Cardiovascular events in patients with gout initiating urate-lowering therapy with or without colchicine for flare prophylaxis: a retrospective new-user cohort study using linked primary care, hospitalisation, and mortality data

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Summary

Background Initiating urate-lowering therapy can trigger gout flares. Gout flares have been associated with a temporally increased risk of cardiovascular events. Therefore, we aimed to estimate the risk of cardiovascular events in patients with gout initiating urate-lowering therapy with flare prophylaxis using colchicine (the drug recommended for gout flare prohphylaxis by many international societies) compared with no prophylaxis.

Methods We did a retrospective new-user cohort study using data from the Clinical Practice Research Datalink Aurum, an English primary-care database linked to hospitalisation and mortality records. People with gout initiating urate-lowering therapy for the first time were eligible for inclusion. We compared people prescribed flare prophylaxis with colchicine with those not prescribed any gout flare prophylaxis. Colchicine prophylaxis (defined as prescription for ≥21 days) prescribed on the same date as urate-lowering therapy was the exposure of interest. A composite of fatal and non-fatal myocardial infarction or stroke within 180 days after urate-lowering therapy initiation regardless of any previous cardiovascular event was the primary outcome. Propensity score overlap weighting was used to balance covariates across study groups. We used Cox regression and performed intention-to-treat and per-protocol analyses, the latter with an inverse probability of censoring weighting. The association was measured using hazard ratio and risk difference with 95% CIs. Members of The UK Gout Society were involved in prioritising the research question.

Findings Of the 111 460 patients eligible for the study, 99 800 patients with gout initiating urate-lowering therapy were included. 25 511 (25·6%) of 99 800 patients were female, 74 289 (74·4%) were male, 84 928 (85·1%) patients were White and the mean age was 62·8 years (SD 15·5). 4063 (4·1%) patients had previous cardiovascular events and 16 028 (16·1%) patients were prescribed colchicine prophylaxis. Patients with colchicine prophylaxis had significantly lower risk of cardiovascular events compared with those without prophylaxis. The weighted rates of cardiovascular events were 28·8 per 1000 person-years (95% CI 25·2 to 33·2) in patients with colchicine prophylaxis and 35·3 per 1000 person-years (33·0 to 37·9) in those without prophylaxis (weighted rate difference –6·5 [95% CI –9·4 to –3·6] per 1000 person-years and weighted hazard ratio 0·82 [0·69–0·94]) in the intention-to-treat analysis. Findings were similar across analytical approaches, stratified analyses, and for secondary outcomes.

Interpretation In patients with gout initiating urate-lowering therapy, the risk of cardiovascular events was reduced in those prescribed colchicine prophylaxis compared with no prophylaxis. These findings provide an additional argument for using colchicine for gout flare prophylaxis.

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Introduction

Gout is the most common form of inflammatory arthritis worldwide and affects 2·5%–5·0% of adults in high-income countries.[1] It occurs due to sustained hyperuricaemia that causes monosodium urate crystals to deposit in and around joints.[2] The release of crystals from pre-formed deposits causes intense inflammatory flares of joint pain and swelling that last for approximately 1–2 weeks.[2] Gout can be effectively managed with long-term urate-lowering therapy, with cessation of gout flares, provided a serum urate concentration of 360 µmol/L or less (≤300 µmol/L in those with tophi) is reached and maintained long-term.[3] However, reduction in serum urate within the first few months of starting urate-lowering therapy can trigger gout flares as the solubilisation and subsequent shedding of monosodium urate crystals can initiate inflammation resulting in flares.[4] Consequently, flare prophylaxis, with colchicine as a first-line drug, is recommended during the first 3–6 months of urate-lowering therapy.[5–7] However, only

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Research in context

Evidence before this study

Urate-lowering therapy (eg, allopurinol and febuxostat) increases the risk of gout flares during the first few months of treatment. Colchicine (0·5–1·0 mg per day), an anti-inflammatory drug, is recommended to prevent such flares. However, it is often not prescribed by general practitioners due to a lack of awareness and concern about side-effects. Colchicine is effective in the secondary prevention of cardiovascular events in people with pre-existing cardiovascular disease. As gout flares are temporally associated with cardiovascular events, finding out whether low-dose colchicine used for gout flare prophylaxis could also prevent cardiovascular events in people with gout starting urate-lowering treatment is important. We searched PubMed for studies published between database inception and May 1, 2024, using the terms "gout" AND ("allopurinol" OR "urate-lowering" OR "febuxostat" OR "lesinurad" OR "pegloticase" OR "probenecid" OR "sulfinpyrazone") AND ("colchicine" OR "flare prophylaxis") AND ("myocardial infarction" OR "stroke" OR "cerebrovascular accident" OR "cardiovascular event"), with no language restrictions, to identify cohort studies and randomised controlled trials that evaluated the risk of cardiovascular events in people with gout initiating urate-lowering therapy with or without colchicine. We also searched the reference lists of these studies. We identified a single observational study conducted in the UK, which reported an association between colchicine prescription and myocardial infarction in patients with gout starting urate-lowering therapy. However, the findings from this study were inconsistent with the findings from two randomised controlled trials in which colchicine was effective in the secondary prevention of cardiovascular events in people with pre-existing ischaemic heart disease. This study was also at risk of bias due to unequal follow-up between the exposed and unexposed, and the use of colchicine prescription of any duration when evaluating the association between colchicine and myocardial infarction. Most primary-care colchicine prescriptions are for less than 1 week and are likely issued to treat gout flare, which is itself associated with cardiovascular events. A previous observational study also showed a protective effect of colchicine on cardiovascular events in people with gout but did not specifically evaluate the period immediately after starting urate-lowering therapy, a time when there is a high risk of flares that are associated with cardiovascular events.

Added value of this study

This study evaluated the association between the prescription of gout flare prophylaxis using colchicine and cardiovascular events among people with gout starting urate-lowering therapy in the UK. The exposure was defined using colchicine prescription for 21 days or more, minimising any potential misclassification bias from shorter prescriptions. The use of linked primary care, hospitalisation (ie, admittance to hospital), and mortality records allowed for a comprehensive ascertainment of outcomes. This study found a negative association between colchicine use for gout flare prophylaxis and cardiovascular events and addresses an important gap in the literature using robust methods and advanced statistical techniques.

Implications of all the available evidence

At a time when people with gout are at an increased risk of cardiovascular events due to gout flares triggered by urate-lowering therapy, flare prophylaxis with colchicine reduces the risk of cardiovascular events. This study provides data to support the cardiovascular benefits of colchicine in people with gout.

10–20% of people with gout are prescribed gout flare prophylaxis.[8,9]

Cardiovascular events have been previously reported to be temporally associated with recent previous gout flares (ie, those within the previous 60 days).[10,11] Given this finding and the fact that starting urate-lowering therapy can trigger gout flares, determining if flare prophylaxis using colchicine prevents cardiovascular events in those who are newly prescribed urate-lowering therapy is important. Although previous clinical trials have shown that long-term low-dose colchicine is effective in the secondary prevention of cardiovascular events in people without gout,[12–14] one study reported an increased risk of myocardial infarction in people with gout prescribed urate-lowering therapy and colchicine on the same date.[15] However, this study was at an increased risk of bias as detailed in the discussion.[16] In the current study, we hypothesised that in people with gout initiating urate-lowering therapy, gout flare prophylaxis with colchicine would be associated with fewer cardiovascular events than in people initiating urate-lowering therapy without any flare prophylaxis.

