

Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study



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Summary

Background Patients with inflammatory bowel disease who develop deep vein thrombosis or pulmonary embolism often have active disease at the time of thromboembolism. We therefore aimed to quantify the risk of venous thromboembolism prospectively during different activity phases of inflammatory bowel disease.

Methods From the General Practice Research Database, we matched patients with prospectively recorded inflammatory bowel disease from November, 1987, until July, 2001 with up to five controls by age, sex, and general practice. A flare was defined as the period 120 days after a new corticosteroid prescription. We used Cox regression analysis with time-varying covariates to accommodate changes in the state of inflammatory bowel disease, and whether patients were at high risk of venous thromboembolism after hospitalisation.

Findings 13 756 patients with inflammatory bowel disease and 71 672 matched controls were included in the analysis, and of these 139 patients and 165 controls developed venous thromboembolism. Overall, patients with inflammatory bowel disease had a higher risk of venous thromboembolism than did controls (hazard ratio 3·4, 95% CI 2·7–4·3; $p < 0\cdot0001$; absolute risk 2·6 per 1000 per person-years). At the time of a flare, however, this increase in risk was much more prominent (8·4, 5·5–12·8; $p < 0\cdot0001$; 9·0 per 1000 person-years). This relative risk at the time of a flare was higher during non-hospitalised periods (15·8, 9·8–25·5; $p < 0\cdot0001$; 6·4 per 1000 person-years) than during hospitalised periods (3·2, 1·7–6·3; $p = 0\cdot0006$; 37·5 per 1000 person-years).

Interpretation Trials of primary prophylaxis of venous thromboembolism are warranted to find out whether this important complication can be prevented.

Funding National Association for Colitis and Crohn's Disease.

Introduction

Venous thromboembolism in the leg is associated with a short-term mortality rate of about 6%, whereas the rate after embolism in the pulmonary circulation is as high as 20%.^{1–4} Infection⁵ and inflammation are thought to predispose to this life-threatening disease, and people with inflammatory bowel disease seem to be particularly at risk.⁶ Research suggests that most patients with inflammatory bowel disease have active disease at the time of developing venous thromboembolism.^{7,8} The three-fold overall increase in risk⁹ has led to the use of thromboprophylaxis as the standard of care for patients with active inflammatory bowel disease admitted to hospital. However, the absolute and relative risks in people with active disease who are not admitted to hospital are not known. Such information is important because much less than 50% of venous thromboembolisms arising in inflammatory bowel disease occur in patients who have been hospitalised within the past 3 months.¹⁰ If ambulant patients also have an increased risk then optimum avoidance of this disease cannot be achieved without consideration of outpatients. Active inflammatory bowel disease might need to be taken into consideration in the design of clinical models to identify high-risk groups of patients that presently include only a few pre-existing morbidities (including active cancer).^{11,12}

Although risk of venous thromboembolism increases for a short period after some events (such as admission to hospital,¹³ long-haul flight,^{14,15} or hip fracture⁴), little is known about how these interact with each other except that some groups of inpatients are at high risk. If we can identify individuals with inflammatory bowel disease at high risk of venous thromboembolism when they are outpatients, then results from thromboprophylaxis in inpatients suggest that much of the associated morbidity and mortality might be preventable.^{16,17} Our aim was therefore to assess different potentially interacting periods to separate out the effects of hospital admission and active inflammatory bowel disease on the risk of venous thromboembolism.

Methods

Study population

The General Practice Research Database (GPRD) is a large longitudinal UK database that was established in 1987 and contains the anonymised primary-care records of more than 8 million patients. Data are audited to ensure at least 95% of medical events and prescriptions are satisfactorily recorded, and have been shown to provide results consistent with other data sources in the UK. The validity of diagnoses of inflammatory bowel disease (and its flares) and venous thromboembolism within this dataset has been specifically assessed, with more than

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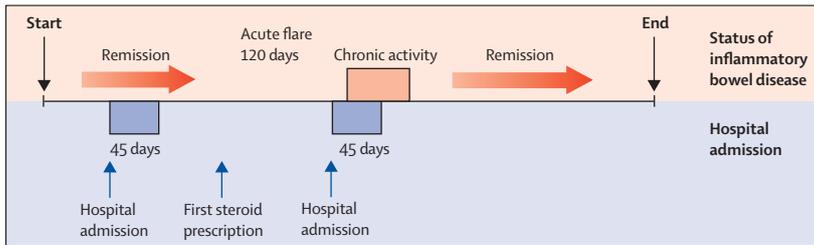


Figure: Activity episodes of inflammatory bowel disease and hospital admission recorded in the General Practice Research Database

80% of diagnoses of Crohn's disease (94%), ulcerative colitis (93%), flares (85%), and episodes of venous thromboembolism (83%) judged to be accurate.^{18–20}

The GPRD's scientific and ethical advisory committee granted permission for the series of studies, including this study.

We identified patients with prospectively recorded inflammatory bowel disease from November, 1987, until July, 2001. Up to five controls matched for age, sex, and general practice were selected for every patient. Controls did not have inflammatory bowel disease, and contributed data at their matched case's inclusion date. Exclusion criteria were fewer than 120 days of follow-up within the GPRD and prescription for warfarin or low-molecular-weight heparin in the 6 months preceding baseline to remove potentially prevalent cases of venous thromboembolism. Individuals with a previous diagnosis of asthma, chronic obstructive airway disease, or rheumatoid arthritis were excluded because we could not assess their disease activity on the basis of corticosteroid prescriptions.

