Venous thromboembolism in patients with gout and the impact of hospital admission, disease duration and urate-lowering therapy

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ABSTRACT

BACKGROUND: Systemic inflammatory diseases have been associated with increased risk of venous thromboembolism. We aimed to quantify the risk of venous thromboembolism in patients with gout, the most common inflammatory arthritis, and to assess how disease duration, hospital admission and urate-lowering therapy affect this risk.

METHODS: We used data from the population-representative, England-based Clinical Practice Research Data-link linked to Hospital Episode Statistics, to identify incident gout cases between 1998 and 2017. We matched cases individually to 1 control without gout on age, gender, general practice and follow-up time. We calculated absolute and relative risks of venous thromboembolism, stratified by age, gender and hospital admission. Among those with gout, we assessed the risk of venous thromboembolism by exposure to urate-lowering therapy.

RESULTS: We identified 62,234 patients with incident gout matched to 62,234 controls. Gout was associated with higher risk of venous thromboembolism compared with controls (absolute rate 37.3 [95% confidence interval (CI) 35.5–39.3] v. 27.0 [95% CI 25.5–28.9] per 10,000 person-years, adjusted hazard ratio [HR] 1.25, 95% CI 1.15–1.35). The excess risk in patients with gout, which was sustained up to a decade after diagnosis, was present during the time outside hospital stay (adjusted HR 1.30, 95% CI 1.18–1.42), but not during it (adjusted HR 1.01, 95% CI 0.83–1.24). The risk of venous thromboembolism was similar among patients prescribed versus not prescribed urate-lowering therapy (incidence rate ratio 1.04, 95% CI 0.89–1.23).

INTERPRETATION: Gout was associated with higher risk of venous thromboembolism, particularly when the patient was not in hospital and regardless of exposure to urate-lowering therapy. Although the observed excess risk may not be sufficient to warrant preventive intervention, clinical vigilance may be required when caring for these patients.

Venous thromboembolism is known to be a major preventable cause of morbidity and mortality worldwide. In order to reduce the morbidity and mortality associated with venous thromboembolism, it is important to reduce the occurrence of the condition. Previous studies have highlighted rheumatological diseases, including rheumatoid arthritis and systemic lupus erythematosus, to be important predictors of venous thromboembolism, the risk of which is increased up to five-fold in these diseases. Chronic inflammatory processes are considered to increase the risk of venous thromboembolism through various mechanisms (e.g., upregulation of procoagulants, suppression of fibrinolysis).

Gout is the most common inflammatory arthritis, affecting 2.4% of adults, and typically affects older populations with an already high baseline risk for venous thromboembolism. It has been suggested that serum urate (the biochemical prerequisite for the development of deposition of monosodium urate crystals and of gout) has a pro-inflammatory effect and can initiate, amplify and sustain inflammatory responses. A linear relation between serum urate and risk of venous thromboembolism has been shown. In addition to the effect of hyperuricemia, a potent inflammatory reaction is triggered by the deposition of monosodium urate crystals in joints and soft tissues, which is pathognomonic of gout. Historically, gout has been viewed as an episodic inflammatory condition, but it is now considered to be a chronic inflammatory arthritis in which inflammation persists between clinical flares.

Few studies have assessed how these effects of hyperuricemia, deposition of monosodium urate crystals and inflammation translate into risk of venous thromboembolism in patients with gout. The only population-based study on the subject reported a 66% increased risk of deep vein thrombosis in patients with
clinically diagnosed gout, but failed to take into account episodes of hospital admission — one of the biggest risk factors for venous thromboembolism — along with other known risk factors (e.g., body mass index, smoking status), or to assess the potential impact of urate-lowering therapy.

The aim of our study was to assess the overall occurrence of venous thromboembolism in patients with gout in a population-based sample and to separate out the effects of hospital stay and exposure to urate-lowering therapy on the risk of venous thromboembolism.