Methods

Study design and participants

We used data from the Clinical Practice Research Datalink Aurum, which includes information on demographic and lifestyle factors, diagnoses, primary-care prescriptions, and laboratory results from more than 38 million individuals gathered during routine clinical care, and is representative of the UK population.[17] The data in England are linked to patient-level index of multiple deprivation scores (a measure of relative deprivation based on income, health, education, employment, barriers to housing and services, living environment, and crime), hospitalisation records via linkage with the Hospital Episode Statistics dataset, and information on date and causes of death via linkage with the Office for National Statistics dataset.

This was a retrospective new-user cohort study with a non-equivalent comparator performed in people with gout initiating urate-lowering therapy co-prescribed flare prophylaxis with colchicine versus no flare prophylaxis using an emulated target trial framework (appendix pp 2–3)[18] and propensity score overlap weighting.[19]

Patients newly diagnosed with gout between Jan 1, 1997, and March 29, 2021 (ie, the start of the Hospital Episode Statistics and the Office for National Statistics linkage and the date of the latest Hospital Episode Statistics and Office for National Statistics data release) and prescribed urate-lowering therapy for the first time on or after gout diagnosis in a primary-care setting were considered for inclusion in the study. They were required to be at least 18 years old at gout diagnosis, to contribute research-quality data to the Clinical Practice Research Datalink Aurum, and to have linkages with the Hospital Episode Statistics and the Office for National Statistics databases. Patients were also required to have been registered with their current general practice for more than 1 year before their gout diagnosis to minimise the risk of prevalent cases appearing as incident. Patients who received one or more prescriptions of colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) for 21 days or more in the 180 days before urate-lowering therapy initiation were excluded to minimise prevalent user bias and to minimise the possibility of long-term use of NSAIDs appearing in the unexposed group and thereby confound the analysis given their well known association with an increased risk of cardiovascular events.[20]

Members of The UK Gout Society were involved in prioritising the research question. The study was approved by Clinical Practice Research Datalink Aurum'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 Aurum allow the use of anonymised patient data for approved research projects and additional patient consent was not required.

Procedures

Comparisons were made between patients co-prescribed gout flare prophylaxis with colchicine and patients without gout flare prophylaxis when initiating urate-lowering therapy. Gout flare prophylaxis was defined as a colchicine prescription that lasted for 21 days or more because according to our clinical experience, a prescription of up to 1–2 weeks is typically issued to treat gout flares.

To be included in the prophylaxis group, patients had to be co-prescribed colchicine for 21 days or more on the same date as urate-lowering therapy initiation. Patients with NSAID co-prescriptions for 21 days or more on the same date were excluded. Patients were included in the no prophylaxis group if they were not co-prescribed either colchicine or NSAIDs for 21 days or more on the same date as urate-lowering therapy initiation.

Patients in the prophylaxis group could have been prescribed a shorter course of NSAIDs whereas those in the no prophylaxis group could have been prescribed a shorter course of either NSAIDs or colchicine on this date. We chose not to compare colchicine with NSAIDs as the latter are well known to be associated with cardiovascular events and any protective effect of colchicine on cardiovascular events with this comparator would be expected.

See Online for appendix

All participants prescribed urate-lowering therapy in the UK are eligible to receive gout flare prophylaxis with colchicine. However, colchicine is more likely to be prescribed in those with frequent or severe gout flares,[21] and tophi, and less likely to be prescribed in those with chronic kidney disease and those of older age due to the risk of side-effects. To minimise imbalance, we used propensity score overlap weighting to ensure the exposed and unexposed groups were comparable on age, chronic kidney disease, presence of tophi, latest serum urate, other traditional cardiovascular risk factors (such as hypercholesterolaemia, arterial hypertension, smoking habit, diabetes with and without target organ damage, previous cardiovascular events, heart failure, and atrial fibrillation and flutter), and the number of primary-care consultations for gout, the number of hospitalisations (ie, admittance to hospital) for gout, the number of anti-inflammatory prescriptions, and the number of gout flare consultations in the preceding 12 months (appendix pp 10–11). A flow chart of the algorithm for processing drug exposure data is shown in the appendix (p 4), as is the algorithm for processing colchicine prescription data (appendix pp 5–6).

Outcomes

The primary outcome was the first cardiovascular event within 180 days after urate-lowering therapy initiation regardless of any previous cardiovascular event. Cardiovascular events included either fatal and non-fatal acute myocardial infarction or fatal and non-fatal stroke (ischaemic or haemorrhagic) ascertained in either primary care (ie, a medical code indicating one or more of these conditions), hospitalisation (ie, hospitalisations with a cardiovascular event as the primary discharge diagnosis), or mortality records (ie, death with a cardiovascular event as the primary cause of death).

Secondary outcomes were: first-ever cardiovascular event (ie, excluding people with a cardiovascular event before cohort entry), fatal cardiovascular events, myocardial infarction, and stroke. This approach was chosen because linkage across all data sources improved the ascertainment of cardiovascular events.[22]

Respiratory tract infection and peptic ulcer disease were chosen as negative control outcomes as they are common and there is no plausible reason for an association with colchicine use. Diarrhoea is a known

side-effect of colchicine and was included as a positive control outcome. Negative and positive control outcomes were ascertained in both primary-care and secondary-care datasets. The date of the first record of these outcomes in the Clinical Practice Research Datalink Aurum, Hospital Episode Statistics, or Office for National Statistics was the outcome date. All the lists of codes used to define the target population, the exposure, and the outcomes are listed in the (appendix pp 21–49).

Statistical analysis

As BMI, smoking status, alcohol intake, index of multiple deprivation, and serum urate had missing data we performed multiple imputation using chained equation (appendix pp 7–8). 20 imputed datasets were created. Propensity score overlap weighting was performed in each imputed dataset to balance baseline characteristics between the two groups.

After checking for proportional hazard assumptions using log–log plots and Schoenfeld residuals (appendix p 9), we used weighted Cox proportional hazards models to examine the association between colchicine flare prophylaxis and outcomes of interest in an intention-to-treat analysis. In the per-protocol analysis alongside propensity score overlap weighting we used the inverse probability of censoring weighting.[24] Weighted hazard ratios (HRs), incidence rates (IR), risk differences (RD), and their 95% CIs were calculated using the propensity score overlap weighting. The weighted number needed to treat over 180 days was calculated for each outcome in the intention-to-treat analysis using the propensity score overlap weighting. The treatment effect was estimated within each imputed dataset using the propensity score overlap weighting. Then, we pooled the estimates using Rubin's rule. An E-value was calculated to evaluate the robustness of our primary outcome to unmeasured confounders.[25]

Details about propensity score overlap weighting and inverse probability of censoring weighting are provided in the appendix (pp 10–11). We assessed the balance of the distribution of covariates before and after weighting by standardised differences (values <0·1 denoted negligible differences).