Disease activity and hospital admission

For patients, the study period was defined as starting from the date of diagnosis of inflammatory bowel disease or entry to the GPRD until their end of follow-up. We used corticosteroid prescription as a surrogate measure for an acute flare. A flare was defined as the period following a new corticosteroid prescription after at least 4 months without such a prescription, as previously validated within this database.¹⁹ With this algorithm, we defined our exposure variable to be flares that were of sufficient severity to require a doctor to prescribe corticosteroids. This definition was extended to define three levels of activity of inflammatory bowel disease: a phase or flare lasting 120 days from the first steroid prescription; a period of chronic activity that started 120 days after this first prescription, when patients received further steroid prescriptions; and remission periods starting 120 days after the date of the last prescription of steroids (figure). When a patient was hospitalised for an event relating to symptoms of inflammatory bowel disease in the 60 days preceding the identification of an active flare, the start date for a flare was backdated to coincide with the date for hospital admission. We also characterised periods during which

patients were at risk after hospital admission (hospitalisation periods) for an event not related to pulmonary embolism or deep vein thrombosis. These were regarded as lasting 45 days after the date of admission to hospital.

We varied the length of time patients with inflammatory bowel disease were regarded as in the flare phase after prescription of corticosteroids to assess the effect this decision had on the findings. We also extended the period of hospital admission to 105 days (starting 30 days earlier and ending 30 days later than previously) to reduce the total ambulatory flare time, thus reducing the possibility of misclassifying ambulatory flare time if dates for hospital admission were recorded inaccurately or if 45 days was an underestimation of the true duration of increased risk.

Venous thromboembolism outcomes

Venous thromboembolism was defined as previously validated in GPRD²⁰ as a medical code relating to diagnosis of deep vein thrombosis or pulmonary embolism that was supported by one of the following: a prescription for warfarin or low-molecular weight heparin within 3 months of the date of diagnosis; evidence of attendance at a clinic for treatment with anticoagulants within 3 months of diagnosis; or death within 1 month of diagnosis. Follow-up was censored at the date of diagnosis of venous thromboembolism for all confirmed cases. To characterise the risk of venous thromboembolism due to episodes of hospitalisation, we needed to assess whether the venous thromboembolism was the cause of an admission (in which case the same admission could not cause this outcome). Medical histories in the month preceding diagnosis of venous thromboembolism were therefore independently reviewed for all confirmed cases by two investigators (JW and TRC) to assess whether this outcome was the cause or consequence of a hospital admission. Agreement about venous thromboembolism being the cause of the admission was achieved for 263 (87%) of 304 cases. When there was disagreement, consensus was achieved by discussion in all instances.

Other potential confounding variables

Smoking status was classified as unknown, current smoker, or non-smoker. Body-mass index was classified into four groups—ie, less than 25 kg/m², 25–30 kg/m², more than 30 kg/m², and missing. Previous diagnoses of cancer were also ascertained and were classified according to whether they occurred before or during the study.

Statistical analysis

Incidence rates of venous thromboembolism were expressed per 1000 person-years as the number of events divided by the total follow-up time in each activity state of inflammatory bowel disease. Hazard ratios were calculated with the Cox proportional hazards model with disease activity and hospital admission fitted as time-varying

covariates, and all other covariates as non-time-varying.²¹ For activity state of inflammatory bowel disease, the risk of venous thromboembolism in controls was taken as the baseline. Covariates included age, sex, body-mass index, cigarette smoking, cancer diagnosis, and history of venous thromboembolism on the basis that all these could be related to venous thromboembolism and to activity of inflammatory bowel disease. In subsequent analyses, we assessed the effect of disease activity during periods at risk after hospitalisation and during non-hospitalised periods by fitting an interaction term between the activity of inflammatory bowel disease and hospitalisation. On this occasion the baseline risk was taken to be the risk of venous thromboembolism in the control group during the hospitalised or ambulatory period. For the Cox regression analysis, we defined analysis time as the period when patients entered the study; this point was taken as the origin of the analysis. We separately analysed our data using calendar time as the origin to account for any temporal effects, and the effect of this change on the results presented here was negligible.

We did a second analysis with data only from patients who developed venous thromboembolism, using self-controlled case-series methods to remove all between-person confounding.²² Information from the entire duration of the study was used to divide the observation time according to activity of inflammatory bowel disease and hospitalisation (both defined as in previous analysis). The outcome measure was the first occurrence of venous thromboembolism. Although inclusion of the cohort without inflammatory bowel disease was necessary to enable improved estimation and hence adjustment for the effect of hospitalisation, only patients in the cohort with inflammatory bowel disease contributed to the estimation of incidence rate ratios relating to acute and chronic activity of this disease. The incidence of venous thromboembolism during remission periods was therefore taken as the baseline risk. All analyses were done with Stata (version 10.1).