**Methods**

**Data source and study population**

We used the Clinical Practice Research Datalink (CPRD), a large database containing UK primary care medical records of anonymized patients. The CPRD covers 7% of the UK population and is representative of the general UK population in terms of age and gender distribution. The Hospital Episodes Statistics (HES) data set contains details of all National Health Service (NHS) inpatient care, outpatient appointments and emergency attendance in England. The CPRD and HES databases have been linked, and for each patient, both primary and secondary care data are therefore available. The linkage is performed by a trusted third party using NHS number, date of birth and gender. The CPRD-HES linked data cover 3% of the total English population and are representative of the general UK population.

We identified individuals in the CPRD with first-ever recorded diagnosis of gout between 1998 and 2016, using previously published methods. Briefly, gout diagnosis was based on a medical code assigned by the general practitioner, which has been previously validated in CPRD and has a positive predictive value of 90%. We assigned each patient an index date corresponding to the date of their gout diagnosis and randomly matched them to 1 control, without gout diagnosis or urate-lowering therapy, on age (± 5 yr), gender, follow-up time available in CPRD (± 3 yr) and general practice. Follow-up commenced from the index date. We excluded those with a history of venous thromboembolism, or less than 1 year of follow-up after the index date.

**Study outcome**

We based the diagnosis of venous thromboembolism on medical codes assigned by a general practitioner. We also identified cases of venous thromboembolism recorded in secondary care and in the Office of National Statistics death register. We considered a diagnosis of venous thromboembolism to be valid only if it was accompanied by anticoagulant prescription within 90 days of the event, or if death was recorded within 30 days of the diagnosis. We considered venous thromboembolism recorded as the underlying cause of death in the Office of National Statistics death register to be valid without any further confirmation. This algorithm has been previously validated in CPRD with an accuracy (positive predictive value) of 84%. For the purpose of this study, we excluded women with pregnancy-related venous thromboembolism events based on medical codes.

**Hospital admission**

To assess the effect of hospital admission (for any reason) on the risk of venous thromboembolism, we obtained information on all hospital admissions that were not for venous thromboembolism and that lasted 1 or more days. The overall person-time in the study was broadly divided into “in-hospital period” (time between admission and discharge) and “ambulatory period” (time not associated with hospital stay, including entire person-time of patients never admitted to hospital during the study period). Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.180717/-/DC1) shows the composition of person-time. The ambulatory period was further divided into “before hospital admission” (time between the index date and first hospital admission) and “postdischarge” period.

To assess the risk of venous thromboembolism arising from hospital stay, we needed to ensure inpatient venous thromboembolism was the consequence rather than the cause of hospital admission. Therefore, we manually reviewed initial hospital diagnoses and a 7-day general practice medical history of all venous thromboembolism events that occurred during the in-hospital period, as previously described. A venous thromboembolism event was deemed to be hospital-related only if there was no evidence of venous thromboembolism or related symptom (e.g., chest pain for pulmonary embolism) in the initial hospital diagnoses of the index hospital admission or in the days preceding admission.

**Exposure to urate-lowering therapy**

Among those with gout, we extracted information on first exposure to urate-lowering therapy after gout diagnosis. We calculated the duration of urate-lowering therapy based on quantity prescribed and numeric daily dose. We considered patients to be “exposed to urate-lowering therapy” only if they were on urate-lowering therapy for more than 6 months from the date of prescription. We considered patients not on urate-lowering therapy or prescribed less than 6 months of urate-lowering therapy to be “not exposed to urate-lowering therapy” (Figure 1). This was based on previous literature and expert consensus, as the usual practice for prescribing allopurinol is to start the medication at a low dose and increase the dose gradually, as it can take several months to escalate the dose to lower serum urate sufficiently to achieve the biochemical target level. Each patient exposed to urate-lowering therapy was individually matched to 1 patient not exposed to gout, on age, gender and year of prescription. For analysis of urate-lowering therapy, follow-up started from the date of first prescription of urate-lowering therapy (randomly assigned date for unexposed patients within 1-yr accrual blocks).