In the intention-to-treat analysis, people were followed from urate-lowering therapy initiation to the earliest date of a cardiovascular event, 180 days after the first urate-lowering therapy prescription, date of death, date of last data collection from the practice (ie, the most recent date on which the Clinical Practice Research Datalink Aurum obtained data from the practice), study end date (ie, March 29, 2021), and the date when a patient left the practice. The follow-up was censored on 180 days as this is the recommended duration of gout flare prophylaxis in several guidelines.[5,6]

In the per-protocol population, additionally, follow-up was censored when the exposed group discontinued the prophylaxis (defined as 14-day gaps between consecutive prescriptions) or when they were prescribed NSAIDs for 21 days or more. Those not prescribed gout flare prophylaxis at the time of urate-lowering therapy initiation were censored when they had a prescription of either colchicine or NSAID flare prophylaxis for 21 days or more.

We stratified the analyses using the following prognostic factors: age (>65 years and ≤65 years), sex (male and female), European Society of Cardiology cardiovascular risk (high or very high and moderate or low), and year of the first urate-lowering therapy prescription (1997–2007 *vs* 2008–2021). This was done because the British Society of Rheumatology recommended gout flare prophylaxis using colchicine for the first time in May, 2007.[23]

We also performed a sensitivity analysis restricting the follow-up up to 90 days after urate-lowering therapy initiation as this is the minimal recommended duration of gout flare prophylaxis in the American College of Rheumatology guidelines.[7] In a further sensitivity analysis, we replaced the propensity score overlap weighting with a multivariable adjustment Cox-regression model using the same set of covariates that were used for propensity score overlap weighting in an intention-to-treat model. Next, we performed a similar per-protocol analysis that was additionally weighted for the inverse probability of censoring weights. All analyses were performed using STATA 18.

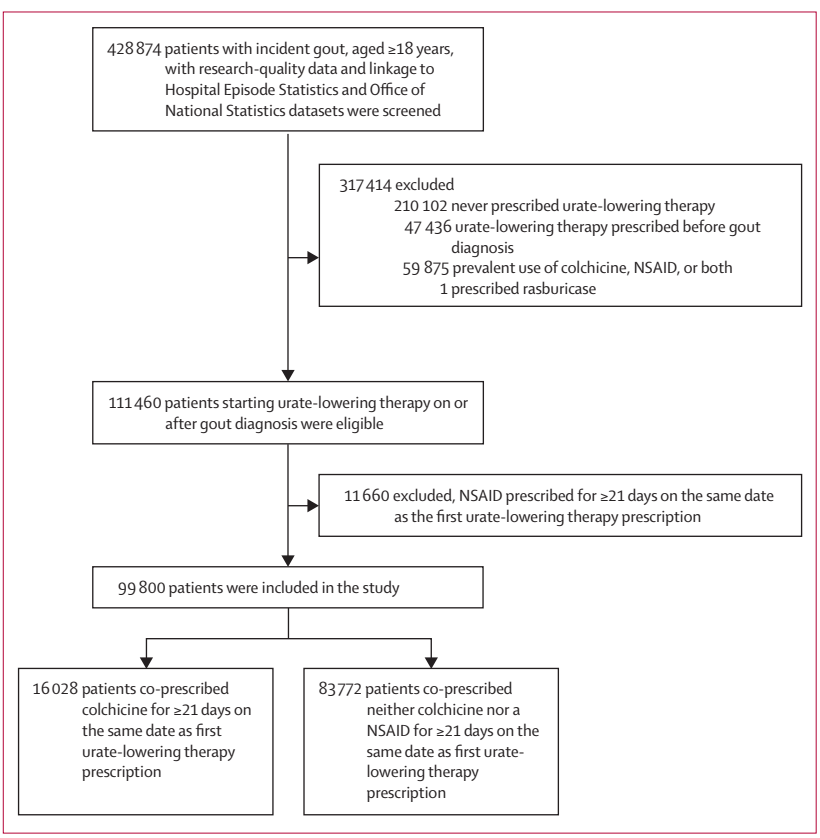

Figure 1: **Study flow chart**
NSAID=non-steroidal anti-inflammatory drug

	Eligible study population			Study population after propensity score overlap weighting		
	No prophylaxis group (N=83 772)	Colchicine prophylaxis group (N=16 028)	Standardised mean difference	No prophylaxis group (N=83 772)	Colchicine prophylaxis group (N=16 028)	Standardised mean difference
Age, years	62·7 (15·5)	63·5 (15·2)	−0·06	63·2 (15·1)	63·2 (15·4)	0·00
Sex	..	..	0·06	..	..	0·00
Female	21 798 (26·0%)	3713 (23·2%)	..	19 810 (23·6%)	3794 (23·7%)	..
Male	61 974 (74·0%)	12 315 (76·8%)	..	63 962 (76·4%)	12 234 (76·3%)	..
Ethnicity	..	..	..*	..	..	..*
White	71 096 (84·9%)	13 832 (86·3%)	..	71 096 (84·9%)	13 832 (86·3%)	..
Black	2000 (2·4%)	297 (1·9%)	..	2000 (2·4%)	297 (1·9%)	..
Chinese	321 (0·4%)	64 (0·4%)	..	321 (0·4%)	64 (0·4%)	..
Indian, Pakistani, or Bangladeshi	2396 (2·9%)	361 (2·3%)	..	2396 (2·9%)	361 (2·3%)	..
Other Asian ethnicities	876 (1·0%)	120 (0·7%)	..	876 (1·0%)	120 (0·7%)	..
Mixed	325 (0·4%)	54 (0·3%)	..	325 (0·4%)	54 (0·3%)	..
Other	1815 (2·1%)	325 (2·0%)	..	1815 (2·1%)	325 (2·0%)	..
Unknown	4943 (5·9%)	975 (6·1%)	..	4943 (5·9%)	975 (6·1%)	..
Alcohol use	..	..	0·07	..	..	0·00
Non-drinker	1471 (1·8%)	237 (1·5%)	..	1427 (1·7%)	274 (1·7%)	..
Past drinker	610 (0·7%)	115 (0·7%)	..	647 (0·8%)	124 (0·8%)	..
Current drinker (≤14 units per week)	48 749 (58·2%)	9441 (58·9%)	..	55 033 (65·7%)	10 537 (65·7%)	..
Current drinker (15–21 units per week)	8631 (10·3%)	1823 (11·4%)	..	10 518 (12·6%)	2009 (12·5%)	..
Current drinker (>21 units per week)	12 247 (14·6%)	2852 (17·8%)	..	16 147 (19·3%)	3084 (19·2%)	..
Missing data	12 064 (14·4%)	1560 (9·7%)	..	..	..	..
BMI status	..	..	0·09	..	..	0·00
<18·5 kg/m²	564 (0·7%)	71 (0·4%)	..	425 (0·5%)	81 (0·5%)	..
18·5–24·9 kg/m²	12 081 (14·4%)	2122 (13·2%)	..	12 339 (14·7%)	2360 (14·7%)	..
25·0–29·9 kg/m²	28 530 (34·1%)	5498 (34·3%)	..	31 221 (37·3%)	5971 (37·3%)	..
≥30·0 kg/m²	33 292 (39·7%)	7222 (45·1%)	..	39 787 (47·5%)	7616 (47·5%)	..
Missing data	9305 (11·1%)	1115 (7·0%)	..	..	..	..
Smoking	..	..	−0·02	..	..	0·00
Non-smoker	41 147 (49·1%)	8047 (50·2%)	..	42 854 (51·2%)	8201 (51·2%)	..
Past smoker	29 152 (34·8%)	6134 (38·3%)	..	32 117 (38·3%)	6143 (38·3%)	..
Current smoker	9781 (11·7%)	1648 (10·3%)	..	8801 (10·5%)	1684 (10·5%)	..
Missing data	3692 (4·4%)	199 (1·2%)	..	..	..	..
2019 English Deprivation Score Index†	5·3 (2·9)	5·1 (2·8)	−0·09	5·1 (2·8)	5·1 (2·8)	0·00
Missing data	123 (0·1%)	18 (0·1%)	..	..	..	..
Gout duration since diagnosis, years	1·7 (3·0)	2·4 (3·7)	0·17	2·3 (3·3)	2·3 (3·6)	0·00
Number of anti-inflammatory prescriptions in the previous year	1·2 (2·0)	2·4 (2·1)	0·55	2·2 (3·2)	2·2 (1·7)	0·00
Number of consultations for gout in the previous year	1·6 (1·4)	1·9 (1·5)	0·19	1·9 (1·7)	1·9 (1·4)	0·00
Number of hospital admissions for gout in the previous year	0 (0·1)	0 (0·1)	0·01	0 (0·1)	0 (0·1)	0·00
Number of gout flares in the previous year	0·2 (0·4)	0·2 (0·4)	−0·09	0·2 (0·4)	0·2 (0·4)	0·00
Latest serum urate measurement in the previous year, µmol/L	516·0 (94·4)	518·2 (92·8)	0·02	517·4 (94·0)	517·5 (93·2)	0·00
Missing data	29 072 (34·7%)	4141 (25·8%)	..	..	..	..
Subcutaneous tophi	1471 (1·8%)	358 (2·2%)	0·03	1709 (2·0%)	328 (2·0%)	0·00
Urate-lowering therapy	..	..	0·00	..	..	0·01
Allopurinol	83 209 (99·3%)	15 889 (99·1%)	..	83 176 (99·3%)	15 893 (99·2%)	..
Febuxostat	462 (0·6%)	131 (0·8%)	..	555 (0·7%)	127 (0·8%)	..
Probenecid	48 (0·1%)	..‡	..	18 (<0·1%)	..‡	..
Sulfinpyrazone	53 (0·1%)	..‡	..	23 (<0·1%)	..‡	..