Role of the funding source

The funder had no role in the design or analysis of the study and had no access to the data. Raw data were obtained from the GPRD by one of the authors (TRC), and all authors had full access to these data. The corresponding author had final responsibility for the decision to submit the report for publication.

Results

13 756 patients with inflammatory bowel disease and 71 672 matched controls met our inclusion criteria (table 1). Individuals with inflammatory bowel disease were less likely to be smokers, had a lower mean body-mass index, but were more likely to have a diagnosis of cancer (before or during the study), and have a history of venous thromboembolism than were controls (all $p < 0.0001$). Patients with inflammatory bowel disease contributed a

total of 53 535 person-years to the analysis (mean 3.9 years [SD 2.7] per patient) compared with 279 772 person-years by controls (3.9 years [2.7] per control).

8009 (58%) patients with inflammatory bowel disease had a total of 11 799 flares that were sufficiently severe to necessitate prescription of corticosteroids during the study. 11 195 (95%) flares lasted for 120 days as per our definition, and 604 (5%) started within 120 days of the study end date. 8383 (71%) flares were followed up by periods of chronic activity beyond 120 days, in addition to 533 patients judged to be in the chronically active phase at the time of study entry (on the basis of steroid prescriptions before the study start date). Table 2 shows the median duration of the activity and remission phases.

42 158 hospital admissions were recorded for the entire cohort of patients and controls, with 6884 (50%) patients and 16 905 (24%) controls having at least one admission. The proportion of the study period during which patients were regarded as at risk after hospitalisation was greater for those with inflammatory bowel disease than for controls (1865 [3%] total person-years vs 3532 [1%] total person-years; $p < 0.0001$). 2626 (22%) acute flares and 2278 (26%) episodes of chronic activity among patients with inflammatory bowel disease coincided with episodes of hospitalisation.

304 episodes of venous thromboembolism among patients ($n=139$) and controls ($n=165$) met our definition. The overall incidence per 1000 person-years was higher among patients with inflammatory bowel disease than among controls (table 3). The incidence rates of venous thromboembolism among patients varied greatly depending on the activity of the inflammatory bowel disease (table 3). After adjustment for hospitalisation and other factors, the risk of venous thromboembolism was greater than eight-fold at the time of a flare, and

	Patients (n=13 756)	Controls (n=71 672)
Ulcerative colitis	6765 (49%)	..
Crohn's disease	4835 (35%)	..
Age (years)	46.1 (17.9)	46.6 (18.1)
Men	6430 (47%)	33 703 (47%)
Smoker*	2656 (27%)	14 624 (32%)
Body-mass index (kg/m ²)	24.7 (4.3)	25.5 (4.5)
Body-mass index (≥30 kg/m ²)†	884 (10%)	5306 (14%)
Any cancer	729 (5%)	2880 (4%)
History of venous thromboembolism	194 (1%)	590 (<1%)
Years in study	3.89 (2.69)	3.90 (2.67)

Data are number (%) or mean (SD). Disease type could not be assessed for 2156 (16%) patients. *Denominator is the number of participants without missing data for smoking: 9697 patients and 46 034 controls. †Denominator is the number of participants without missing data for body-mass index: 8476 cases and 39 029 controls.

Table 1: Characteristics of patients with inflammatory bowel disease and controls

	Episodes (n)	Median duration (days; IQR)	Maximum duration (days)	Total person-years of follow-up
Patients with ≥ 1 flare (n=8009)				
Flare	11 799	120 (120–120)	120	3782.3
Chronic activity	8916	164 (54–423)	3914	8358.7
Remission	11 022	461 (238–937)	4420	21284.9
Patients without flare (n=5747)				
Remission	5747	1060 (492–1858)	4602	20108.6

Table 2: Disease activity in cohort with inflammatory bowel disease

greater than six-fold during the chronic phase (table 3). Even in remission, however, patients had a significantly greater risk of venous thromboembolism than did controls (table 3).

Absolute risks of venous thromboembolism during all activity phases of inflammatory bowel disease were greater while patients were at risk after hospitalisation than during ambulatory periods (table 3). The overall incidence of venous thromboembolism was 0.6 per 1000 person-years during non-hospitalised periods and 17.8 per 1000 person-years while hospitalised. In hospitalised periods, risks were increased about three-fold overall for patients with acute disease (flare) compared with controls (table 3). In ambulatory periods, the relative risks, compared with the general population, were more pronounced during the acute and chronic periods (table 3). An interaction term between our two time-varying covariates in our Cox regression analysis was highly significant ($p < 0.0001$), in favour of an increased relative risk resulting from active

inflammatory bowel disease outside of hospital. We noted similar relative risks of venous thromboembolism during a flare in ambulatory periods when we assessed risks separately for patients with ulcerative colitis (hazard ratio [HR] 15.3, 95% CI 8.4–27.6) and those with Crohn's disease (17.0, 7.8–37.0).

When the flare duration was reduced to 60 days, the HRs during non-hospitalised periods increased to 20.9 (95% CI 12.0–36.6) at the time of an acute flare and to 11.3 (7.1–18.1) during chronic activity. When the duration of a flare was increased to 180 days, the HR at the time of an acute flare during ambulatory periods was reduced (12.7, 8.0–20.2), whereas the risk during periods of chronic activity was not greatly affected (10.3, 7.0–15.1). HRs for patients with inflammatory bowel disease while in remission and for hospitalised patients during all disease phases did not change noticeably when we altered the duration of a flare (data not shown).

