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Risk of Venous Thromboembolism With Gout Flares

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Objective. Previous studies demonstrated that the risk of venous thromboembolism (VTE) is increased in patients with gout, but not whether there was a temporal association between gout flare and VTE. This study was undertaken to evaluate potential temporal associations between gout flare and VTE.

Methods. Data were obtained from electronic primary-care records from the UK's Clinical Practice Research Datalink, which links data from hospitalization and mortality registers. Using self-controlled case series analysis adjusted for season and age, we evaluated the temporal association between gout flare and VTE. The 90 days after primary-care consultation or hospitalization for gout flare was designated the exposed period. This was divided into three 30-day intervals. The baseline period was up to 2 years before the start of and up to 2 years after the end of the exposed period. The association between gout flare and VTE was measured using adjusted incidence rate ratios (IRRs) with 95% confidence intervals (95% CIs).

Results. In total, 314 patients met the inclusion criteria (age ≥18 years, incident gout, no presence of VTE or use of a primary-care anticoagulant prescription before the start of the pre-exposure period). Among the 314 patients, VTE incidence was significantly higher in the exposed period than in the baseline period (adjusted IRR 1.83, 95% CI 1.30–2.59). The adjusted IRR of VTE during the first 30 days after gout flare was 2.31 (95% CI 1.39–3.82) relative to the baseline period. No increase in the adjusted IRRs was observed in days 31–60 (adjusted IRR 1.49, 95% CI 0.79–2.81) and days 61–90 (adjusted IRR 1.67, 95% CI 0.91–3.06) relative to baseline. Results were consistent across sensitivity analyses.

Conclusion. Among patients with gout, there was a transient increase in the rate of VTE within 30 days after primary-care consultation or hospitalization for gout flare.

INTRODUCTION

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), affects ~10 million people worldwide annually (1). In the US alone, 900,000 people are affected by VTE and up to 100,000 people die as a result of VTE each year (2). Gout is a common inflammatory rheumatic disease with a prevalence of 4% in the US (3,4). Large cohort studies have demonstrated a higher incidence of VTE in people with gout compared with the general population (5–8). However, to the best of our knowledge, whether gout flares are temporally associated with VTE has not been evaluated.

Flares are the most common and dominant manifestation of gout (9,10). Flares are characterized by intense articular, periarticular, and systemic inflammation, and frequently lead to reduced mobility because they commonly occur in the lower limb joints (10). These changes could transiently increase the risk of VTE by promoting vascular stasis and up-regulating blood coagulation, platelet aggregation, and endothelial dysfunction (11).

The main objective of this study was to examine the temporal association between recent prior gout flare and the incidence of VTE in the 90 days following the prior flare. Additional objectives were to estimate the incidence of VTE in people with incident gout, and the incidence of VTE in the 90 days following an incident gout flare.

This study used data from the Clinical Practice Research Datalink. These data were provided under a licence that does not permit data sharing with third parties. Access to data from the Clinical Practice Research Datalink and the linked data from Hospital Episode Statistics and the UK Office for National Statistics was funded by The University of Nottingham.

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PATIENTS AND METHODS

Study design. We used a self-controlled case series (SCCS) study design, which is suited for evaluating the association between a transient exposure (i.e., gout flare) and an outcome (i.e., VTE) (12). An SCCS design uses information from individuals who have experienced both the exposure and the outcome; separate controls are not required, as the outcome event rate is compared between the individual's exposed and unexposed periods using a Poisson model (12). This method avoids between-person confounding due to factors such as comorbidities, socioeconomic status, genetics, and lifestyle factors (12).

A cohort study design was used to evaluate the incidence of VTE in those with incident gout, and in the 90 days after a consultation/hospitalization for a gout flare.

Data source and study population. We extracted data from the Clinical Practice Research Datalink (CPRD) GOLD data set, which is linked to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality registries in England. CPRD contains anonymized data on sociodemographics, lifestyle factors, diagnoses, consultations, and prescriptions recorded from >18 million individuals, originating during routine care with their general practitioner, and it is representative of the UK population (13). HES contains data on diagnoses from hospitalization episodes, and the ONS mortality database holds information on the date and causes of death (13).

The study population consisted of patients ages ≥18 years for whom research-quality data were available in the CPRD GOLD data set. Incident gout was defined as a diagnosis of gout at least 1 year after the patient's registration at the current general practice, to minimize the risk of prevalent cases appearing as incident (14).

The study period spanned between January 1, 1997 and December 31, 2020. Previously published Read Code lists were updated to develop the lists used in this study (see Supplementary Material S1, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42480).

Exposure. Gout flare was the exposure of interest. A gout flare was defined as presence of any of the following criteria: 1) specific Read Code for gout flares; 2) prescriptions for antiinflammatory drugs (i.e., nonsteroidal antiinflammatory drugs [NSAIDs], glucocorticoids, or colchicine) on the same date as a primary-care consultation for gout; and 3) hospitalizations with a primary hospitalization diagnosis of gout.