(Table 1 continues on next page)

	Eligible study population			Study population after propensity score overlap weighting		
	No prophylaxis group (N=83 772)	Colchicine prophylaxis group (N=16 028)	Standardised mean difference	No prophylaxis group (N=83 772)	Colchicine prophylaxis group (N=16 028)	Standardised mean difference
(Continued from previous page)						
Urate-lowering therapy starting dose§	..	..	−0·33	..	..	0·00
Low	60 599 (72·3%)	14 058 (87·7%)	..	70 438 (84·1%)	13 459 (84·0%)	..
High	23 173 (27·7%)	1970 (12·3%)	..	13 334 (15·9%)	2569 (16·0%)	..
Charlson Comorbidity Index¶	1·7 (2·1)	1·8 (2·2)	0·04	1·8 (2·1)	1·8 (2·2)	0·00
Number of hospitalisation admissions for any cause in the previous year	0·3 (1·7)	0·3 (0·9)	−0·03	0·3 (0·8)	0·3 (0·9)	0·00
European Society of Cardiology high or very high cardiovascular risk category[26]	33 475 (40·0%)	6594 (41·1%)	0·03	34 653 (41·4%)	6481 (40·4%)	−0·02
History of acute coronary syndrome or stroke	3503 (4·2%)	560 (3·5%)	−0·03	2928 (3·5%)	563 (3·5%)	0·00
Peripheral artery disease	3813 (4·6%)	659 (4·1%)	−0·02	3435 (4·1%)	658 (4·1%)	0·00
Chronic kidney disease (stages 3–5)	18 970 (22·6%)	4301 (26·8%)	0·10	21 830 (26·1%)	4188 (26·1%)	0·00
Chronic kidney disease (stages 4–5)	3094 (3·7%)	531 (3·3%)	−0·02	3684 (4·4%)	523 (3·3%)	−0·06
Diabetes	13 359 (15·9%)	2612 (16·3%)	0·01	13 572 (16·2%)	2598 (16·2%)	0·00
Diabetes with target organ damage[26]‖	871 (1·0%)	159 (1·0%)	−0·01	862 (1·0%)	160 (1·0%)	0·00
Atrial fibrillation or atrial flutter	13 316 (15·9%)	2885 (18·0%)	0·04	14 730 (17·6%)	2827 (17·6%)	0·00
Hypercholesterolaemia	8908 (10·6%)	1786 (11·1%)	0·02	9224 (11·0%)	1765 (11·0%)	0·00
Arterial hypertension	47 760 (57·0%)	9166 (57·2%)	0·01	47 717 (57·0%)	9133 (57·0%)	0·00
Prescription of oral anticoagulants	9956 (11·9%)	2279 (14·2%)	0·07	11 483 (13·7%)	2203 (13·7%)	0·00
Prescription of sodium-glucose co-transporter-2	62 (0·1%)	23 (0·1%)	0·01	96 (0·1%)	18 (0·1%)	0·00
Prescription of other lipid-lowering drugs	1560 (1·9%)	338 (2·1%)	0·02	1639 (2·0%)	313 (2·0%)	0·00
Prescription of statins or biological lipid-lowering drugs	14 329 (17·1%)	3284 (20·5%)	0·07	16 476 (19·7%)	3156 (19·7%)	0·00
Prescription of fibrates	786 (0·9%)	126 (0·8%)	−0·01	648 (0·8%)	125 (0·8%)	0·00
Prescription of low-dose aspirin	17 021 (20·3%)	2842 (17·7%)	−0·05	15 064 (18·0%)	2883 (18·0%)	0·00
Prescription of non-aspirin anti-platelet agents	3561 (4·3%)	708 (4·4%)	0·01	3706 (4·4%)	708 (4·4%)	0·00
Prescription of sacubitril	82 (0·1%)	31 (0·2%)	0·01	113 (0·1%)	35 (0·2%)	0·02
Prescription of other blood pressure-lowering drugs	4392 (5·2%)	881 (5·5%)	0·01	4559 (5·4%)	872 (5·4%)	0·00
Prescription of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	36 133 (43·1%)	7281 (45·4%)	0·05	37 629 (44·9%)	7208 (45·0%)	0·00
Prescription of calcium channel blockers	16 748 (20·0%)	3328 (20·8%)	0·02	17 308 (20·7%)	3307 (20·6%)	0·00
Prescription of β-blockers	15 050 (18·0%)	3375 (21·1%)	0·07	17 174 (20·5%)	3299 (20·6%)	0·00
Prescription of thiazides or loop diuretics	31 200 (37·2%)	5125 (32·0%)	−0·10	27 357 (32·7%)	5244 (32·7%)	0·00
Prescription of potassium-sparing diuretics	5909 (7·1%)	1050 (6·6%)	−0·02	5492 (6·6%)	1058 (6·6%)	0·00