Extension of hospitalisation periods to 105 days in the second sensitivity analysis resulted in a slight increase in the HRs during the ambulatory flare (HR 17.3, 95% CI 10.4–28.9) and chronic activity phases (12.3, 8.2–18.4), although the incidence of venous thromboembolism during an ambulatory flare fell to 6.0 per 1000 person-years. HRs for patients with inflammatory bowel disease in remission remained unaffected (data not shown).

In the within-person analysis, the risk of venous thromboembolism was raised during a flare and during the phases of chronic activity when compared with periods of remission (table 4). The magnitude of this finding was similar to the results obtained with Cox

	Events (n)	Person-years of follow-up	Risk per 1000 person-years (unadjusted)	Hazard ratio* (95% CI)	p value
All periods					
Overall inflammatory bowel disease	139	53534.5	2.6	3.4 (2.7–4.3)	<0.0001
Flare	34	3782.3	9.0	8.4 (5.5–12.8)	<0.0001
Chronic activity	45	8358.7	5.4	6.5 (4.6–9.2)	<0.0001
Remission	60	41393.5	1.4	2.1 (1.6–2.9)	<0.0001
Control	165	279772.2	0.6	1.0	..
Hospitalised periods					
Overall inflammatory bowel disease	48	1907.5	25.2	2.1 (1.4–3.2)	0.0003
Flare	12	320.3	37.5	3.2 (1.7–6.3)	0.0006
Chronic activity	13	443.0	29.3	2.8 (1.5–5.2)	0.001
Remission	23	1102.2	20.9	1.7 (1.1–2.9)	0.03
Control	49	3532.2	13.9	1.0	..
Ambulatory periods					
Overall inflammatory bowel disease	91	51669.0	1.8	4.3 (3.3–5.7)	<0.0001
Flare	22	3462.1	6.4	15.8 (9.8–25.5)	<0.0001
Chronic activity	32	7915.7	4.0	9.9 (6.7–14.7)	<0.0001
Remission	37	40291.2	0.9	2.2 (1.5–3.2)	<0.0001
Control	116	276239.2	0.4	1.0	..

*Adjusted for age, sex, body-mass index (<25 kg/m², 25–30 kg/m², >30 kg/m², information missing), smoking (current smoker, non-smoker, information missing), cancer diagnosis (in exposure period or before study), and history of pulmonary embolism or deep vein thrombosis.

Table 3: Risks of venous thromboembolism by activity of inflammatory bowel disease and hospitalisation

regression analysis when we allowed for the different reference category. In ambulatory periods, the size of this increase in risk was more pronounced during acute and chronic phases than during remission (table 4). In hospitalised periods, the increase in risk was less than two-fold in both phases and was not significant (table 4). When we repeated the analysis by incorporating the effect of age as an additional covariate (adjusted for use of 5-year and 10-year age bands), the effect on the results was negligible (data not shown).

Discussion

Inflammatory bowel disease was associated with a roughly three-fold increase in the risk of venous thromboembolism. Compared with the general population while ambulatory, the risk of venous thromboembolism was increased about 16-fold for non-hospitalised patients with active inflammatory bowel disease. Despite the low absolute risks during non-hospitalised periods, these results suggest that active inflammatory bowel disease in ambulatory patients might be a far greater risk factor for venous thromboembolism than previously recognised.

The extent to which we can rely on these results when planning patient care depends on the reliability of the methods used and the extent to which the populations assessed are representative of the populations with and without inflammatory bowel disease for whom care is being planned. The strength of this study in this respect is that being population-based, the results will be generalisable to all patients with inflammatory bowel disease in the UK at least. One limitation to this generalisability is that we excluded individuals likely to have been given corticosteroids for chronic respiratory disease and rheumatoid arthritis, but we see no reason why the associations studied should be different in these people. A potential weakness of this study is that since we are using anonymised patient records and have no direct access to the patients, we are dependent on the family doctors inputting data in GPRD for the validity of the diagnoses of inflammatory bowel disease, flare, and venous thromboembolism, which we have analysed. Since these diagnoses have been previously validated, we believe that they are accurate in almost all cases analysed in our study. We must, however, accept that the absence of diagnoses is not validated and hence if in clinical practice venous thromboembolism is more completely ascertained for patients with than without inflammatory bowel disease (perhaps because of the recognition that they are at risk), this difference might increase the apparent excess of venous thromboembolism in this group. We were unable to estimate the number of deaths attributed to venous thromboembolism in this cohort because of the absence of cause-specific mortality data within the database. To extrapolate our conclusions to include fatal venous thromboembolism we would therefore need to assume that the risk of death after venous thromboembolism is not dependent on inflammatory bowel disease.