Previous validation studies demonstrated that this strategy would yield the highest positive predictive value (PPV) for gout flare ascertainment (14–16). Zheng et al studied data from 3.6 million people (gathered from 14 hospitals and 202 family doctors) and found that the PPV for claims-based gout flare (defined using consultation and type of prescription/procedure) was 95% when ascertaining people with ≥1 gout flare over a 15-month period (17). They used the date of medical claim for gout or joint pain consultation as the gout flare date. They allowed a 7-day window between diagnosis of the gout flare and either receipt of qualifying prescriptions or the initiation of procedures. We modified this definition to require that the consultation and fulfillment of the prescription occur on the same date, to minimize the chances of misclassifications, as steroids and NSAIDs may be prescribed for other reasons such as asthma and pain due to osteoarthritis, respectively. In a tertiary center study, restricting the window from 7 days to 1 day improved the PPV for ascertainment of a similarly defined gout flare (18). Furthermore, an algorithm for defining gout flare that was less parsimonious than the one used in the present study, which included the prescription of colchicine alone and allowed for a 7-day window for drug prescriptions and consultations for gout to occur, was validated against a manual review of 100 random UK primary-care charts (16).

As gout flares typically last for 1–2 weeks, gout-related consultations, hospitalizations, or prescriptions within 14 days of the first consultation/hospitalization were considered part of the same flare (19). The date of gout flare was the earliest occurrence of the above in the 14-day window.

Outcome. VTEs were ascertained using a previously validated definition combining primary-care diagnoses, primary-care prescriptions, hospital discharge diagnoses, and cause of death data (20). Patients were considered to have a VTE according to any of the following definitions: given a primary-care diagnosis of either DVT or PE, and having received at least one prescription of anticoagulant therapy (e.g., heparin, warfarin sodium, etc.) in primary care or having been evaluated in an anticoagulation clinic or having underwent specific laboratory tests (i.e., international normalized ratio [INR] blood test) within 90 days after the primary-care diagnosis of DVT or PE; hospitalized with a primary diagnosis of either DVT or PE, and having received at least one prescription of anticoagulant therapy (e.g., heparin, warfarin sodium, etc.) in primary care or having been evaluated in an anticoagulation clinic or having underwent specific laboratory tests (i.e., INR blood test) within 90 days after the hospitalization date; had a fatal episode of VTE (DVT or PE as the first cause of death) or died from any cause within 30 days of either primary-care diagnosis or hospitalization with a primary diagnosis of DVT or PE.

This algorithm has a PPV of 94% for ascertainment of VTEs based on CPRD data (20). The date of VTE was defined using the earliest date of primary-care diagnosis, hospitalization, or death due to VTE. Patients with VTE (i.e., a prior diagnosis or anticoagulant prescription) prior to the start of the SCCS observation period were excluded as it is not possible to ascertain recurrent VTEs in electronic health records and there are no validated definitions for these events. This may be due to varying lengths of the oral anticoagulation treatment for VTE, varying duration of individual primary-care prescriptions that make it difficult to ascertain

gaps in treatment, and the use of oral anticoagulation for other indications such as atrial fibrillation. For the same reasons, we considered only the first VTE in the SCCS observation period for each patient in the analyses.

SCCS analysis observation periods. Each case's observation time was divided into exposed, baseline, and induction periods. The exposed period was defined as extending up to 90 days immediately after the gout flare and was categorized as days 1–30, 31–60, and 61–90 immediately after the gout flare. It ended at the earliest of 90 days after the gout flare date or the next gout flare date.

The induction period consisted of the 15 days immediately before the gout flare.

The baseline period consisted of a pre-exposure period of up to 715 days before the start of the induction period and a post-exposure period of up to 730 days after the end of the exposed period. The pre-exposure baseline period started at the latest of study start date, current registration date, general practice's up-to-standard data quality date, gout diagnosis date, or 730 days before the first gout flare. It ended on the day before the induction period. The post-exposure baseline period started immediately after the end of the exposed period. It ended at the earliest date of study end, transfer-out, date of data collection from the general practice, death, or 730 days after the gout flare date or the next gout flare date (Figure 1).

Statistical analysis. *SCCS.* The SCCS study method involved fitting a Poisson model conditioned on the number of VTEs. Incidence rate ratios (IRRs) with 95% confidence intervals (95% CIs) were calculated for each stratum of the exposed period compared with the baseline period (12). We adjusted for season and age (2-year age bands) to account for the seasonal trend of gout flares and VTE (21,22), and increasing incidence of gout flares and VTE with age (23,24). Supplementary Material S2 shows the sample size estimation (available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42480).

Sensitivity analyses of the SCCS. We carried out the following sensitivity analyses to test the strength of the temporal association between VTE and gout flare: 1) We excluded participants with risk factors for VTE (chosen a priori based on previously published data [23]) ascertained at the start of the exposed period.

2) We excluded those with ≥1 of the following high-risk factors for VTE: fracture of the lower limb (i.e., pelvis, femur, tibia, and fibula) within the previous 3 months, hospitalization for heart failure or atrial fibrillation/flutter within the previous 3 months, knee or hip joint replacement within the previous 3 months, major trauma within the previous 3 months, myocardial infarction within the previous 3 months, or spinal cord injury.