Data are n (%) or mean (SD). *Ethnicity was not included in the propensity score overlap weighting. †This index is ranked on deciles, 1 is the least deprived and 10 is the most deprived. ‡Not reported due to Clinical Practice Research Datalink policy of not disclosing data for ≤five patients. §A low urate-lowering therapy starting dose was defined as a dose of allopurinol of ≤100 mg per day, probenecid of ≤500 mg per day, or sulfinpyrazone of ≤100 mg per day. A high urate-lowering therapy starting dose was defined as a dose of allopurinol of >100 mg per day, febuxostat of ≥40 mg per day, probenecid of >500 mg per day, or sulfinpyrazone of >100 mg per day (appendix p 12). ¶Range from 0 to 33. ‖Target organ damage was defined as an estimated glomerular filtration (GFR) rate of <45 mL per min/1·73m² irrespective of albuminuria or an estimated GFR of 45–59 mL per min/1·73m² and microalbuminuria (albumin-to-creatinine ratio 30–300 mg/g) or proteinuria (albumin-to-creatinine ratio >300 mg/g) or the presence of microvascular disease in at least three different sites (eg, microalbuminuria, retinopathy, and neuropathy).

Table 1: **Baseline clinical and demographic data of patients with gout included in the study**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

111 460 people newly diagnosed with gout between Jan 1, 1997, and March 29, 2021, with linkage to Hospital Episode Statistics and Office for National Statistics datasets, and first prescribed urate-lowering therapy on or after the first recorded gout diagnosis were eligible for inclusion in the study. 11 660 patients were excluded as they were also co-prescribed NSAIDs for 21 days or more on the date of first urate-lowering therapy prescription. 99 800 patients were included in the study; 16 028 were co-prescribed gout flare prophylaxis with colchicine and 82 772 were not were not prescribed gout flare prophylaxis with colchicine nor NSAIDs (figure 1).

25 511 (25·6%) of 99 800 patients were female, 74 289 (74·4%) were male, 84 928 (85·1%) were White and the mean age was 62·8 years (SD 15·5) (table 1).

Baseline gout-related characteristics at urate-lowering therapy initiation were median disease duration 0·2 years (IQR 0·0–2·4), mean serum urate 516·4 µmol/L (SD 94·1), and 1829 (1·8%) of 99 800 patients had subcutaneous tophi (table 1). In the exposed group, the mean duration of colchicine flare prophylaxis was 47·3 days (SD 33·7). The mean daily dose of colchicine was 0·97 mg (SD 0·16) at cohort entry. After propensity score overlap weighting, baseline covariates were well balanced (all standardised mean differences <0·10; appendix p 13). The distribution of the propensity score is shown in the appendix (p 14).

Patients starting colchicine prophylaxis were followed-up for a mean of 175·5 days (SD 29·7) and those who were not prescribed any flare prophylaxis were followed up for a mean of 176·9 days (26·7), both in the intention-to-treat analysis. The mean follow-up in the per-protocol analysis was 45·7 days (33·1) and 161·1 days (49·5) in the two groups, respectively. Reasons for censoring are reported in the appendix (p 15).

Information about serum urate concentration measured during the follow-up was available for 41 553 (41·6%) of 99 800 patients: 9265 (57·8%) of 16 028 patients in the colchicine prophylaxis group and 32 288 (38·5%) of 83 772 in the no prophylaxis group. The mean serum urate concentration were comparable: 384 µmol/L (SD 95·0) in the colchicine prophylaxis group and 389 µmol/L (99·2) in the no prophylaxis group with a mean decrease of –135·2 µmol/L (108·6) and –130·3 µmol/L (113·4), respectively.

The primary outcome of fatal and non-fatal myocardial infarction or stroke occurred in 217 (1·4%) of 16 028 patients (patients=events) in the colchicine prophylaxis group and 1528 (1·8%) of 83 772 patients in the no prophylaxis group (table 2). The weighted cumulative incidence rate in the intention-to-treat analysis was 1·4% (95% CI 1·2 to 1·6) in the colchicine prophylaxis group and 1·7% (1·6 to 1·8) in the no prophylaxis group (figure 2). The crude IR was 28·2 per 1000 person-years (95% CI 24·7 to 32·2) in

	No prophylaxis group (N=83 772)			Colchicine prophylaxis group (N=16 028)					
	Number of events	Follow-up time (person-years)	Weighted incidence rate, events per 1000 person-years (95% CI)	Number of events	Follow-up time (person-years)	Weighted incidence rate, events per 1000 person-years (95% CI)	Weighted hazard ratio (95% CI)	Weighted risk difference, events per 1000 person-years (95% CI)	Weighted number needed to treat, or the number needed to harm over 180 days (95% CI)
Main outcome									
Cardiovascular events	1528	40 566·6	35·3 (33·0 to 37·9)	217	7700·4	28·8 (25·2 to 33·2)	0·82 (0·69 to 0·94)	–6·5 (–9·4 to –3·6)	154 (94 to 425)
Stratified analysis									
Males*	1022	30 092·8	32·9 (30·3 to 35·8)	155	5918·9	27·1 (23·1 to 32·0)	0·82 (0·57 to 0·97)	–5·8 (–8·6 to –3·0)	172 (96 to 834)
Females*	506	10 473·8	43·0 (38·1 to 48·7)	62	1781·4	34·5 (26·9 to 45·1)	0·81 (0·58 to 1·01)	–8·5 (–11·6 to –5·4)	118 (56 to 1214)
>65 years old†	1233	20 699·4	55·1 (51·0 to 59·5)	175	4081·3	44·6 (38·4 to 52·1)	0·81 (0·67 to 0·95)	–10·5 (–14·0 to –7·0)	95 (57 to 290)
≤65 years old†	295	19 867·2	13·7 (11·8 to 16·1)	42	3619·1	11·7 (8·7 to 16·3)	0·85 (0·56 to 1·15)	–2·0 (–3·8 to –0·2)	500 (171 to 538)
European Society of Cardiology high or very high cardiovascular risk‡	1231	15 905·6	69·4 (64·3 to 75·1)	180	3138·7	60·0 (51·7 to 69·9)	0·86 (0·72 to 1·00)	–9·4 (–13·5 to –5·3)	106 (54 to 4985)
European Society of Cardiology low or moderate cardiovascular risk‡	297	24 660·9	11·9 (10·3 to 13·9)	37	4561·7	8·1 (5·9 to 11·5)	0·69 (0·44 to 0·94)	–3·8 (–5·4 to –2·2)	263 (149 to 1152)
First urate-lowering therapy prescription 1997–2007§	425	10 659	51·4 (43·1 to 61·9)	37	897·5	42·9 (30·9 to 61·2)	0·84 (0·52 to 1·27)	–8·5 (–12·0 to –5·0)	118 (45 to 185)
First urate-lowering therapy prescription 2008–2021§	1103	29 907·6	33·3 (30·9 to 35·9)	180	6802·9	27·1 (23·4 to 31·5)	0·81 (0·68 to 0·95)	–6·2 (–9·0 to –3·4)	161 (95 to 544)
Secondary outcomes									
First-ever cardiovascular events	746	39 100·6	18·7 (17·0 to 20·7)	110	7465·1	14·8 (12·3 to 18·0)	0·80 (0·62 to 0·97)	–3·9 (–6·0 to –1·8)	256 (144 to 1177)
Fatal cardiovascular events	181	40 566·6	3·7 (3·0 to 4·7)	20	7700·4	2·7 (1·8 to 4·4)	0·74 (0·37 to 1·10)	–1·0 (–1·9 to –0·1)	1000 (435 to 3323)
Myocardial infarction	796	40 566·6	18·2 (16·5 to 20·0)	115	7700·4	15·1 (12·6 to 18·3)	0·84 (0·66 to 1·00)	–3·1 (–5·2 to –1·0)	323 (163 to 12275)
Stroke	982	40 566·6	23·0 (21·1 to 25·0)	168	7700·4	22·1 (19·0 to 26·0)	0·94 (0·79 to 1·11)	–0·9 (–3·4 to 1·6)	1111 (223 to 371)
Control outcomes									
Respiratory tract infections	2130	40 062·4	55·1 (52·0 to 58·5)	372	7611·8	50·2 (45·4 to 55·6)	0·92 (0·82 to 1·02)	–4·9 (–9·3 to 0·2)	..
Peptic ulcer disease	363	27 896·9	12·2 (10·7 to 13·9)	59	4972·1	12·3 (9·6 to 16·2)	1·01 (0·72 to 1·31)	0·1 (–1·8 to 2·0)	..
Diarrhoea	1209	40 219·1	33·8 (31·4 to 36·5)	288	7617·1	38·0 (33·7 to 42·9)	1·12 (0·98 to 1·28)	4·2 (1·0 to 7·4)	238 (113 to 2258)¶

