Cardiovascular outcomes of treat-to-target vs fire-and-forget urate-lowering therapy in patients with gout starting urate-lowering therapy. An emulated multicentre open-label two-parallel arm superiority trial carried out in primary care

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Study Planned

Administrative details

EU PAS number

EUPAS1000000086

Study ID

1000000086

DARWIN EU® study

No

Study countries

Sweden

United Kingdom

Study status

Planned

Research institutions and networks

Institutions

The University of Nottingham

University of Gothenburg

Contact details

Study institution contact

Edoardo Cipolletta edoardo.cipolletta@notingham.ac.uk

Study contact

edoardo.cipolletta@notingham.ac.uk

Primary lead investigator

Abhishek Abhishek

Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 01/09/2023

Study start date
Planned: 01/05/2024

Data analysis start date
Planned: 01/05/2024

Date of final study report
Planned: 01/09/2024

Sources of funding

- Non-for-profit organisation (e.g. charity)

More details on funding

This project was supported by a research grant from the Foundation for Research in Rheumatology (FOREUM). The funder had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Study protocol

Protocol - T2T-ULT and cardiovascular events 25032024.pdf (335.68 KB)

Protocol - T2T-ULT and cardiovascular events 15042024.pdf (298.89 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 type list

Study topic:

Disease /health condition

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Safety study (incl. comparative)

Study design:

This study will emulate an investigator-initiated, pragmatic, multicentre, two-arm, open-label, randomised, superiority treatment strategy trial in gout patients initiating ULT for the first time using a cloning, censoring, and weighting approach.

Main study objective:

To compare the risk of cardiovascular events among patients with gout who initiate ULT and achieve the serum urate target of ≤360 umol/l within 12 months from ULT initiation with those who initiate ULT and do not have a recorded serum urate measurement of ≤360 umol/l within 12 months from ULT start.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

Colchicine

Anatomical Therapeutic Chemical (ATC) code

(M04AC01) colchicine

colchicine

Medical condition to be studied

Gout

Population studied

Short description of the study population

The study population will consist of English and/or Swedish patients for whom research-quality data are available, who are aged ≥18 years at first gout diagnosis in either primary care or secondary care (whichever came first), are newly diagnosed with gout (defined as a new diagnostic code for gout or gout flare at least 12 months after registration at their current general practice, and no prior codes indicating history of gout to ensure only incident cases are included) within the study period, receive their first ULT prescription on or after the day of new gout diagnosis and with serum urate level >360 micromol/l before ULT initiation.
Previous research has found a positive predictive value of gout diagnosis in electronic health records to be acceptable when compared to classification criteria for gout.

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Estimated number of subjects

64000

Study design details

Setting

This study will be carried out in England and Sweden using data recorded in the course of routine clinical care for people with gout managed in primary care. General Practices contributing to the Clinical Practice Research Datalink (CPRD) Aurum and the Western Sweden Regional Healthcare Database (VEGA) will be included in the study.
We will extract CPRD data for the period between 01/01/2007 and 29/03/2021 and VEGA data for the period between 01/01/2007 and 31/12/2017 covering the periods over which linkage with secondary-care data will be available. Indeed, the first recommendations for the management of gout by the BSR and the EULAR were published in 2007 and 2006, respectively.
• Clinical Practice Research Datalink Aurum
CPRD database includes information from more than 38 million individuals, representative of the English population in terms of age, sex, and ethnicity. CPRD data include information on demographic characteristics, lifestyle factors, diagnoses, primary care prescriptions, laboratory results, and immunisations. Primary care data are linked to patient-level index of multiple deprivation (IMD) scores, hospitalization records via linkage with the Hospital Episode Statistics (HES) dataset, and information on date and causes of death via linkage with the Office for National Statistics (ONS) dataset.
• Western Swedish Health Care Register
VEGA contains information about all healthcare contacts for both primary and secondary healthcare in western Sweden (~1.7 million inhabitants). All diagnoses given by physicians are registered according to the Swedish version of the International Classification of Disease (ICD) 10 codes.

Comparators

Intervention arm (T2T-ULT arm): To emulate ULT initiation aiming to achieve the serum urate target of <360 micromol/l within 12 months after ULT initiation, serum urate target will be ascertained by the earliest recorded serum urate

measurement <360 micromol/l within 12 months after ULT initiation.
Comparison arm (FAF-ULT arm): Emulation of ULT initiation without an aim to achieve a serum urate target will use patients without any recorded serum urate measurements or with serum urate >360 micromol/l within 12 months after ULT initiation.
Previous randomised controlled trials showed that the serum urate target can be achieved within 6 months from the first ULT prescription. However, the proportion of patients achieving the serum urate target in clinical practice is expected to be lower. Therefore, we will allow 12 months of grace after ULT initiation for participants to achieve the serum urate target.