3) We excluded those with ≥1 of the following moderate-risk factors for VTE: arthroscopic knee surgery within the previous 3 months, autoimmune diseases (such as inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematosus), congestive heart failure, respiratory failure, hormonal therapy (oral or transdermal contraceptive use, hormone replacement therapy, testosterone, and tamoxifen), infection requiring hospitalization (specifically pneumonia, urinary tract infection, and HIV) within the previous 3 months, cancer, stroke, and thrombophilia (inherited thrombophilia [including protein C and protein S deficiency, Leiden V factor, antithrombin III deficiency] and acquired thrombophilia [including antiphospholipid syndrome and nephrotic syndrome]).

4) We excluded participants with ≥1 high-risk or moderate-risk factor for VTE. All 4 of these analyses were repeated after excluding those with risk factors for VTE ascertained at the VTE date.

5) We excluded patients with VTE within 7 days after the gout flare consultation, as this could reflect potential misdiagnosis of VTE as gout flare.

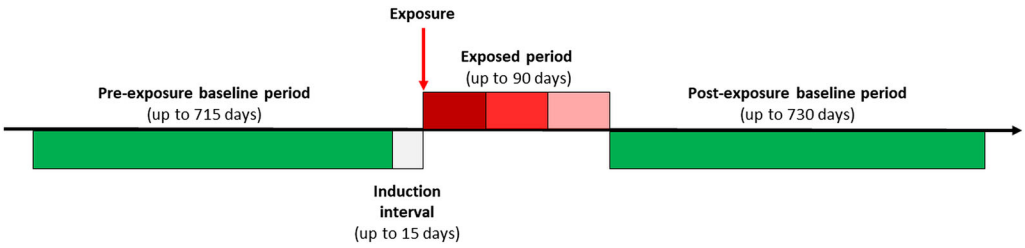

Figure 1. Schematic description of self-controlled case series. The exposed period (in shades of red) was defined as the period following the exposure (the gout flare). It lasted up to 90 days, and it ended at the earliest of 90 days after the gout flare date or the next gout flare date. The baseline period (in green) consisted of a pre-exposure and a post-exposure period. The pre-exposure period lasted up to 715 days, while the post-exposure period lasted up to 730 days. The pre-exposure baseline period started at the latest of study start date, current registration date, up-to-standard date, gout diagnosis date, or 715 days before the induction period. It ended on the day before the induction period. The post-exposure baseline period started immediately after the end of the exposed period. It ended at the earliest date of study end, transfer-out, date of data collection from the general practice, death, or 730 days after the gout flare date or the next gout flare date. A 15-day induction period prior to gout flare is shaded in gray. Data are from patients with a single gout flare recorded in the Clinical Practice Research Datalink GOLD. In such a case, the length of the "exposed" period was 90 days, while the length of the pre-exposure (+ induction) and post-exposure period was up to 730 days at most.

6) We conducted analyses in which we considered the exposed period according to periods of shorter intervals (days 0–15, days 16–30, days 31–60, and days 61–90).

7) We excluded patients with fatal VTE, to show that violations of SCCS by death did not influence the association between VTE and gout flares.

8) We evaluated if the association between gout flares and VTE was influenced by whether the gout flare required hospitalization or was preceded by a new urate-lowering therapy (ULT) prescription, defined as a ULT prescription within 6 months before the gout flare date and without any ULT prescriptions in the 12 months preceding the prescription.

9) We increased the induction period to 90 days.

10) To reduce the potential effects of time-varying confounders, we reduced the length of the pre-exposure and post-exposure baseline periods to up to 365 days each.

11) We considered only the post-flare period as the baseline period. As patients get older and accrue comorbidities, considering the post-flare baseline period only allowed us to estimate the association in a "worse-case scenario."

12) Stratified analyses were conducted to consider patients grouped on the basis of the following: a) the number of NSAID prescriptions over the SCCS observation period (below the median to median and above the median number of prescriptions) to account for the potential confounding effect of the use of these medications in the association between gout flares and VTE; b) the number of anticoagulant prescriptions between the start of the SCCS observation period and the date of the VTE (no prescription versus one or more prescriptions) to account for the potential confounding effect of the use of these medications in the association between gout flares and VTE; c) antiinflammatory drug prescribed to treat the gout flares, since previous data have shown an association between certain drugs (i.e., glucocorticoids and NSAIDs) and VTE (25,26). Gout flares for which patients required hospitalization were excluded as details of drugs used to treat gout flares in hospitals are not available in the CPRD; d) Charlson comorbidity index (calculated on the gout flare date), in which patients were divided according to those with a low score (≤1) and those with a moderate/high score (>1).