**Other potential confounding factors**

For each individual, we extracted information on body mass index (BMI), alcohol consumption, smoking status and Charlson comorbidity index, using the most recent recording before the study end date. We defined information on socioeconomic status based on the location of the general practice at which the patient was registered (quintiles by rank of Indices of Multiple Deprivation). We also extracted information on diabetes and hypertension and previous prescriptions for acetylsalicylic acid (ASA) or thiazide.
Statistical analysis
We calculated absolute rates of venous thromboembolism per 10,000 person-years and 95% confidence intervals (CI) for patients in the gout and control groups. We stratified these by age, gender and calendar year. We calculated hazard ratios (HR) using a Cox proportional hazards regression model, adjusting for the stated confounding factors. We categorized those with missing BMI status as a separate category and included them in the analysis, as we assumed BMI to be not missing at random. We tested the proportional hazards assumption using Schoenfeld residuals. To assess the impact of hospital admission, we calculated the absolute and relative rate of venous thromboembolism during in-hospital and ambulatory periods. To assess the impact of disease duration, we calculated the risk of venous thromboembolism in the years after gout diagnosis and compared this risk to that in controls using incidence rate ratios (IRRs) calculated using a Poisson regression analysis. Similarly, among those with gout, we assessed the risk of venous thromboembolism by exposure to urate-lowering therapy. Based on the sample of 62,234 patients with gout matched to the same number of control patients and assuming the annual incidence of venous thromboembolism to be 0.2%, we had more than 80% power to detect a hazard ratio of 1.38 at 5% level of significance.

We performed all statistical analyses using Stata version 14.

Ethics approval
This study was approved by the CPRD in-house Independent Scientific Advisory Committee reference number: reference number: 15_214RA.

Results
We identified 62,234 patients with incident gout who were individually matched to the same number of controls from the general population (Figure 1). Compared with control patients, patients with gout had higher BMIs and more comorbidities overall, and were more likely to have hypertension, use ASA and thiazides, and consume more units of alcohol per week, but were less likely to be current smokers (Table 1).

Risk of venous thromboembolism
Compared with control patients, those with incident gout had a higher absolute rate of venous thromboembolism (37.3 [95% CI 35.5–39.3] v. 27.0 [95% CI 25.5–28.9] per 10,000 person-years) and an excess risk after adjusting for baseline covariates (adjusted hazard ratio [HR] 1.25 95% CI 1.15–1.35) (Table 2). This finding was consistent for both men (adjusted HR 1.20, 95% CI 1.09–1.33) and women (adjusted HR 1.32, 95% CI 1.14–1.52).

![Figure 1: Flow diagram of data structure. Note: ULT = urate-lowering therapy, VTE = venous thromboembolism.](image-url)
Although the absolute rate of venous thromboembolism increased with age (p value for trends > 0.001), the excess risk was particularly high for younger patients (aged < 50 yr, adjusted HR 1.79, 95% CI 1.30–2.48).

Impact of admission to hospital
In total, 142,474 unique hospital admissions occurred after the index date. Initially, 529 cases of venous thromboembolism occurred during in-hospital stay and were deemed to be the consequence of a hospital stay. However, after reviewing medical records for those patients, we recategorized 121 of those cases of venous thromboembolism as the cause of hospital admission. We found no difference in the rate of venous thromboembolism between patients with gout and control patients during the in-hospital period (IRR = 1.01, 95% CI 0.83–1.24; Table 3). In contrast, the rate of venous thromboembolism was higher for patients with gout during the ambulatory period (IRR = 1.30, 95% CI 1.18–1.42) compared with the control group.

