Title

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

Authors detail

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Roles and responsibilities

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EC, CL, GN, AJA, MAM, LJT, and AA all contributed and participated in the design of the study. EC, CL, and AA were mainly responsible for writing this protocol, but all other authors critically reviewed the protocol multiple times. All authors have given approval to the final protocol

Background and rationale

Gout is the only form of arthritis that can potentially be “cured” - with freedom from recurrent flares and disease progression - provided long-term treat-to-target urate-lowering therapy (T2T-ULT) is prescribed and adhered with [1]. The goal of T2T-ULT is to achieve and maintain a serum urate treatment target of <360 micromol/l [1].

The T2T strategy is a strategy that defines a treatment and applies tight control (for example, monthly visits and respective treatment adjustments) to reach and maintain this target.

However, only a suboptimal proportion (around 40%) of patients with gout who start ULT will achieve the serum urate treatment target within 12 months after ULT initiation [2]. Although not recommended by international scientific societies, the fire-and-forget (FAF) approach is still widely adopted by physicians treating gout patients. It mainly consists of prescribing treatment (e.g., ULT) without further dose adjustment based on markers of its effectiveness (e.g., serum urate levels) [3].

Gout has traditionally been conceptualised as an intermittent inflammatory joint disease. However, articular and systemic inflammation during the inter-critical period (i.e. between gout flares) has been described recently [4]. Of greater concern, recent publications have demonstrated that flares are temporally associated with subsequent cardiovascular events and death due to cardiovascular events in the following 30-60 days [5,6]. As T2T-ULT is effective in preventing gout flares after the

first year of treatment, long-term T2T-ULT may prevent cardiovascular events and cardiovascular mortality by reducing the number of flares [1].

There is, however, considerable controversy over whether T2T-ULT reduces the risk of adverse cardiovascular events in people with gout, despite the potential for such an effect. Two systematic literature reviews showed conflicting results, however, demonstrated several limitations in the existing studies' ability to estimate effects on cardiovascular outcomes [7,8]. Firstly, included clinical trials that recruited gout patients were underpowered and relatively short (<52 weeks) [7,8]. Secondly, observational studies that evaluated the association between ULT and cardiovascular mortality compared people prescribed ULT with ULT non-initiators so confounding by indication and healthcare-seeking behaviour biases may have affected the results [7,8]. Thirdly, no attempts were made to ascertain whether the ULT initiators met the serum urate treatment target in all but one of these studies [7–9].

A recent randomised controlled trial, the ALL-HEART study, showed that allopurinol does not improve cardiovascular outcomes in patients with ischaemic heart disease, but gout was an exclusion criterion for this study [10].

Aim

The main aim of this study will be to compare the risk of cardiovascular events among patients with gout who initiate ULT and achieve the serum urate target of ≤360 micromol/l within 12 months from ULT initiation with those who initiate ULT and do not have a recorded serum urate measurement of ≤360 micromol/l within 12 months from ULT initiation.

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 [11]. Cloning is used to assign people to treatment duration strategies at time zero (i.e., at ULT initiation), eliminating immortal time bias and creating two identical study arms at baseline. Then, a clone is censored when their available data (i.e., the serum urate levels) are no longer compatible with the treatment strategy of the arm they entered, but the follow-up continues for that individual in the arm of the compatible strategy. This induces informative censoring [12], which will be addressed using inverse probability weighting [13].

The emulation of target trials using real-world data can lead to high-quality evidence and high concordance with randomised controlled trials when closer emulation of trial design and measurements is adopted [14].

Study setting and data source

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 [15,16].

- 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 [17]. CPRD data include information on demographic characteristics, lifestyle factors, diagnoses, primary care prescriptions, laboratory results, and immunisations [17]. 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.

Eligibility criteria

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 [18]) within the study period, receive their first ULT prescription on or after the day of new gout diagnosis and have a 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 [19–21].

Treatment strategies

Intervention arm (T2T-ULT arm): To emulate ULT initiation aiming to achieve the serum urate target of $\leq$360 micromol/l within 12 months after ULT initiation, serum urate target will be ascertained by the earliest recorded serum urate measurement $\leq$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 [1,22,23]. However, the proportion of patients achieving the serum urate target in clinical practice is expected to be lower [2]. 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 [24–26]. 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 [5].

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) [27]. Negative control outcomes s can serve as a diagnostic tool for assessing uncontrolled confounding [27].

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.

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 [28], cardiovascular comorbidities not included in the Charlson Comorbidity index (i.e., hypertension, atrial fibrillation, and hypercholesterolemia), heart failure, diabetes with and without target organ damage, chronic kidney disease (stage 3,4,5), dementia, peripheral vascular disease, COPD, cancer, HIV/AIDS European Society of Cardiology cardiovascular risk (high/very high vs moderate/low), history of cardiovascular events before ULT initiation, number of consultations in primary care for any reason and number of hospitalisations for any cause in the 12 months before ULT initiation,
- medications (low-dose acetylsalicylic acid (ASA), non-ASA antiplatelet agents, statins, fibrates, other lipid-lowering agents, potassium-sparing diuretics, thiazides, loop diuretics, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, other anti-hypertensive agents, nitrates, and oral anticoagulants. Prescriptions will be categorised as current (last prescription within 60 days before ULT initiation in CPRD and last prescription within 120 days before ULT initiation in VEGA) or past/no prescription. The duration was selected based on clinical input as the mean length of prescriptions in the UK and in Sweden differs.