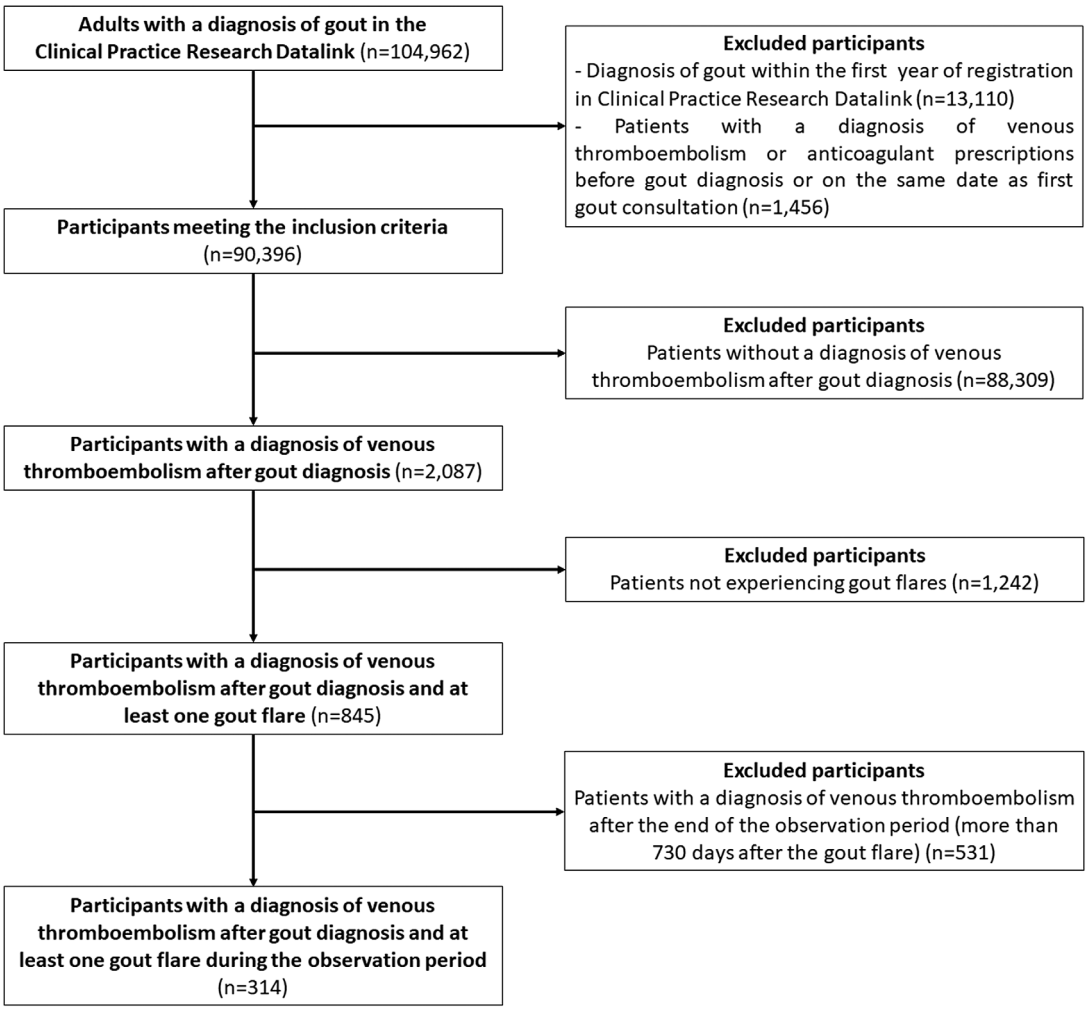

Figure 2. Flow chart of patient selection.

Table 1. Demographic and clinical characteristics of the study population (n = 314)*

Age, mean ± SD years	72.8 ± 12.3
Sex, female, no. (%)	107 (34.1)
Gout duration, mean ± SD years	2.0 ± 3.3
BMI, mean ± SD kg/m^2†	29.5 ± 5.4
English Index of Multiple Deprivation 2015, mean ± SD†	3.2 ± 1.4
Smoking habit, no. (%)	
Current smokers	33 (10.5)
Previous smokers	137 (43.6)
Non-smokers	137 (43.6)
Missing data	8 (2.5)
Alcohol intake, no. (%)	
Current drinkers	233 (74.2)
Previous drinkers	16 (5.1)
Non-drinkers	50 (15.9)
Missing data	16 (5.1)
Number of primary-care consultations in previous year, median (IQR)	21.0 (12.0–31.0)
Number of hospitalizations in previous year, median (IQR)	2.0 (1.0–3.0)
Any high-risk factors for VTE ascertained on first flare date, no. (%)	22 (7.0)
Fracture of lower limb (i.e., pelvis, femur, tibia, and fibula) within previous 3 months, no. (%)	1 (0.3)
Hospitalization for heart failure, atrial fibrillation/flutter, or myocardial infarction within previous 3 months, no. (%)	20 (6.4)
Hospitalization for major trauma within previous 3 months, no. (%)	0
Spinal cord injury, no. (%)	0
Knee or hip joint replacement within previous 3 months, no. (%)	1 (0.3)
Any moderate-risk factors for VTE ascertained on first flare date, no. (%)	86 (27.4)
Arthroscopic knee surgery within previous 3 months	12 (3.8)
Autoimmune diseases	2 (0.6)
Congestive heart failure	64 (20.4)
Respiratory failure	6 (1.9)
Hormonal therapy	0
Infections requiring hospitalization within previous 3 months	4 (1.3)
Cancer	39 (12.4)
Stroke	26 (8.3)
Pregnancy and/or puerperium	0
Thrombophilia	9 (2.9)
Any high- and/or moderate-risk factors for VTE, no. (%)	102 (32.5)
VTE diagnosis, no. (%)	
Deep vein thrombosis	182 (58.0)
Pulmonary embolism	132 (42.0)
Setting of VTE ascertainment, no. (%)	
Primary care diagnosis of VTE	176 (56.1)
Hospital admission for VTE	90 (28.7)
Fatal VTE	48 (15.3)
Charlson comorbidity index, median (IQR)	2.0 (1.0–4.0)
Latest serum urate level, mean ± SD μm/liter†	439.2 ± 126.2
Urate-lowering therapy, no. (%)‡	
Current user	161 (51.3)
Past user	10 (3.2)
Never user	143 (45.5)
Number of flares during study period, no. (%)	
One flare	295 (93.9)
Two flares	19 (6.1)
Number of NSAID prescriptions over SCCS observation period, median (IQR)	3 (1–9)
Number of anticoagulant prescriptions between start of SCCS observation period and date of the VTE, median (IQR)	0 (0–1)
Medications prescribed to treat gout flare, no. (%)	
Colchicine	146 (46.5)
Glucocorticoids	34 (10.8)
NSAIDs	93 (29.6)
Not reported	41 (13.1)
Setting of gout flare ascertainment, no. (%)	
Primary care (antiinflammatory medication prescription on the same date as a consultation for gout)	266 (84.7)
Primary care, specific Read Codes for acute gout arthritis	12 (3.8)
Hospital admission with gout as the primary discharge diagnosis	36 (11.5)