Outcomes

Primary outcome: first major adverse cardiovascular event (MACE) in the 5 years following ULT initiation. MACEs (i.e., either non-fatal acute myocardial infarction or non-fatal stroke (ischemic or haemorrhagic) or cardiovascular death), will be ascertained using hospitalization, primary care, and mortality records as follows:
Non-fatal myocardial infarction or non-fatal stroke documented in general practice records,
- hospitalization with non-fatal myocardial infarction or non-fatal stroke as the primary discharge diagnosis,
- cardiovascular death as the primary cause of death (i.e., the primary cause of death is fatal myocardial infarction, fatal stroke, cardiac arrest, heart failure, aortic dissection, or arrhythmias).
Linkage across all data sources has been shown to improve the ascertainment of MACEs in CPRD. The date of the MACE will be the earliest date of the above.
Secondary outcomes: first-ever MACE, MACE requiring hospitalisation or leading to death, acute myocardial infarction, stroke, all-cause mortality, first gout flare requiring consultation in primary care or hospitalisation, and number of gout

flares over the study period.
Negative control outcomes: acute bronchitis, cataract, and appendicitis over the study period. A negative control outcome is a variable that has no plausible mechanism by which it can be caused by the treatment of interest (i.e., colchicine prophylaxis) and is expected to share the same potential sources of bias with the primary outcome (i.e., cardiovascular events). Negative control outcomes s can serve as a diagnostic tool for assessing uncontrolled confounding.
Negative control outcomes and secondary outcomes will be ascertained in both primary care and secondary care datasets, and mortality records. The date of the first record of these outcomes will be the outcome date.

Data analysis plan

Follow up:
People will be followed up from the first ULT prescription to the earliest date of a cardiovascular event, transfer out of the primary-care practice, death, 5 years from the first ULT prescription, study end, and last consultation in primary care.
Artificial censoring will be applied as follows: 1) clones assigned to the T2T-ULT arm will be censored at 12 months from ULT initiation if they do not achieve the serum urate target, 2) clones assigned to the FAF-ULT arm will be censored at the time they achieve the serum urate target within 12 months after the first ULT prescription.

Covariates:
We will collect the following covariates ascertained on or before ULT initiation to build the inverse probability of censoring weighting as detailed above:
- demographics: age, sex (male or female), latest body mass index (BMI) available only in CPRD, socioeconomic deprivation assessed using the index of multiple deprivation (IMD) at patient level in CPRD and income and educational

level in VEGA, latest smoking status (current, past, or non-smoker) available only in CPRD, latest alcohol intake (current, past, or no intake) available only in CPRD. Demographic variables will be ascertained within the 5 years before ULT initiation,
- gout-related variables: gout duration (years), presence of subcutaneous tophi, number of anti-inflammatory prescriptions (colchicine, NSAIDs, and corticosteroids) in 12 months before ULT initiation, number of consultations in primary care for gout and number of hospitalisations for gout in the 12 months before ULT initiation, ULT molecule (i.e., febuxostat, allopurinol, uricosurics) and dose (high vs low starting dose), co-prescription of gout flare prophylaxis with colchicine and/or non-steroidal anti-inflammatory drugs on the date of ULT initiation (i.e., prescription length ≥21 days);
- general health and other cardiovascular comorbidities: Charlson Comorbidity Index, cardiovascular comorbidities not included in the Charlson Comorbidit.

Summary results

Statistical analysis:
All descriptive statistics will be reported as number (percentage), mean (standard deviation (SD), or median (interquartile range (IQR)) as appropriate. Although cloning allows us to account for observed confounding at baseline, the artificial censoring introduced is usually informative. The proposed approach to address this problem is to use inverse probability of censoring weighting. The purpose of the weights is to up-weight patients remaining adherent to the protocol so that they represent censored patients, and as such, maintain the comparability of the study arms throughout the grace period. Survival curves will be estimated using a non-parametric Kaplan-Meier estimator weighted for the inverse probability of censoring weights. The 95% confidence intervals for the difference in 5-year survival and the difference in restricted mean survival times will be obtained using a non-parametric bootstrap with 1000 replicates. First, data from Sweden and the UK will be analysed separately. Then, results

will be meta-analysed.

All analyses will be performed using Stata, version 18 (StataCorp, Texas, USA).

Inverse probability of censoring weighing

In this study, we will estimate the inverse probability of censoring weights by fitting a pooled logistic model for the monthly probability of remaining uncensored, including variables for time (in its linear and/or quadratic terms depending on the data structure) and the baseline covariates. To avoid undue influence of outliers, weights will be truncated at the 99.5th percentile in case of extreme weights.

The inverse probability of censoring weighting will be built using two different models including a different set of covariates as shown in the protocol.

Sensitivity analyses will be carried out to test the robustness of the association between the exposure and the outcome.

Documents

Study, other information

Emulated target trial framework T2T-ULT 15042024.pdf (148.18 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.

Data sources

Data source(s)

Clinical Practice Research Datalink

Data source(s), other

Western Swedish Health Care Register (VEGA)

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

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Not applicable