*$P_{interaction}$=0·93. †$P_{interaction}$=0·57. ‡$P_{interaction}$=0·86. §$P_{interaction}$=0·24. ¶Results in the column are all number needed to treat except for this cell, which is the number needed to harm.

Table 2: **Results of intention-to-treat analysis comparing colchicine prophylaxis versus no prophylaxis**

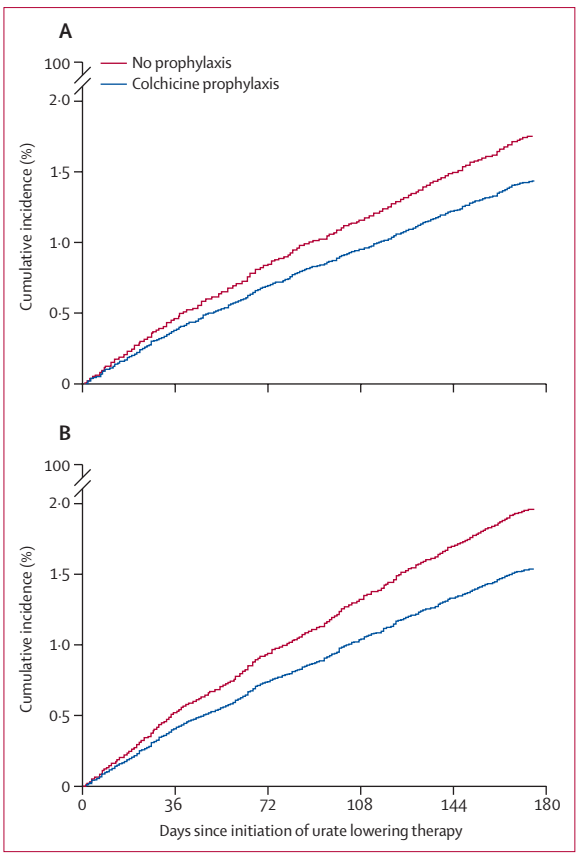

Figure 2: **Cumulative incidence of the primary outcome**
The cumulative incidence of the primary outcome in the (A) intention-to-treat and (B) per-protocol analysis.

the colchicine prophylaxis group and 37·7 per 1000 person-years (35·8 to 39·6) in the no prophylaxis group. The weighted IR was 28·8 (25·2 to 33·2) and 35·3 (33·0 to 37·9) events per 1000 person-years, respectively (table 2). The crude HR and RD were 0·72 (0·63 to 0·84) and –9·5 events per 1000 person-years (–13·6 to –5·4) whereas the adjusted HR and RD were 0·82 (0·69 to 0·94) and –6·5 events per 1000 person-years (–9·4 to –3·6; table 2) in the intention-to-treat analysis. The crude needed to treat was 105 whereas the weighted needed to treat was 154.

In the per-protocol analysis, the primary outcome occurred in 69 (0·4%) of 16 028 patients in the colchicine prophylaxis group and 1416 (1·7%) of 83 772 patients in the no prophylaxis group (table 3). The weighted cumulative incidence rate was 0·5% (95% CI 0·4 to 0·6) in the colchicine prophylaxis group and 1·7% (1·6 to 1·8) in the no prophylaxis group (figure 2). The crude IR was 35·6 events per 1000 person-year (28·3 to 45·5) in the colchicine prophylaxis group and 43·5 events per 1000 person-year (41·1 to 46·2) in the no prophylaxis group, whereas the adjusted IR was 35·8 events per 1000 person-year (29·1 to 42·4) in the colchicine prophylaxis group and 39·7 events per 1000 person-years (36·9 to 42·9) in the no prophylaxis group (table 3). The crude HR and RD were 0·66 (95% CI 0·51 to 0·85) and –7·9 events per 1000 person-years (–15·3 to –2·9), while the adjusted HR and RD were 0·79 (0·58 to 0·99) and –3·9 events per 1000 person-years (–7·1 to –0·7; table 3).

There was a statistically significant decrease in risk of first-ever cardiovascular event in people with gout starting urate-lowering therapy with colchicine prophylaxis compared with those starting urate-lowering therapy without any flare prophylaxis in the intention-to-treat analysis (adjusted HR for first-ever cardiovascular event 0·80 [95% CI 0·62 to 0·97]; RD –3·9 [95% CI –6·0 to –1·8] events per 1000 person-years; number needed to treat 256 [95% CI 144 to 1177]; table 2). There was no statistically significant effect on the first-ever cardiovascular event in the per-protocol analysis (table 3). There was no association between colchicine prophylaxis and fatal cardiovascular event, myocardial infarction, and stroke (tables 2, 3).

We did not observe any statistically significant association between the treatment strategy and negative control outcomes. Patients starting colchicine prophylaxis had a statistically significant higher risk of diarrhoea in the per-protocol analysis (adjusted HR 1·32 [95% CI 1·04–1·60]; RD 28·7 [24·5–32·9] events per 1000 patient-years; table 3) but not in the intention-to-treat analysis (1·12 [0·98–1·28]; 4·2 [1·0–7·4] events per 1000 patient-years; table 2). The E-value was 1·74 (95% CI lower bound 1·32) for the intention-to-treat and 1·85 (1·11) for the per-protocol analyses (appendix p 20).