* For time-varying variables (age, body mass index [BMI], gout duration, Charlson comorbidity index), the most recent recorded data prior to first gout flare were used for the analyses. IQR = interquartile range; VTE = venous thromboembolism; NSAID = nonsteroidal antiinflammatory drug; SCCS = self-controlled case series.

† Data on BMI, English Index of Multiple Deprivation 2015, and serum urate levels were missing for 24 patients (7.6%), 5 patients (1.6%), and 74 patients (23.6%), respectively.

‡ Current user was defined as patients for whom the supply of the most recent prescription lasted until the start of the flare date or ended in the 60 days before this date. Past user was defined as those patients who had at least one prescription, but the supply of the most recent prescription ended more than 60 days before the date of the flare.

Cohort study of VTE incidence. To provide estimates of the absolute rate of VTE following gout diagnosis and following gout flares, we conducted separate cohort studies using the original population with incident gout diagnosis (as defined earlier**)**. The incidence (95% CI) of VTE was calculated per 1,000 person-years.

To estimate the incidence of VTE following gout diagnosis, we followed up people ages ≥18 years with incident gout from the latest date of the incident diagnosis of gout, study start, current registration, or general practice's up-to-standard data quality date, to the earliest date of the first incident VTE, study end, transfer-out, last data collection from the general practice, or death.

To estimate the incidence of VTE in the 90 days after a gout flare, we followed up all patients with incident gout who had at least one gout flare (as defined earlier) from their gout flare date to the earliest date of first incident VTE, study end, transfer-out, last data collection from the general practice, death, next gout flare, or 90 days after the flare.

Ethics approval. This study was approved by CPRD Research Data Governance (protocol no. 20_000233). CPRD has overarching Research Ethics Committee approval for research studies using anonymous data (approval reference no. 05/MRE04/87). Practices that contributed data to the CPRD consented to use anonymized patient data for approved research projects, and additional consent was not required prior to individual studies.

This report was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (27).

RESULTS

SCCS analysis of VTEs following gout flare. Among 104,962 patients identified as having gout in the CPRD, 90,396 met the definition of a new incident diagnosis of gout in the study period (Figure 2). Of these, 2,087 patients were diagnosed as having VTE after their incident diagnosis of gout. Among the 2,087 gout patients experiencing VTE, 845 patients (36.5%) had a gout flare within the study period, and 314 patients were included in the SCCS analysis because they were first diagnosed as having VTE within the exposed period or within 2 years of its start or end, respectively (Figure 2 and Table 1). Forty-one patients (13.1%) were newly prescribed a ULT within 6 months before the gout flare date. None were prescribed glucocorticoids (oral, intraarticular, or intramuscular), NSAIDs, or colchicine in the 60 days before the gout flare date.

In total, 37 and 274 VTEs occurred during the exposed and baseline periods over a total follow-up time of 26,653 person-days and 85,562 person-days, respectively. Three VTEs occurred in the induction period. The incidence of VTE was higher in the 90-day exposed period than in the baseline period (adjusted IRR 1.83, 95% CI 1.30–2.59). The VTE incidence was significantly higher in the 30 days immediately following the gout flare (adjusted IRR 2.31, 95% CI 1.39–3.83) compared to the baseline period. There was no increase in the subsequent 31–60 days and 61–90 days (adjusted IRR 1.49, 95% CI 0.79–2.81 and adjusted IRR 1.67, 95% CI 0.91–3.06, respectively) (Figure 3).