Table 1: Basic characteristics of the study population

| Characteristic                      | No. of control patients (%) | No. of patients with gout (%) | Standardized difference† |
|------------------------------------|-------------------------------|-------------------------------|---------------------------|
| Age at index, mean ± SD            | 62.3 ± 15.1                   | 62.4 ± 15.1                   |                           |
| Male                               | 45,951 (73.8)                 | 45,951 (73.8)                 |                           |
| Median follow-up (IQR)             | 5.7 (3.1–9.1)                 | 5.7 (3.1–9.1)                 |                           |
| Body mass index                    |                               |                               |                           |
| Normal (18.5–24.9)                 | 19,602 (31.5)                 | 12,312 (19.8)                 | 0.440                     |
| Underweight (< 18.5)               | 1,393 (2.2)                   | 694 (1.1)                     |                           |
| Overweight (25.29.9)               | 22,149 (35.6)                 | 23,340 (37.5)                 |                           |
| Obese (> 30)                       | 12,333 (19.8)                 | 22,285 (35.8)                 |                           |
| Missing                            | 6,757 (10.9)                  | 3,603 (5.8)                   |                           |
| Smoking status                     |                               |                               |                           |
| Never or ex-smoker                 | 53,234 (85.5)                 | 55,764 (89.6)                 | 0.123                     |
| Current smokers                    | 9,000 (14.5)                  | 6,470 (10.4)                  |                           |
| Charlson index (IQR)               |                               |                               |                           |
| 0                                  | 30,429 (48.9)                 | 23,633 (38.0)                 | 0.272                     |
| 1–2                                | 18,113 (29.1)                 | 18,297 (29.4)                 |                           |
| 3–4                                | 8,312 (13.4)                  | 11,088 (17.8)                 |                           |
| > 5                                | 5,380 (8.6)                   | 9,216 (14.8)                  |                           |
| Deprivation                        |                               |                               |                           |
| 1 (least deprived)                 | 15,438 (24.8)                 | 15,211 (24.4)                 | 0.009                     |
| 2                                  | 15,537 (25.0)                 | 15,552 (25.0)                 |                           |
| 3                                  | 12,639 (20.3)                 | 12,739 (20.5)                 |                           |
| 4                                  | 10,770 (17.3)                 | 10,880 (17.5)                 |                           |
| 5 (most deprived)                  | 7,788 (12.5)                  | 7,794 (12.5)                  |                           |
| Missing                            | 62 (0.1)                      | 58 (0.1)                      |                           |
| Diabetes                           | 6,004 (9.6)                   | 7,677 (12.3)                  | 0.086                     |
| Hypertension                       | 13,172 (21.2)                 | 21,318 (34.3)                 | 0.297                     |
| Acetylsalicylic acid use           | 13,235 (21.3)                 | 18,505 (29.7)                 | 0.195                     |
| Thiazide use                       | 11,936 (19.2)                 | 21,033 (33.8)                 | 0.335                     |
| Alcohol consumption                |                               |                               |                           |
| Never or ex-drinker                | 8,530 (13.7)                  | 7,729 (12.4)                  | 0.269                     |
| Current (< 10 units/wk)            | 28,198 (45.3)                 | 26,005 (41.8)                 |                           |
| Current (≥ 10 units/wk)            | 14,096 (22.6)                 | 20,898 (33.6)                 |                           |
| Missing                            | 11,410 (18.3)                 | 7,602 (12.2)                  |                           |

Note: IQR = interquartile range, SD = standard deviation.  
*Unless stated otherwise.  
†Standardized difference = difference in means or proportion divided by standard error; imbalance defined as absolute value > 0.10 (small effect size).
Impact of disease duration

In terms of the risk of venous thromboembolism in relation to time since gout diagnosis, we observed higher rates of venous thromboembolism compared with controls within 1 year of gout diagnosis (34 v. 19 per 10 000 person-years), which remained consistently high up to 10 years after diagnosis (Table 3). However, the excess risk was not statistically different between patients with gout and control patients beyond 10 years since gout diagnosis.

Table 2: Absolute rate of venous thromboembolism per 10 000 person-years and hazard ratios