	All periods		Hospitalised periods		Ambulatory periods	
	Events	IRR (95% CI)*	Events	IRR (95% CI)*	Events	IRR (95% CI)*
Flare	34	4.5 (2.6–7.8)	12	1.8 (0.8–4.1)	22	8.7 (4.4–16.9)
Chronic activity	45	2.7 (1.5–4.8)	13	1.1 (0.5–2.5)	32	4.6 (2.3–9.1)
Remission	60	1.0	23	1.0	37	1.0

Data are number, unless otherwise indicated. Results for all periods were adjusted for hospitalisation. IRR=incidence rate ratio. *139 individuals in the inflammatory bowel disease cohort contributed to the IRR estimates for disease activity because controls remained in the same disease state throughout the study, therefore risk during disease remission rather than in controls was used as the baseline period.

Table 4: Results from self-controlled case-series analysis of state of inflammatory bowel disease at time of first venous thromboembolism

Our definition of active inflammatory bowel disease might deserve more scrutiny. We have arbitrarily assumed that a flare leaves all patients at risk for 120 days, whereas the true duration of risk would vary from individual to individual, perhaps considerably, and analysis of cohorts with even more precise measurement of severity and duration of flare than we have available would be advantageous. However, we used a definition that had good validity within the GPRD, and, though the choice of risk period is inevitably important when we did the sensitivity analyses of flare duration, our results were not appreciably altered. Use of corticosteroid prescription as a surrogate measure for active inflammatory bowel disease would be difficult if it had a direct effect on risk of development of venous thromboembolism. Use of corticosteroids might increase platelet functions, and therefore promote haemostasis.²³ We believe any direct effect would only account for a small part of the increase in risk recorded in our study, and high rates of venous thromboembolism have not been noted in other populations, including patients with asthma and rheumatoid arthritis, routinely treated with corticosteroids. Our definition of active inflammatory bowel disease perhaps excluded some mild cases that could be treated with regimens such as derivatives of 5-aminosalicylic acid and hence the risks we describe relate to flares severe enough to require corticosteroid prescription.

Our results might have been misleading if dates for hospital admissions were incorrectly recorded. Since one of the most important findings was the increase in risk of venous thromboembolism during ambulatory flares, we therefore guarded against classifying periods in hospital (or individuals at risk because of recent admission to hospital) as ambulatory and hence increasing the apparent risk of ambulatory flares by extending the period defined as hospital admission, but some effect cannot be excluded. Similarly if some periods of treatment in hospital were entirely unrecorded, risks in the ambulant state would be overstated. Although this effect cannot be entirely excluded, it is likely to have been kept to a minimum because of the requirements for data quality in GPRD.

To address the residual confounding, which is always a concern in epidemiological studies, we did a self-controlled case-series analysis of the risk estimates for

the effect of flare and chronic activity in which the effect of variation in all potential confounding factors between individuals was removed.²² For this analysis, the incidence of venous thromboembolism in remission periods was taken as the baseline risk. In hospitalised periods, the incidence rate ratios with case series were not significantly raised for acute and chronic inflammatory bowel disease. In ambulatory periods, the corresponding effect sizes were equivalent to those obtained with Cox regression analysis. These results indicate that some between-person confounding might have led to an overestimation of the effect sizes for the in-hospital analysis, but not for the ambulatory periods. We have presented the Cox regression analysis as our primary method of analysis since it enabled us to present risks relative to the general population and allowed the presentation of absolute risks that are needed for health-care planning purposes and clear communication to patients.²⁴ However, results from the Cox regression analysis might be less accurate for hospitalised than for non-hospitalised patients.

Our finding that the risk of venous thromboembolism in patients with inflammatory bowel disease in hospital is very high is not new. In two studies,^{25,26} 1–2% of all hospital admissions among patients with inflammatory bowel disease resulted in venous thromboembolism. These data cannot be directly compared with our data, however, because we extended the period at risk on the basis that an increased risk of embolism persists several weeks after discharge. Our study is larger than the only previous cohort study about this subject by Bernstein and colleagues⁹ in which the risk of venous thromboembolism was higher in a cohort of 5529 patients with inflammatory bowel disease from Manitoba, Canada, compared with matched controls. An additional advantage was that we were able to assess the risks of venous thromboembolism on the basis of the activity of inflammatory bowel disease. Our results concur with the three-fold to four-fold overall increase in risk of embolism in inflammatory bowel disease in a previous cohort study⁹ and a single-centre cross-sectional study of hospital attendees.²⁷ Additionally, Solem and colleagues⁷ showed that the occurrence of venous thromboembolism in these patients clustered around active inflammatory bowel disease; however, because their study was cross-sectional, they were unable to specifically characterise risks on the basis of disease activity. Grip and colleagues²⁸ reported no increase in the risk of venous thromboembolism in a group of patients with inflammatory bowel disease when compared with the general population; however, they reported that venous thromboembolism in their group occurred at a younger age for patients with inflammatory bowel disease than for those without. When these results are considered as a whole, comparison of the risk in patients with inflammatory bowel disease with that in well recognised high-risk groups shows that the absolute

risk of venous thromboembolism in ambulant flares is greater than that in pregnancy and the post-partum period,²⁹ and is at least a similar size to that in patients with cancer³⁰ (notwithstanding the much younger age of patients with inflammatory bowel disease).