The results of the sensitivity analyses were consistent with those of the main analysis (Figure 4 and Supplementary Material S3, available on the *Arthritis & Rheumatology* website at

Time period	Number of events [a]	Total follow-up time (person-days)	aIRR (95%CI) [b]
Induction period [c]	-/-	4,396	0.92 (0.30 to 2.88)
Flare date to day 30	16	9,376	2.31 (1.39 to 3.82)
Day 31-60	10	9,160	1.49 (0.79 to 2.81)
Day 61-90 days	11	9,057	1.67 (0.91 to 3.06)
Baseline period [d]	274	390,276	Reference

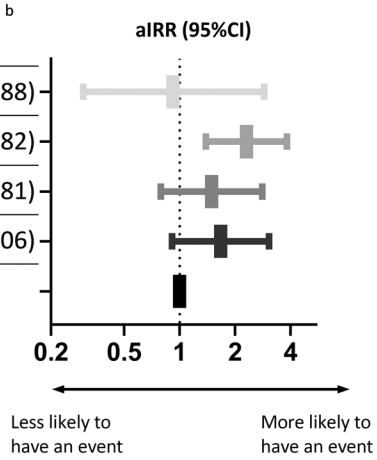

Figure 3. Results of the main analysis of the self-controlled case series data (n = 314 pateints with gout). **-/-** = not reported due to Clinical Practice Research Datalink policy of not disclosing data for ≤5 patients. [a] = Events of venous thromboembolism (VTE) were defined as either deep vein thrombosis or pulmonary embolism. [b] = The analyses of adjusted incidence rate ratios (aIRRs) with 95% confidence intervals (95% CIs) for VTEs were adjusted for age and calendar season. [c] = The induction interval consisted of the 15 days before the gout flare date. [d] = The baseline period consisted of a pre-exposure period of up to 715 days before the start of the induction period and post-exposure period of up to 730 days after the exposed period at most.

Time period	Number of events [a]	Total follow-up time (person-days)	aIRR (95%CI) [b]
Excluded participants with the VTE within one week from the gout flare [c] [N=311]			
Induction period [d]	-/-	4,354	0.92 (0.30 to 2.88)
Day 7 post flare to day 30	13	9,291	1.88 (1.07 to 3.28)
Day 31-60	10	9,115	1.49 (0.79 to 2.80)
Day 61-90 days	11	9,027	1.66 (0.91 to 3.04)
Baseline period [e]	274	287,445	Reference
Excluded participants with any moderate-or high-risk factor for VTE ascertained on the first flare date [c] [N=212]			
Induction period [d]	-/-	2,968	0.92 (0.23 to 3.72)
Flare date to day 30	13	6,323	2.83 (1.61 to 4.98)
Day 31-60	6	6,194	1.34 (0.59 to 3.03)
Day 61-90 days	9	6,117	1.84 (0.98 to 4.01)
Baseline period [e]	182	264,891	Reference
Excluded participants with any moderate-or high-risk factor for VTE ascertained on the VTE date [c] [N=158]			
Induction period [d]	-/-	2,212	1.24 (0.31 to 5.02)
Flare date to day 30	12	4,703	3.51 (1.93 to 6.37)
Day 31-60	4	4,599	1.20 (0.44 to 3.25)
Day 61-90 days	4	4,554	1.22 (0.45 to 3.31)
Baseline period [e]	136	200,282	Reference
Applied shorter exposure intervals [c] [N=314]			
Induction period [d]	-/-	4,396	0.92 (0.29 to 2.88)
Flare date to day 15	6	4,700	1.72 (0.77 to 3.88)
Day 16-30	10	4,676	2.89 (1.54 to 5.45)
Day 31-60	10	9,160	1.49 (0.79 to 2.81)
Day 61-90 days	11	9,057	1.67 (0.91 to 3.06)
Baseline period [e]	274	390,276	Reference
Considered only the post-flare period as the baseline period [c] [N=314]			
Induction period [d]	-/-	3,864	0.67 (0.21 to 2.10)
Flare date to day 30	16	8,261	1.70 (1.02 to 2.82)
Day 31-60	10	8,068	1.11 (0.59 to 2.10)
Day 61-90 days	11	7,977	1.24 (0.68 to 2.28)
Baseline period [e]	236	220,493	Reference
Excluded participants with fatal VTE [c] [N=266]			
Induction period [d]	-/-	3,724	1.13 (0.36 to 3.53)
Flare date to day 30	12	7,955	2.11 (1.18 to 3.78)
Day 31-60	8	7,861	1.43 (0.71 to 2.90)
Day 61-90 days	9	7,800	1.63 (0.84 to 3.18)
Baseline period [e]	234	341,112	Reference