There was no evidence of effect modification across stratified analyses on the primary outcome (ie, age, sex, year of urate-lowering therapy prescription, and cardiovascular risk categories; tables 2, 3). The treatment effect was consistent with the main analysis when the follow-up time was restricted to up to 90 days in both the intention-to-treat and per-protocol analyses (appendix pp 16–17). The results were also consistent when we replaced the propensity score overlap weighting with a multivariable adjustment Cox-regression model (appendix pp 18–19).

Discussion

In patients with gout starting urate-lowering therapy, gout flare prophylaxis (mean duration of prophylaxis about 50 days) with colchicine was associated with a lower risk of a composite outcome of fatal and non-fatal myocardial infarction or stroke than no flare prophylaxis. Absolute risk reduction in the prophylaxis with colchicine group ranged between –6·5 cardiovascular events per 1000 person-years intention-to-treat analysis to –3·9 cardiovascular events per 1000 person-years in the per-protocol analysis. This observed risk reduction was statistically significant and in line with the results of randomised controlled trials that were mostly conducted in people without gout.[12–14] The effects of colchicine flare prophylaxis appeared to be consistent irrespective of the

	No prophylaxis group (N=83 772)			Colchicine prophylaxis group (N=16 028)			Weighted hazard ratio (95% CI)	Weighted risk difference, events per 1000 person-years (95% CI)
	Number of events	Follow-up time (person-years)	Weighted incidence rate, events per 1000 person-years (95% CI)	Number of events	Follow-up time (person-years)	Weighted incidence rate, events per 1000 person-years (95% CI)		
Main outcome								
Cardiovascular events	1416	36 948·3	39·7 (36·9 to 42·9)	69	2004·7	35·8 (29·1 to 42·4)	0·79 (0·58 to 0·99)	−3·9 (−7·1 to −0·7)
Stratified analyses								
Males*	939	27 272·1	37·4 (34·2 to 41·1)	47	1534·2	33·9 (25·5 to 46·2)	0·76 (0·52 to 1·00)	−3·5 (−6·6 to −0·4)
Females*	477	9676·3	47·0 (41·0 to 54·0)	22	470·5	46·0 (30·3 to 73·4)	0·88 (0·46 to 1·29)	−1·0 (−4·5 to 2·5)
>65 years old†	1146	19 057·7	59·5 (54·8 to 64·9)	56	1087	55·3 (42·5 to 73·3)	0·81 (0·59 to 1·06)	−4·2 (−8·1 to −0·3)
≤65 years old†	270	17 890·6	14·7 (12·4 to 17·7)	13	917·7	15·4 (9·0 to 28·7)	0·82 (0·31 to 1·36)	0·7 (−1·4 to 2·8)
European Society of Cardiology high or very high cardiovascular risk‡	1148	14 628·6	77·0 (70·7 to 83·9)	60	841·8	76·4 (59·2 to 100·3)	0·79 (0·57 to 1·00)	−0·6 (−5·1 to 3·9)
European Society of Cardiology low or moderate cardiovascular risk‡	268	22 319·7	13·4 (11·3 to 16·0)	9	1162·9	8·7 (4·6 to 16·7)	0·82 (0·21 to 1·44)	−4·7 (−6·3 to −3·1)
First urate-lowering therapy prescription 1997–2007§	389	9813·5	57·7 (47·4 to 70·9)	12	234·4	57·1 (32·5 to 110·3)	0·87 (0·30 to 1·43)	−0·6 (−4·5 to 3·3)
First urate-lowering therapy prescription 2008–2021§	1027	27 134·8	36·4 (33·7 to 39·5)	57	1770·3	34·2 (26·4 to 45·2)	0·79 (0·57 to 1·02)	−2·2 (−5·3 to 0·9)
Secondary outcomes								
First-ever cardiovascular event	690	35 595·4	20·7 (18·6 to 23·1)	29	1935·4	15·5 (10·8 to 21·1)	0·84 (0·50 to 1·17)	−5·2 (−7·3 to −3·1)
Fatal cardiovascular events	167	36 948·3	4·3 (3·4 to 5·4)	9	2004·7	4·6 (2·4 to 10·2)	1·11 (0·34 to 1·88)	0·3 (−0·8 to 1·4)
Myocardial infarction	746	36 948·3	21·1 (19·0 to 23·4)	39	2004·7	20·2 (14·8 to 28·4)	0·83 (0·54 to 1·12)	−0·9 (−3·3 to 1·5)
Stroke	902	36 863·3	25·6 (23·3 to 28·3)	50	2001·0	24·8 (21·1 to 37·4)	0·90 (0·62 to 1·18)	−0·8 (−2·6 to 3·0)
Control outcomes								
Respiratory tract infections	1936	36 500·7	59·6 (56·3 to 65·3)	97	1996·7	52·3 (31·4 to 65·3)	0·88 (0·70 to 1·06)	−7·6 (−15·4 to 0·4)
Peptic ulcer disease	334	25 449·2	12·8 (11·2 to 14·7)	18	1281·2	14·1 (8·9 to 23·7)	1·13 (0·53 to 1·74)	1·3 (−0·7 to 3·3)
Diarrhoea	1098	36 642·7	43·4 (39·7 to 47·5)	132	1992·7	72·1 (60·7 to 86·5)	1·32 (1·04 to 1·60)	28·7 (24·5 to 32·9)

*$P_{interaction}$=0·78. †$P_{interaction}$= 0·62. ‡$P_{interaction}$=0·25. §$P_{interaction}$=0·90.

Table 3: **Results of per-protocol analysis comparing colchicine prophylaxis versus no prophylaxis**

history of previous cardiovascular disease, across different analytical approaches, for secondary outcomes, and in stratified analyses. The effect was smaller when people with a previous cardiovascular event before cohort entry were excluded.

Even among those engaged with pharmacotherapy, there was evidence of suboptimal care of gout. Only 16 028 (16·1%) of 99 800 patients with gout initiating urate-lowering therapy were co-prescribed gout flare prophylaxis with colchicine in this nationwide study. Similar findings have been reported elsewhere.[8,9]

This study has several strengths. First, we only considered colchicine prescriptions of 21 days or more issued on the same date as urate-lowering therapy initiation to assign the exposure status. This approach excluded short-term colchicine prescriptions that could be used to treat current or future gout flares to be sufficient to assign patients to the flare prophylaxis group and introduce misclassification bias. Second, we minimised the risk of confounding by using propensity score overlap weighting. Third, the lack of association with negative control outcomes and the statistically significant association with the positive control outcome in the per-protocol analysis supports the internal validity of our findings. Fourth, we used different analytical approaches and sensitivity analyses, and our results were consistent across them. Fifth, we used routinely collected primary-care, secondary-care, and mortality data extracted from a nationwide database (ie, the UK National Health Service)with universal coverage for the general population that is free at the point of use. This makes our results generalisable. Sixth, the use of primary-care, hospitalisation, and mortality data makes it unlikely that any outcomes would have been missed. The hospitalisation and mortality data are collected directly from hospital discharge summaries and death registration records. Nevertheless, there is a possibility that patients prescribed colchicine gout flare prophylaxis had a better overall quality of care and would have a more accurate primary care recording of cardiovascular events than those who were not prescribed any flare prophylaxis. Such an effect would only minimise a negative association

between colchicine prescription and cardiovascular events.