We believe that the medical profession needs to recognise the increased risk in people with inflammatory bowel disease when assessing the likelihood of venous thromboembolism and to address the difficulty of reducing this risk in patients with a flare who are not admitted to hospital. Guidance for interventions to prevent adverse outcomes during flares of inflammatory bowel disease is already available—eg, for individuals prescribed corticosteroids, concurrent osteoporosis prophylaxis is recommended to reduce the risk of fracture.^{31,32} However, the absolute risks of embolism we have described are at least three-fold greater than those for hip fracture in the same population.³³ Such strategies to achieve a reduction in risk might include those used for inpatients such as brief courses of low-molecular-weight heparin or perhaps newly available oral anticoagulants. We believe that trials of such strategies should be considered.

Contributors

MJG, JW, and TRC participated in the design of the study, interpretation of the analysis, and writing of the report; MJG did the analysis. All authors have seen and approved the final version of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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Prophylaxis of venous thromboembolism in IBD

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Venous thromboembolism is an extraintestinal manifestation of inflammatory bowel disease that can lead to substantial morbidity and mortality.¹ Population-based and hospital-based studies suggest that patients with inflammatory bowel disease might have a 2–3-fold increased risk of developing venous thromboembolism compared with those without inflammatory bowel disease.^{2,3} Although nearly 80% of patients will have active disease when venous thromboembolism is diagnosed,¹ the effect of disease activity on risk of this thromboembolism has not been assessed in population-based studies.

In *The Lancet* today, Matthew Grainge and colleagues⁴ analysed the UK's General Practitioner Research Database and showed that patients had an overall 8.4-fold increased risk of developing venous thromboembolism during acute flares of inflammatory bowel disease

compared with the risk in the general population. When acute flares were stratified into periods of non-hospitalisation and hospitalisation, the risk of developing venous thromboembolism during inflammatory bowel disease was 15.8-fold higher than that of controls in the ambulatory setting, which contrasted with a 3.2-fold increase in the hospital setting. Ambulatory patients who had chronic active inflammatory bowel disease and those who were in clinical remission were also at increased risk of developing venous thromboembolism, but the magnitudes of risk were lower (ie, 9.9-fold and 2.2-fold higher than that of controls, respectively). A within-person analysis additionally showed that, on average, a non-hospitalised patient's risk of developing venous thromboembolism during an acute flare of inflammatory bowel disease was 8.7-fold higher than the same person's risk during clinical remission.

The use of steroid prescriptions as a surrogate indicator of acute disease flare restricts the applicability of Grainge and colleagues' findings to flares that are moderate to severe. Whether patients with mild flares are also at increased risk is not clear. Recognition of venous thromboembolism might be increased during periods of frequent contact with doctors, such as during flares compared with during remission of inflammatory bowel disease, thus potentially introducing a bias in ascertainment of venous thromboembolism.⁵ This study was done retrospectively with administrative data that lacked information about the clinical detail, such as indices of disease activity or duration of flares, that might have improved characterisation of the link between active disease and risks of developing venous thromboembolism.



Photolibary

With these caveats, how should these data affect our management of flares of inflammatory bowel disease in the ambulatory setting? Perhaps patients with moderate-to-severe flares should be given prophylactic-dose anticoagulant drugs that could reduce risks of developing venous thromboembolism by half.⁶ However, most regimens need to be administered by subcutaneous injection, which is not only inconvenient but is also without proven efficacy in the outpatient setting. Additionally, although acute flares were associated with increased risk of venous thromboembolism in ambulatory patients with inflammatory bowel disease, the absolute risk remained less than that in patients without this inflammatory disease who were hospitalised (6.4 per 1000 person-years vs 13.9 per 1000 person-years). If 50% reduction in risk of venous thromboembolism is assumed, prophylaxis would be needed for 312 person-years during flares of inflammatory bowel disease to prevent one person developing venous thromboembolism. Consequently, we believe that the clinical efficacy and cost-effectiveness of pharmacological prophylaxis in the population with inflammatory bowel disease should be proven before it is routinely recommended during acute flares. The ascertainment of efficacy data through clinical trials might, however, be a formidable challenge in view of the facts that the absolute risk of venous thromboembolism is low and a sample size of thousands of people with inflammatory bowel disease during active flares might be required.

A pragmatic initial approach to reduction of the rates of morbidity and mortality resulting from venous thromboembolism in ambulatory patients with inflammatory bowel disease would be non-pharmacological thromboprophylaxis, including patients' education and awareness of risk and signs and symptoms of venous thromboembolism, and use of support stockings. Physicians should clinically assess for signs and symptoms of this embolism during visits for acute flare of inflammatory bowel disease.⁷ Additional studies are needed to quantify the prevalence of asymptomatic venous thromboembolism in patients with inflammatory bowel disease to assess whether prevalence is substantial enough to warrant use of screening methods, such as ultrasound, or tests for markers, such as D-dimer.⁸

The other implication of today's study is the importance of prophylaxis of venous thromboembolism

for hospitalised patients with inflammatory bowel disease who have a 3-fold higher risk of the embolism than do those without inflammatory bowel disease. The guidelines for treatment of inflammatory bowel disease by the British Society of Gastroenterology recommend pharmacological prophylaxis for venous thromboembolism in hospitalised patients with severe ulcerative colitis, whereas those from the American College of Chest Physicians advocate prophylaxis for non-ambulating hospitalised patients.^{9,10} Results of clinical trials in which anticoagulant drugs were used as the first treatment for inflammatory bowel disease have shown that they are safe during flares with respect to complications of bleeding.¹¹ Grainge and colleagues' study substantiates the need to widely disseminate and reinforce recommendations for prophylaxis of venous thromboembolism in guidelines for the management of inpatients with inflammatory bowel disease.