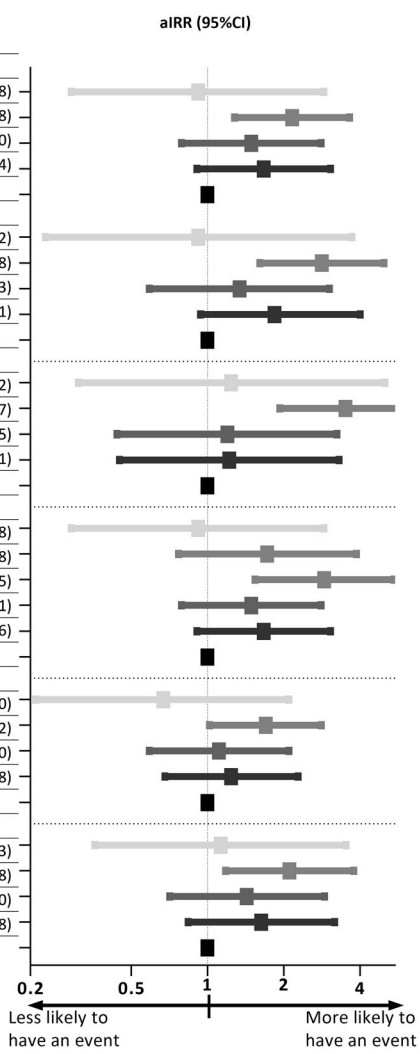

Figure 4. Results of the sensitivity analyses of the self-controlled case series data. **-/-** = not reported due to Clinical Practice Research Datalink policy of not disclosing data for ≤5 patients. [a] = Events of venous thromboembolism (VTE) were defined as either deep vein thrombosis or pulmonary embolism. [b] = The analyses of adjusted incidence rate ratios (aIRRs) with 95% confidence intervals (95% CIs) for VTEs were adjusted for age and calendar season. [c] = The number of individuals included in each analysis is reported in square brackets. [d] = The induction interval consisted of the 15 days before the gout flare date. [e] = The baseline period consisted of a pre-exposure period of up to 715 days before the start of induction period and post-exposure period of up to 730 days after the exposed period at most.

https://onlinelibrary.wiley.com/doi/10.1002/art.42480). In particular, the VTE incidence was highest at 16–30 days following the gout flare (adjusted IRR 2.89, 95% CI 1.54–5.45).

Cohort study of VTE incidence. Among the 90,396 patients with an incident gout diagnosis (mean age ± SD at diagnosis 62.9 ± 15.5 years, 26.3% female), 2,087 were subsequently diagnosed as having a first VTE during 571,782 person-years of follow-up, resulting in a VTE incidence of 3.65 (95% CI 3.50–3.81) per 1,000 person-years.

Of this cohort, 34,354 patients met the definition of primary-care consultation or hospitalization for gout flare on at least one occasion. Their mean ± SD age at gout flare was 65.4 ± 15.3 years, and 26.3% were female. In this cohort, 39 patients were diagnosed as having their first VTE within the 90 days following the flare during 8,295 person-years of follow-up, resulting in a VTE incidence of 4.70 (95% CI 3.43–6.43) per 1,000 person-years.

DISCUSSION

In this population-based study of patients with a new diagnosis of gout, our SCCS analysis revealed that the incidence of VTE was significantly higher in the 90 days immediately after a gout flare. On further analyses, we found that this increased risk was restricted to the 30 days immediately after a gout flare. The association between gout flare and VTE in the next 30 days was

statistically significant when the post-flare baseline period was the reference category despite there being a higher incidence of VTE in the post-exposure baseline period, the latter likely attributable to the association of increasing age and more burden of comorbidities with incidence of VTE. This association, despite a worse-case comparator (i.e., the post-flare baseline period), further supported the validity of our findings.

It should be noted that although we found a substantial increase in the relative risk of VTE in the 90 days immediately after a gout flare, the observed absolute increase in risk was 4.70/1,000 person-years in the 90 days after a gout flare, in comparison with 3.65/1,000 person-years in the entire period after gout diagnosis. Previous studies from Canada and the UK reported a similar overall incidence of VTE in people with gout, i.e., 2.63/1,000 person-years (5) and 3.73/1,000 person-years (6), respectively. The incidence of VTE in the 90 days immediately after a gout flare in the present cohort study was higher than those reported in general population–based studies among individuals of similar age profile in Western countries that included people with and without gout or other chronic conditions (28–31). For instance, the incidence of VTE was 3.03 per 1,000 person-years in people ages 60–79 years in Alberta, Canada, and 3.48 per 1,000 person-years in people ages 65–74 years in Minnesota (29–31). In the UK, the incidence of VTE was reported to be 1.77 and 3.28 per 1,000 person-years in the ages 60–69 years and ages 70–79 years groups (28).

Antiinflammatory medications (e.g., NSAIDs and glucocorticoids) have been associated with VTE (25,26), although their use is not an established risk factor for VTE (23). We carried out sensitivity analyses stratified according to the antiinflammatory drug prescription used to ascertain gout flare in our study. We observed a significant association between gout flares for which NSAIDs were prescribed and VTE in the subsequent 30 days. Contrary to this, gout flares for which glucocorticoids were prescribed were not associated with a transient increase in VTE incidence. There was an association between gout flares for which colchicine was prescribed and VTE in the next 30 days. However, this was not statistically significant, and the 95% CI just crossed the cutoff of 1.0. The lack of statistical significance could be related to small sample size. The results of these post hoc sensitivity analyses should be interpreted cautiously, as the sample size was small and these analyses were not adequately powered. On further stratified analyses, the association between recent prior gout flare and VTE was present in those with 1–3 NSAID prescriptions and those with >3 NSAID prescriptions in the up to 4-year SCCS observation period.

Anticoagulants prescribed before the VTE date for conditions different from VTE (e.g., surgical procedures and atrial fibrillation) may have influenced the association between gout flares and VTE. In our study population, most patients with gout did not receive any anticoagulant prescriptions before the date of the VTE (207 [65.9%] of 314). On stratified analyses, the temporal association between gout flare and VTE was present in those without anticoagulant prescriptions before the VTE date. Also, there was an association between gout flares and VTE in patients with one or more anticoagulant prescriptions before the VTE date. However, this was not statistically significant ($P = 0.08$). The lack of statistical significance could be related to either the small sample size or the fact that patients with frequent use of anticoagulants would have been less prone to have VTE.