However, there are several limitations to this study. First, data were retrospectively extracted from a prospective database in which patient information, treatment, and events are prospectively recorded during routine clinical care, and as such are subject to variations in follow-up and data completeness that reflects routine clinical care. Second, this study spanned 25 years and data from earlier years might be less applicable to current practice. However, analyses stratified on the year of urate-lowering therapy initiation yield similar findings. Third, patients with cardiovascular events before cohort entry were included in the study and could have introduced surveillance bias. However, we specifically investigated the first-ever cardiovascular event as a secondary outcome and the findings were unchanged. Fourth, as in any observational study, there is the risk of residual confounding. To minimise such risk, we included many measures of gout severity and cardiovascular risk in the propensity score. Besides, the non-significance of negative control outcomes supports the validity of our findings. Furthermore, our E-values indicated that an unmeasured covariate would need to be associated with both cardiovascular events and flare prophylaxis with colchicine by an HR of 1·74 and 1·85 to nullify our findings in the intention-to-treat and per-protocol analyses, respectively. Colchicine prophylaxis is unlikely to have been prescribed for secondary cardiovascular prevention as it was recommended for the secondary prevention of cardiovascular events by the US Food and Drug Administration only in June 2023, after our study end-date.[26] Colchicine has never been licenced for preventing cardiovascular events in the UK. Fifth, although we have adjusted the analyses for cardiovascular risk factors, cardiovascular comorbidities, and their treatments, we did not adjust the analysis for the level of control of those risk factors. This could be undertaken in future studies that attempt to replicate our findings. Sixth, we did not include a group for whom NSAIDs were used for gout flare prophylaxis. This was because NSAIDs have a well known association with an increased risk of cardiovascular events.[27] However, whether flare prophylaxis using NSAIDs in people with gout initiating urate-lowering therapy is associated with an increased risk of cardiovascular events as expected from findings of population-based studies, or a reduced risk via prevention of gout flares should be evaluated in the future. Seventh, we cannot discount the possibility that a proportion of patients with gout might be misclassified. Eighth, we were unable to verify the adherence to urate-lowering therapy and colchicine flare prophylaxis as only information about prescriptions was available in the Clinical Practice Research Datalink Aurum. Ninth, we used a composite outcome as the primary outcome, which can be considered as a limitation. However, this composite outcome is widely accepted in cardiovascular research as a primary outcome and as such has external validity. Tenth, stroke included both ischaemic and haemorrhagic cerebrovascular accidents because it is not possible to separate them reliably in electronic health records such as the Clinical Practice Research Datalink Aurum. These two groups of conditions have different pathogenesis, and this was an additional limitation to the study. However, this is unlikely to result in a differential bias.

Gout flares have been associated with cardiovascular events.[10,11] Existing evidence suggests that inflammation plays a causal role in the pathogenesis of cardiovascular diseases and that interventions to mitigate inflammation could reduce the risk of cardiovascular events.[12,13] Colchicine might reduce cardiovascular risk in patients with gout initiating urate-lowering therapy by both limiting vascular inflammation and preventing flares. The latter effect was shown in an earlier seminal clinical trial.[28] The efficacy of canakinumab in reducing both cardiovascular events and gout flares provides further proof-of-concept that controlling inflammation prevents cardiovascular events.[29,30] Thus, prescribing gout flare prophylaxis with colchicine might lead to better overall outcomes for patients with gout by both preventing gout flares and cardiovascular events. The validity of the latter finding is supported by our findings of no association with negative control outcomes and an association with positive control outcome in the per-protocol analysis.

Colchicine use in gout flare prophylaxis differs from its use in secondary cardiovascular prevention in terms of duration and dosage. In this study, the mean duration of prophylaxis was about 50 days compared with a median follow-up of 28·6 and 36 months in the LoDoCo2 and LoDoCo randomised controlled trials.[12,14] Furthermore, these trials included no or very few people with gout. Therefore, the findings of our study build upon those of previous trials.[12,14] The current knowledge on the cardiovascular effect of colchicine in people with gout starting urate-lowering therapy relies on one observational study at risk of bias due to the use of per-protocol analysis alone with different follow-up periods in the exposed and unexposed categories (3·1 *vs* 5·8 months).[16] Additionally, the inclusion of people prescribed colchicine for a few days in the exposed group could introduce channelling bias as such prescriptions issued for treating ongoing gout flares that are themselves associated with a short-term increase in the risk of cardiovascular events.[10,11] Short-term colchicine prescriptions are also commonly issued as a rescue pack to be used in case of future flares and their use to classify patients would potentially introduce misclassification bias.

In patients with gout initiating urate-lowering therapy, gout flare prophylaxis with colchicine was associated with a lower rate of cardiovascular events for up to the next 180 days compared with no prophylaxis. These findings provide an additional argument for using gout flare prophylaxis when starting urate-lowering therapy. In

countries in which colchicine is licenced for cardiovascular disease prevention, the findings of our study and previously published studies[12,13] support consideration for the use of colchicine in people with gout and cardiovascular diseases. These findings could be confirmed in an adequately powered randomised controlled trial. However, such a trial would be practically prohibitive because withholding colchicine flare prophylaxis from people starting urate-lowering therapy as is recommended in rheumatology clinical practice guidelines is unethical, even though there is limited supporting evidence.[4,28]

Contributors

AA conceived the idea for the study and contributed to the study design, supervised data analysis and interpreted the results, co-wrote the first draft of the manuscript, critically reviewed the manuscript, and approved the submitted manuscript. AJA, CY, and NM contributed to the study design, interpreted the results, critically reviewed the manuscript, and approved the submitted manuscript. EC conceived the idea for the study and contributed to the study design, performed data management and analysis, co-wrote the first draft of the manuscript, critically reviewed the manuscript, and approved the submitted manuscript. GN and LJT contributed to the study design, supervised data analysis and interpreted the results, critically reviewed the manuscript, and approved the submitted manuscript. HKC and MAM conceived the idea for the study and contributed to the study design, interpreted the results, critically reviewed the manuscript, and approved the submitted manuscript. EC, GN, and AA had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All UK based authors had access to the full data. Authors based in the USA did not have full access due to Clinical Practice Research Datalink policy restrictions.

Declaration of interests

AA reports consulting fees from Limbic, royalties from UpToDate and Springer, lecturing fees from Cadilla Pharmaceuticals and Swedish Orphan Biovitrum, outside the submitted work. EC reports institutional grants from FOREUM, consulting fees from Horizon Therapeutics, lecturing fees from Novartis and Institut Biochimique SA and travel grants from the European Alliance of Associations for Rheumatology, outside the submitted work. All other authors declare no competing interests.

Data sharing

This study used data from the Clinical Practice Research Datalink Aurum. These data were provided under licence that does not permit data sharing with third parties. They can be obtained from Clinical Practice Research Datalink Aurum . STATA codes are available upon reasonable request from the corresponding author.

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