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Disease activity and venous thromboembolism in inflammatory bowel disease

Matthew Grainge and colleagues (Feb 20, p 657),¹ analysing the UK's General Practice Research Database, report a 15.8-fold increased risk of venous thromboembolism among ambulatory patients with active inflammatory bowel disease (IBD) compared with controls. On the basis of these data, the authors suggest that active disease in ambulatory patients with IBD is a greater risk factor for venous thromboembolism than previously thought. We think that the correct interpretation of their results is rather that the risk of venous thromboembolism is extremely increased in ambulatory IBD patients who are treated with corticosteroids. In this setting, both disease activity and corticosteroids could independently contribute to the increased risk of thromboembolism. The use of corticosteroids not only increases platelet functions, as mentioned by the authors, but it is an independent risk factor for venous thromboembolism² and induces both hypercoagulability and a hypofibrinolytic state.³

We agree with the comment by Nguyen and Yeo⁴ about the limitations of the study, and that its findings are related to moderate-to-severe flares treated with corticosteroids. However, during the past decade, many advances in the treatment of IBD have been developed. Today many patients with moderate-to-severe disease are treated as ambulatory patients with immunosuppressants or anti-tumour-necrosis-factor agents. There is evidence that infliximab, by contrast with corticosteroids, decreases the coagulation biomarkers and activates the fibrinolytic system.⁵

Future prospective population-based studies should stratify patients according to disease activity and the medications they are treated with, to assess accurately risks that will affect the management of IBD.

We declare that we have no conflicts of interest.

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Matthew Grainge and colleagues are to be commended on raising awareness of the increased risk of venous thromboembolism in patients with inflammatory bowel disease (IBD).¹ Although trials for primary thromboprophylaxis in IBD should be undertaken, there are certain areas of caution that need to be addressed before its widespread acceptance. Pharmacological agents to prevent thromboembolism do increase the risk of bleeding in individuals with mucosal erosions. This can become more troublesome in those with the flare-ups of IBD who, unfortunately, are the very group who are at higher risk of thrombosis. Vitamin K antagonists such as warfarin might not be an automatic choice in these circumstances since malabsorption of these agents can cause their

concentrations to fluctuate, which in turn leads to difficulties with overanticoagulation and underanticoagulation. Prolonged use of low-molecular-weight heparin can also be fraught with problems such as osteoporosis, which is not an uncommon problem in those with IBD, especially patients on steroid treatment. These problems call for an individualised approach to weigh-up the risk-benefit ratio of commencing and continuing thromboprophylaxis in individuals with IBD, as with any other pharmacological interventions.

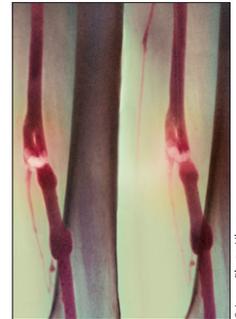
It is also useful to bear in mind the strong bidirectional correlation between inflammation and the haemostatic system in the development of thrombosis in IBD.² This is exemplified by the decreased incidence of thromboses in individuals with haemophilia and Von Willebrand disease.³ An interesting prospect in this context would be to analyse the role of thromboprophylaxis in decreasing the incidence of flare-ups of IBD in addition to thromboembolic risk in these patients. As platelet activation has been shown to be a key factor in the active stages of IBD,⁴ and also an important player in the thrombotic process, antiplatelet agents might be an attractive alternative to those who do not respond or are unable to receive anticoagulants.

I declare that I have no conflicts of interest.

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We read with interest the article by Matthew Grainge and colleagues¹ examining the risk of venous thromboembolism in inflammatory bowel disease (IBD). Other investigators have reported an increased risk of venous thromboembolism in IBD.² The exact mechanism is unknown, but is likely to be due to a combination of genetic and acquired factors.³

The authors reported a more than eight-fold increased risk of venous thromboembolism during flare-ups of IBD, even in non-hospitalised ambulatory patients. They suggested that trials of primary prophylaxis with anticoagulants in these patients are warranted.

Although the association between IBD activity and venous thromboembolism was significant, the study does have some limitations. First, the data from the General Practice Research Database are anonymised, hence there is a potential for misclassification bias although the outcomes they studied have been validated previously.^{4,5} Second, the use of corticosteroid prescriptions as a surrogate marker of disease activity will fail to detect flares managed with increased doses of oral 5-aminosalicylate preparations, or flares of distal colitis treated with topical rectal preparations. Third, the extent of disease, which can act as a potential confounding factor, was not assessed. Finally, although hazard ratios were high, the absolute risk of developing venous thromboembolism during a flare-up in ambulatory patients was low, at 6.4 events per 1000 person-years. It is unlikely that a trial of primary prophylaxis could be done with sufficient power to show a difference at these low absolute rates. Based on these considerations, we believe that before drawing significant conclusions this result should be validated in other populations.