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 [12]. 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 [29].

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 following table.

Variables	Model 1	Model 2
Age	Y	Y
Sex (male vs female)	Y	Y
Body Mass Index	N	Y
Socioeconomic deprivation	Y	Y
Smoking status	N	Y
Alcohol intake	N	Y
Gout duration (years)	Y	Y
Subcutaneous tophi (y/n)	Y	Y
Number of anti-inflammatory prescriptions (colchicine, NSAIDs, and corticosteroids) in 12 months before ULT initiation	Y	Y
Number of consultations in primary care for gout and number of hospitalisations for gout in the 12 months before ULT initiation	Y	Y
ULT molecule (i.e., febuxostat, allopurinol, uricosurics)	Y	Y
ULT dose (high vs low starting dose)	Y	Y
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)	Y	Y
Charlson comorbidity index	N	Y
Cardiovascular comorbidities not included in the Charlson Comorbidity index (i.e., hypertension, atrial fibrillation, and hypercholesterolemia)	Y	Y
Acute or chronic ischaemic heart disease, heart failure, diabetes with and without target organ damage, chronic kidney disease (stage 3,4,5), dementia, peripheral vascular disease, COPD, cancer, HIV/AIDS	Y	Y
History of cardiovascular events before ULT initiation	Y	Y
European Society of Cardiology cardiovascular risk	Y	Y
Number of consultations in primary care for any reason and number of hospitalisations for any cause in the 12 months before ULT initiation	Y	Y
Proportion of days covered by ULT between the date of ULT initiation and the end of the grace period	Y	Y
Low-dose ASA	Y	Y
Non-ASA antiplatelet agents	Y	Y
Statins	Y	Y
Fibrates	Y	Y
Other lipid-lowering agents	Y	Y
Potassium-sparing diuretics	Y	Y
Thiazides	Y	Y
Loop diuretics	Y	Y
Beta-blockers	Y	Y
Calcium-channel blockers	Y	Y
Angiotensin-converting enzyme inhibitors	Y	Y
Angiotensin receptor blockers	Y	Y
Other anti-hypertensive agents	Y	Y
Nitrates	Y	Y
Oral anticoagulants	Y	Y
Y: yes, N: no.		

Model 1 will be used to meta-analyse the results from CPRD and VEGA datasets. Model 2 will be used to test the internal validity of the association between exposure and outcome and to check whether the variables available only in CPRD could represent major confounders.

Missing data

BMI, smoking status, alcohol intake status, and socioeconomic deprivation can have missing data in CPRD. The pattern of missingness will be compared and missingness at random assumed. Missing

data will be imputed using chained equations. BMI, smoking status, alcohol intake status, and socioeconomic deprivation will be modelled using multinomial logistic regression.

Subgroup analyses

We will perform some sensitivity analyses to test the robustness of the association between the exposure and the outcome.

- We will consider a SU target of ≤300 micromol/l to define the T2T-ULT arm and we will compare it with not achieving a SU target of ≤360 micromol/l,
- We will further censor the follow-up when people will discontinue ULT,
- We will exclude from the FAF-ULT arm, those patients who will not have measured serum urate levels within 12 months after ULT initiation.

Also, we will stratify the analyses using the following prognostic factors:

- Age (>65 and ≤65 years),
- Gender (male and female).

Feasibility count and sample size considerations

In a previous study, we identified 96,000 patients with incident gout in CPRD. Of them, 48% (~46,000) were ever prescribed ULT, and 28% (~12,000) and 16% (~7,000) achieved serum urate targets of $\leq$360 micromol/l and $\leq$300 micromol/l within 1 year after the first ULT prescription, respectively [2].

Approximately, 20,000 patients with an incident diagnosis of gout were ascertained in VEGA. Of them, 42% (~8,000) were prescribed ULT [30]. We assume a similar rate of success as in CPRD. Thus, data for approximately 14,000 exposed and 30,000 unexposed patients and 8,000 exposed and 30,000 unexposed patients will be available for the main aim and the secondary aim, respectively.

Based on these data, our study will have more than 99% power to detect a risk difference of 1/1,000 person-years assuming a rate of MACE of 17/1,000 person-years [5] in the unexposed and an alpha error of 0.025.

Ethics, funding, and patient partner in research involvement

This study was approved by Clinical Practice Research Datalink's Research Data Governance (protocol 23_002701), which has overarching research ethics committee approval for research studies using anonymous data (reference 05/MRE04/87). Practices that contribute data to the Clinical Practice Research Datalink allow the use of anonymized patient data for approved research projects and additional patient consent is not required.

This study followed the recommendations of the RECORD (Reporting of Studies Conducted using Observational Routinely Collected Data) statement.

Patient organisations (The UK Gout Society) were involved in prioritising the research question.

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