Our findings, combined with previous evidence that gout flares are associated with a transient increase in cardiovascular events, support international guidelines (32,33) that advocate for long-term treat-to-target ULT (T2T-ULT) with flare prophylaxis in people with recurrent gout flares.

SCCS analysis requires several assumptions to be met. First, there should be no association between an outcome and subsequent exposure (12). To the best of our knowledge, VTE is not associated with gout flare. Nevertheless, we included an induction interval to detect and minimize bias related to reverse causality, confounding by healthcare-seeking behavior or other biases (34). Next, the occurrence of an outcome should not appreciably affect subsequent outcomes (12). As prior VTE is a risk factor for future VTEs, this assumption could be violated if we had included recurrent VTEs. We considered only the first VTE, a valid approach to overcome this problem (12). SCCS also requires that the outcome should not increase the probability of death. However, this method has been applied to outcomes that increase mortality (33). We conducted a sensitivity analysis excluding subjects with fatal VTE within the observation period to account for violation of this assumption, as recommended (12).

A strength of this study is that we used routinely collected data from the management of patients in the National Health System (NHS) to ascertain exposures and outcomes. NHS has universal coverage in the UK and is free at the point of use, minimizing any potential issues with the use of insurance claims databases. The data included in this study cover the whole of England, thus increasing generalizability. Using consultation, prescription, and hospitalization records from the entire nation reduces issues related to selection and recall bias. The use of SCCS design is another strength, as it is specifically designed to evaluate the association between transient exposures and outcomes of interest. Also, it controls for between-person confounding. Time-varying confounders such as season and age were adjusted for in the analyses, and extensive sensitivity analyses considered the effects of other confounders. Both the exposures and outcomes were defined using validated definitions. We used an incident gout cohort, minimizing any survival bias from a prevalent gout cohort. Finally, the results of the sensitivity analyses were consistent with those of the main analysis, thereby increasing confidence in the validity of our findings.

The study had several limitations. First, there was uncertainty regarding the date of onset of gout flares, as their onset likely preceded the date of consultation/prescription in general practice or the date of hospitalization. However, as most gout flares resolve

within 10–14 days, the effect of this misclassification is likely to be small. A 15-day pre-flare induction period removed this time from the rest of the baseline period.

Second, there was potential for confounding due to comorbidities accrued over time. However, the observation period (baseline + induction + exposed periods) was truncated to up to 2 years before the start of and up to 2 years after the end of the exposed period to reduce confounding. Also, sensitivity analyses that included only the post-flare baseline period and the one that truncated the baseline (+ induction) period to up to ±1 year yielded similar results. Furthermore, the association between gout flare and VTE was present in both those with a moderate/high score on the Charlson comorbidity index and those with a low score.

Third, we were unable to evaluate separately the contribution of the gout flare and the antiinflammatory medications prescribed to treat it to the increasing risk of VTE after the gout flare. Our stratified analysis suggested that both gout flares treated with NSAIDs and gout flares treated with colchicine were associated with VTE. However, these analyses should be interpreted with caution due to the low sample size.

A fourth limitation is that these results apply only to gout flares that are of sufficient severity to require medical attention and not to those with milder symptoms that are self-managed.

Fifth, we did not have data on joints affected by the gout flare and cannot comment on whether this observed association was for flares only affecting the lower limbs.

Sixth, DVT may be initially misdiagnosed as a gout flare. However, the association was observed in the sensitivity analysis that excluded patients diagnosed as having a VTE within 7 days after the gout flare – a period in which misdiagnosis would be rectified. Furthermore, the association was present in days 16–30 in the sensitivity analysis in which shorter exposure periods were applied. Thus, it is unlikely that the association was due to initial misdiagnosis of VTEs as gout flares.

Seventh, certain environmental and dietary factors, such as dehydration, dietary excess, and excessive consumption of alcoholic beverages that may trigger both gout flares and VTE, were not accounted for in the analyses, as these data are not routinely recorded in electronic medical records such as the CPRD. Infection requiring hospitalization is a risk factor for VTE (23) and these cases were excluded in a sensitivity analysis that yielded similar results.

Eighth, the relatively low sample size is a study limitation. However, this sample size was sufficient to detect an IRR of 1.85 with a power of 0.80 and an alpha error of 0.05.

In conclusion, in this study using SCCS analysis, we reported a significant transient association between gout flares and VTE in the subsequent 90 days, with most of the excess risk in the first 30 days immediately after a gout flare consultation/hospitalization. Patients with gout should be counseled about the increased risk of VTE and advised to remain well hydrated and active in the 30 days after the gout flare. As T2T-ULT treatment prevents gout flares in the long-term (35,36), our findings provide an additional reason to use T2T-ULT with flare prophylaxis in people with recurrent gout flares. The temporal association between gout flare and VTE suggests that further research is required to test whether pharmacologic thromboprophylaxis can prevent VTE in patients that have recently experienced a gout flare.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Cipolletta had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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