| Variable                  | Control patients | Patients with gout | Unadjusted HR (95% CI) | Adjusted HR* (95% CI) |
|---------------------------|------------------|-------------------|------------------------|-----------------------|
|                           | N Person-years   | Rate (95% CI)     | N Person-years         | Rate (95% CI)         |                        |
| Overall                   | 1071 396 095     | 27.0 (25.5–28.9)  | 1481 396 990           | 37.3 (35.5–39.3)      | 1.38 (1.28–1.49)       |
|                           |                  |                   |                        |                       | 1.25 (1.15–1.35)       |
| Gender                    |                  |                   |                        |                       |                        |
| Male                      | 721 297 075      | 24.3 (22.6–26.1)  | 953 298 577            | 31.9 (30.0–34.0)      | 1.31 (1.19–1.45)       |
|                           |                  |                   |                        |                       | 1.20 (1.09–1.33)       |
| Female                    | 350 99 020       | 35.3 (31.8–39.3)  | 528 98 413             | 53.7 (49.3–58.4)      | 1.52 (1.33–1.74)       |
|                           |                  |                   |                        |                       | 1.32 (1.14–1.52)       |
| Age, yr                   |                  |                   |                        |                       |                        |
| < 50                      | 63 97 437        | 6.5 (5.1–8.3)     | 126 97 224             | 13.0 (10.9–15.4)      | 2.00 (1.48–2.71)       |
|                           |                  |                   |                        |                       | 1.79 (1.30–2.48)       |
| 50–59                     | 140 86 944       | 16.1 (13.6–19.0)  | 214 86 633             | 24.7 (21.6–28.2)      | 1.53 (1.24–1.90)       |
|                           |                  |                   |                        |                       | 1.40 (1.12–1.75)       |
| 60–69                     | 269 93 635       | 28.7 (25.5–32.4)  | 393 93 734             | 41.9 (38.0–46.3)      | 1.46 (1.25–1.70)       |
|                           |                  |                   |                        |                       | 1.25 (1.06–1.47)       |
| 70–79                     | 377 81 384       | 46.3 (41.9–51.2)  | 482 82 440             | 58.5 (53.5–63.9)      | 1.26 (1.10–1.44)       |
|                           |                  |                   |                        |                       | 1.18 (1.02–1.36)       |
| > 80                      | 222 36 694       | 60.5 (53.0–69.0)  | 266 36 960             | 72.0 (63.8–81.2)      | 1.19 (0.99–1.42)       |
|                           |                  |                   |                        |                       | 1.16 (0.96–1.39)       |
| Deprivation index quintiles |                  |                   |                        |                       |                        |
| 1 (least deprived)        | 251 101 402      | 24.8 (21.9–28.0)  | 345 99 888             | 34.5 (31.0–38.4)      | 1.40 (1.19–1.64)       |
|                           |                  |                   |                        |                       | 1.31 (1.10–1.54)       |
| 2                         | 271 99 615       | 27.2 (24.2–30.6)  | 360 99 706             | 36.1 (32.6–40.0)      | 1.33 (1.13–1.55)       |
|                           |                  |                   |                        |                       | 1.22 (1.03–1.44)       |
| 3                         | 213 79 824       | 26.7 (23.3–30.5)  | 308 80 398             | 38.3 (34.3–42.8)      | 1.44 (1.21–1.71)       |
|                           |                  |                   |                        |                       | 1.28 (1.06–1.53)       |
| 4                         | 192 66 674       | 28.8 (25.0–33.2)  | 283 67 770             | 41.8 (37.2–47.0)      | 1.45 (1.20–1.74)       |
|                           |                  |                   |                        |                       | 1.29 (1.07–1.57)       |
| 5 (most deprived)         | 143 48 219       | 30.0 (25.2–35.0)  | 183 48 879             | 37.4 (32.4–43.3)      | 1.26 (1.01–1.57)       |
|                           |                  |                   |                        |                       | 1.09 (0.87–1.37)       |

Table 3: Absolute and relative rate of venous thromboembolism by hospital admission and time after gout diagnosis