We declare we have no conflicts of interest.

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Matthew Grainge and colleagues¹ showed a significant increase in the risk of venous thromboembolism associated with inflammatory bowel disease (IBD). The authors' conclusion accords with previous reports² and we recognise the importance of this study to promote the use of appropriate prophylaxis for these high-risk patients. Nonetheless, we raise the question of whether the basal risk of thromboembolic complications in patients with IBD remained stable over the course of the study. The authors reported within-person analyses showing pronounced risk during flare episodes, especially in the ambulatory setting. Unfortunately, they made no mention of the number of flares and the risk of thrombosis. It would have been interesting to know whether the number of previous acute episodes shows any relation with the risk of thrombosis. Considering that inflammation might have an important role in the pathophysiology of the thrombotic events, it would not be illogical to think that repetitive episodes of endothelial damage will lead to a sustained prothrombotic state.³ We believe that addressing this issue might help with the final risk assessment of these patients, mainly

in the outpatient setting, where the role of thromboprophylaxis is less clear.

We declare that we have no conflicts of interest.

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Authors' reply

We are delighted to have succeeded in provoking a debate on the potential for prophylaxis in ambulatory patients with inflammatory bowel disease (IBD), and we are grateful for the opportunity to respond to those issues raised which have not already been discussed in our paper or the accompanying Comment.^{1,2}

We acknowledge concerns by Ioannis Koutroubakis and Amado Salvador Pena that our conclusions should be restricted to patients who are undergoing steroid use. Nevertheless, as stated in the paper, our belief is that the increase in risk of venous thromboembolism we describe is related to disease, and not to therapy. The possibility that steroids do cause an appreciable pro-coagulant effect in this population is one we are unable to address, since we used their prescription as a proxy for disease activity. However, the extant literature for other uses of corticosteroids does not strongly support the assertion that they are the main driver of the increased risk. We also cannot address the question of whether anti-tumour-necrosis-factor therapy

produces a lower risk of venous thromboembolism than does steroid therapy. This is because these drugs were not available for most of the period to which the data used relate.

We believe that the first priority of further studies should be an attempt to reproduce or refute our results, since no single observational study should be viewed as proof of any association. Assuming our findings are replicated then we agree that the exact nature of any proposed prophylaxis will need careful consideration, and the benefits of such a course will need to be carefully weighed against the risks as outlined by Jecko Thachil. Since randomised controlled trials would need to be very large to determine the utility of prophylaxis, as Tilak Ghosh and colleagues point out, these might not be feasible even for conventional thromboprophylaxis, which might achieve risk reductions of about 50%.³ Such considerations will be even more important for any less efficacious therapy. Among the most important considerations in determining whether any prophylaxis might be warranted will be the true duration of risk. We chose by necessity a long exposure period, but if future work could identify a shorter period in which risk resides, or take into account the cumulative effect of all previous flares, as proposed by Matias Valsecchi and Cecilia Damilano, then the potential risks of prophylaxis might be greatly reduced and the benefit increased.

We declare that we have no conflicts of interest.

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Ischaemic conditioning for myocardial salvage after AMI

We congratulate Hans Bøtker and colleagues (Feb 27, p 727)¹ on their proof-of-concept trial of remote ischaemic conditioning for myocardial salvage after acute myocardial infarction (AMI). However, there is an important issue that might need to be further explored: the medication patients were taking before AMI could have been a confounding factor, especially considering the low sample size and large number of exclusions.

According to the data presented, the two groups of included patients were quite balanced for all risk factors except hypertension, which was much higher in the conditioning group, and properly acknowledged by Bøtker and colleagues. But beyond the presence of hypertension itself, the class of antihypertensive drug the patients were taking might have had a role in the enhanced cardioprotection seen in the conditioning group.

In particular, patients who receive β blockers before an AMI have been shown to exhibit smaller infarcts than patients not receiving β blockers.² Furthermore, previous β blockade is associated with reduced release of myocardial necrosis enzymes after percutaneous coronary intervention.³ In fact, the administration of the β 1-selective antagonist metoprolol can increase myocardial salvage, as we showed by magnetic resonance imaging.⁴

The cardioprotective effect associated with β blockade seems only to occur when the drug is given before coronary reperfusion,⁵ suggesting

that β -receptor antagonists might have a role in reducing reperfusion injury. We encourage Bøtker and colleagues to study this issue further and assess the proportion of patients who were on blockers before the ischaemic event.

We declare that we have no conflicts of interest.

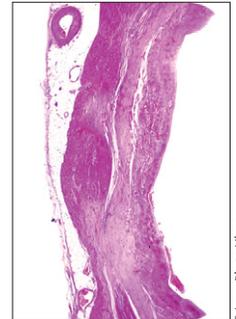
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I applaud Hans Bøtker and colleagues on their interesting and highly clinically relevant findings of remote ischaemic conditioning in patients with acute myocardial infarction.¹

Bøtker and colleagues suggest that the mechanism underlying the beneficial effect of remote ischaemic conditioning could be due to effects on mitochondria, circulating inflammatory cells, or transcriptional upregulation of protective pathways. This could be true. Another plausible mechanism could be the ability of remote ischaemic conditioning to mediate the release of fibrinolytic



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