#### Primary outcome: Sudden Cardiac Death

Primary outcome is defined as sudden cardiac death

#### Secondary outcome: All-Cause mortality

Outcome is defined as any-death

#### Secondary outcome: Drug Hypersensitivity

Index rule defining the index date:

* Occurrence of a TEN (toxic epidermal necrolysis), SJS (Stevens-Johnson Syndrome) and DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) code as a diagnosis in an inpatient or emergency room setting

#### Secondary outcome: Gout flare

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Gout1
  + visit occurrence is any of: Emergency Room - Hospital, Emergency Room Visit, Emergency Room and Inpatient Visit, Emergency Room Critical Care Facility

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Inclusion Rules

Inclusion Criteria #1: Medication or procedure for gout flare

Having any of the following criteria:

* at least 1 occurrences of a drug exposure of Medication for gout flares2

starting between 0 days Before and 7 days After event index date

* or at least 1 occurrences of a procedure of Procedure for gout flares3

starting between 0 days Before and 7 days After event index date

Limit qualifying cohort to: **all events per person.**

#### Secondary outcome: Acute Myocardial Infarction

Index rule defining the index date:

* Occurrence of a myocardial infarction code as a diagnosis in an inpatient or emergency room setting

#### Secondary outcome: Heart Failure

Index rule defining the index date:

* Occurrence of a heart failure code as a diagnosis in an inpatient or emergency room setting

#### Secondary outcome: Stroke

Index rule defining the index date:

* Occurrence of a heart failure code as a diagnosis in an inpatient or emergency room setting

### Potential confounders

The following will be included as potential covariates: (note: most covariates are assessed on or in the 365 days prior to index date)

* Demographics (age in 5-year increments, gender, race, ethnicity, year of index date, month of index date)
* Condition occurrence (one or more variables per diagnose code)
* Condition era (one or more variables per diagnose code)
* Condition group (one or more variables per MedDRA group or SNOMED groups)
* Drug exposure (one or more variables per drug code)
* Drug era (one or more variables per RxNorm ingredient)
* Drug group (one or more variables per ATC group)
* Procedure occurrence (one or more variables per procedure code)
* Risk scores (including Charleston, DCSI, CHADS2, CHADS2VASc

For the full details see the OHDSI CohortMethod package (<https://github.com/OHDSI/CohortMethod>).

Variables with less than 100 non-zero values are discarded. All covariates were used in both the propensity model and the outcome model.

### Negative controls

We believe that negative controls are necessary for confidentiality of study design and statistical method.

### Other variables

None

## Data Sources

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 4 or OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 4 is available at: <http://omop.org/cdm>. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>.

## Sample Size and Study Power

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## Quality control

We will evaluate the PS by

* Inspection of the fitted PS model for large coefficients (indicative of model-misspecification) and predictors that we cannot explain (post-hoc).
* Inspection of the PS distribution.
* Evaluation of covariate balance after matching using the standardized difference in means between treatment and comparator cohort before and after matching [[5](#_ENREF_5)]. Standardized differences greater than 0.2 will be reported and investigated.

We will investigate the outcome model by

* Inspection of the fitted outcome model for large coefficients and predictors that we cannot explain (post-hoc).

The error distribution estimated using the negative controls will be used to estimate residual bias after adjustments.

The CohortMethod package itself, as well as other OHDSI packages on which CohortMethod depends, use unit tests for validation.

## Strengths and Limitations of the Research Methods

Strength

* Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
* PS matching and full outcome models allow balancing on a large number of baseline potential confounders.
* Use of negative control outcomes allow for evaluating the study design as a whole in terms of residual bias.

Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders.
* The outcome of interest, angioedema, is rare and typically captured only in inpatient settings, so we may have insufficient numbers of patients to generate reliable evidence on this drug-outcome association.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

# References

1. Becker, M. A. *et al.* Febuxostat Compared with Allopurinol in Patients with Hyperuricemia and Gout. *N. Engl. J. Med.* **353,** 2450–2461 (2005).

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3. Rassen, J. A. *et al.* One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol. Drug Saf.* **21,** 69–80 (2012).