| Variable                  | Control patients | Patients with gout | IRR (95% CI) adjusted* |
|---------------------------|------------------|-------------------|------------------------|
|                           | N Person-years   | Rate (95% CI)     | N Person-years         | Rate (95% CI)         |                        |
| Hospital admission        |                  |                   |                        |                       |                        |
| In-hospital period        | 178 2145         | 829.8 (716.3–961.1) | 230 2787             | 825.2 (725.1–939.0)   | 0.99 (0.82–1.21)       |
|                           |                  |                   |                        |                       | 1.01 (0.83–1.24)       |
| Ambulatory period         | 893 399 950      | 22.7 (21.2–24.2)  | 1251 394 203          | 31.7 (30.0–33.5)      | 1.40 (1.28–1.53)       |
|                           |                  |                   |                        |                       | 1.30 (1.18–1.42)       |
| Before hospital admission | 439 306 627      | 14.3 (13.0–15.7)  | 574 283 368           | 20.3 (18.7–22.0)      | 1.41 (1.25–1.60)       |
|                           |                  |                   |                        |                       | 1.37 (1.19–1.56)       |
| Postdischarge period      | 454 87 323       | 52.0 (47.4–57.0)  | 677 110 835           | 61.1 (56.5–65.9)      | 1.17 (1.04–1.32)       |
|                           |                  |                   |                        |                       | 1.15 (1.02–1.31)       |
| Time after gout diagnosis |                  |                   |                        |                       |                        |
| 1                         | 119 62 179       | 19.1 (16.0–22.9)  | 208 62 134            | 33.5 (29.2–38.4)      | 1.75 (1.40–2.19)       |
|                           |                  |                   |                        |                       | 1.70 (1.35–2.16)       |
| > 1–6                     | 611 221 787      | 27.5 (25.5–29.8)  | 817 222 456           | 36.7 (34.3–39.3)      | 1.33 (1.20–1.48)       |
|                           |                  |                   |                        |                       | 1.22 (1.10–1.37)       |
| > 6–10                    | 231 79 517       | 29.1 (25.5–33.1)  | 320 79 826            | 46.1 (35.9–44.7)      | 1.38 (1.17–1.63)       |
|                           |                  |                   |                        |                       | 1.28 (1.06–1.52)       |
| > 10                      | 110 32 613       | 33.7 (28.0–40.7)  | 136 32 574            | 41.7 (35.3–49.4)      | 1.24 (0.96–1.59)       |
|                           |                  |                   |                        |                       | 1.06 (0.81–1.38)       |

Note: CI = confidence interval, HR = hazard ratio.
*Adjusted for age, gender, Charlson index calendar year, smoking status, hospital admission, deprivation, hypertension, diabetes, acetylsalicylic acid use, thiazide use, alcohol consumption and body mass index.
Impact of urate-lowering therapy

Of the total patients with gout, 30% received at least 6 months of urate-lowering therapy during the follow-up period. After applying exclusion criteria (Figure 1), we included 15 661 matched pairs in the analysis. Patients receiving at least 6 months of urate-lowering therapy had higher BMIs and more comorbidities overall and were more likely to have hypertension or diabetes and to use ASA (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.180717/-/DC1). However, after adjustment for baseline characteristics, such patients showed no difference in the risk of venous thromboembolism overall (adjusted IRR 1.04, 95% CI 0.89–1.23) (Table 4) or in the in-hospital and ambulatory periods (data not shown).

Interpretation

Using data from a large, nationally representative cohort, we quantified the risk of venous thromboembolism among patients with gout. Compared with the those in the control group, patients with gout were 25% more likely to develop venous thromboembolism after their diagnosis. Although the risk of venous thromboembolism increased with age, the excess risk was higher for younger patients (aged < 50 yr). The excess risk of venous thromboembolism remained consistently high up to a decade after diagnosis and was particularly observed during the time not associated with hospital admission. Finally, among patients with gout, we found no difference in the risk of venous thromboembolism by prescription of urate-lowering therapy. Our findings remained unchanged when we stratified our analysis by hospital admission.

A major strength of this study is that we have used large, routinely collected data to conduct our analysis. This allowed us to assess the risk of venous thromboembolism in patients with gout with minimum information bias, as identification of outcome was independent of gout status. Using large, representative data means that our findings are generalizable to not only the UK population, but also to others with similar health care systems. Further strengths include the large number of venous thromboembolism events and long duration of follow-up.

Few studies have reported the risk of venous thromboembolism in patients with gout. A recent hospital-based case–control study from Japan reported a ninefold increased risk of pulmonary embolism in patients with gout or hyperuricemia, but the number of events was very small and the study was therefore underpowered to provide precise estimates (CI between 1.6 and 46.0). In contrast, another study from the United States reported no statistically significant association between gout and subsequent venous thromboembolism. The positive association between gout and venous thromboembolism in the previous study may have been masked, as gout ascertainment was conditional on survival and participation in follow-up visits occurring more than 5 years after initial recruitment, which may have resulted in selection bias. Although the relative risk in our study is slightly lower, it may be explained by the difference in the study population and more comprehensive consideration of confounding factors that include BMI, smoking status and hospital admission in our study. Our finding of higher relative risk observed in the younger population has been previously reported. Allopurinol has been shown to decrease cardiovascular risk, but we found no statistically significant association between prescription of urate-lowering therapy and venous thromboembolism. This finding may be owing to the fact that in the UK, allopurinol is often prescribed at a low dose by primary care practitioners and most patients do not reach target serum uric acid levels.

The excess risk of venous thromboembolism associated with gout in this study is small compared with risks reported in other inflammatory rheumatological diseases, such as rheumatoid arthritis. This may reflect the fluctuant nature of inflammation in gout with intense acute inflammation during flares and lower-grade inflammation in the intercritical period between flares, or a differing cause from autoimmune disorders. Because recurrent flares are commonly unrecorded in CPRD, as patients may self-manage without consultation, we were unable to explore this concept further.

Limitations

A potential weakness of this study is the use of anonymized patient records. As we had no access to individual patients, we relied on physicians to have accurately recorded information on gout and venous thromboembolism. However, gout diagnosis has been previously validated in CPRD with high accuracy, and therefore it is unlikely that there is any major error in our findings owing to misclassification of our case patients. These findings are in line with another study in which 83% of cases of gout diagnosed by general practitioners were independently validated by a rheumatologist on clinical grounds. Similarly, our algorithm to define venous thromboembolism had also been previously validated in CPRD with a positive predictive value of 84%. However, the absence of diagnosis is not validated in these data; therefore, in practice, if venous thromboembolism is more completely ascertained in patients with than those without gout, it would lead to apparent excess risk of venous thromboembolism in this group.

Table 4: Absolute risk of venous thromboembolism per 10 000 by exposure to urate-lowering therapy

| Variable | N | Person-years | Rate (95% CI) | IRR (95% CI) | IRR (95% CI) adjusted* |
|----------|---|--------------|--------------|--------------|------------------------|
| All periods | | | | | |
| Not exposed to ULT | 268 | 66 168 | 40.5 (35.9–45.7) | 1.00 | 1.00 |
| Exposed to ULT | 363 | 80 798 | 44.9 (39.7–48.5) | 1.10 (0.95–1.30) | 1.04 (0.89–1.23) |

Note: CI = confidence interval, IRR = incidence rate ratio, UL T = urate-lowering therapy.

*Adjusted for age, gender, Charlson index calendar year, smoking status, hospital admission, deprivation, gout duration, hypertension, diabetes, acetylsalicylic acid use, thiazide use, alcohol consumption and body mass index.
Second, the results of our analysis of urate-lowering therapy may be generalizable only to those prescribed ≤300 mg of allopurinol, a dose level widely used in primary care. We were unable to explore whether patients adhered to urate-lowering therapy, or whether target serum uric acid levels were reached in patients prescribed urate-lowering therapy, and our finding of no association may reflect suboptimal urate-lowering rather than the true effect of urate-lowering therapy. It is possible that higher doses may have significant impact on venous thromboembolism risk, for which further studies may be needed. Third, we were unable to measure adherence in our data set. However, a previous study using a similar database (CPRD) used the proportion of days covered as a proxy to measure nonadherence. This was calculated as the number of days of prescribed medication divided by the total duration of follow-up. Finally, in the UK, all patients undergo a risk assessment to identify their risk of venous thromboembolism and bleeding on admission to hospital. This may explain our null findings during the in-hospital period and higher venous thromboembolism risk during the ambulatory period. Unfortunately, we were not able to account for thromboprophylaxis owing to the lack of information on prescriptions originating in secondary care.

Conclusion
In our large population-based study, we found that gout is associated with increased risk of first venous thromboembolism. The increased risk is independent of hospital admission and is particularly high in the younger population. Furthermore, among patients with gout, we found no difference in the risk of venous thromboembolism by prescription of urate-lowering therapy. Although our observed excess risk may not be sufficient to warrant preventive intervention on its own, there may be need for clinical vigilance in younger patients with a new diagnosis of gout, with further research needed to establish the impact of gout severity on risk of venous thromboembolism.

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Data sharing: Clinical Practice Research Datalink (CPRD) data were provided under a licence that does not permit data sharing. However, data can be obtained directly from CPRD under its standard conditions.

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