Inflammatory Bowel Disease Is a Risk Factor for Recurrent Venous Thromboembolism

GOTTFRIED NOVACEK,* ANSGAR WELTERMANN,‡ ANNA SOBALA,* HERBERT TILG,§ WOLFGANG PETRITSCH,‖ WALTER REINISCH,* ANDREAS MAYER,¶ THOMAS HAAS,# ARTHUR KASER,** THOMAS FEICHTENSCHLAGER,‡‡ HARRY FUCHSSTEINER,§§ PETER KNOFLACH,‖‖ HARALD VOGELSANG,* WOLFGANG MIEHSLER,* REINGARD PLATZER,¶¶ WOLFGANG TILLINGER,## BERNHARD JARITZ,*** ALFONS SCHMID,‡‡‡ BENEDIKT BLAHA,§§§ CLEMENS DEJACO,* and SABINE EICHINGER‖‖‖

*Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; ‡Department of Internal Medicine 1, Elisabethinen Hospital Linz, Linz, Austria; §Department of Medicine, Academic Teaching Hospital Hall in Tirol, Hall in Tirol, Austria; ‖Department of Internal Medicine, Medical University of Graz, Graz, Austria; ¶Department of Internal Medicine, General Hospital of St Pölten, St Pölten, Austria; #Department of Internal Medicine 1, Paracelsus Private Medical University, Salzburg, Austria; **Department of Internal Medicine II, Innsbruck Medical University, Innsbruck, Austria; ‡‡Department of Internal Medicine 4, Hospital Rudolfstiftung, Vienna, Austria; §§Department of Internal Medicine 4, Elisabethinen Hospital Linz, Linz, Austria; ‖‖Department of Gastroenterology, Klinikum Wels, Wels, Austria; ¶¶Department of Internal Medicine 1, General Hospital of Wiener Neustadt, Wiener Neustadt, Austria; ##Department of Internal Medicine 1, General Hospital Hietzing, Vienna, Austria; ***Department of Internal Medicine 2, Landesklinikum Mistelbach-Gänserndorf, Mistelbach, Austria; ‡‡‡Department of Internal Medicine 2, Danube Hospital, Vienna, Austria; §§§Department of Internal Medicine 4, Wilheminenspital der Stadt Wien, Vienna, Austria; ‖‖‖Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria

This article has an accompanying continuing medical education activity on page e12. Learning Objective: Upon completion of this exercise, successful learners will be able to identify the risk of recurrent venous thromboembolism in patients with inflammatory bowel disease.

See related article, Schaefer ME et al, on page 789 in *CGH*.

BACKGROUND & AIMS: Patients with inflammatory bowel disease (IBD) are at increased risk of a first venous thromboembolism (VTE), yet their risk of recurrent VTE is unknown. We performed a cohort study to determine the risk for recurrent VTE among patients with IBD compared with subjects without IBD. **METHODS:** We assessed 2811 patients with IBD for a history of VTE, recruited from outpatient clinics at 14 referral centers (June 2006–December 2008). Patients with VTE before a diagnosis of IBD or those not confirmed to have VTE, cancer, or a VTE other than deep vein thrombosis or pulmonary embolism, were excluded. Recurrence rates were compared with 1255 prospectively followed patients without IBD that had a first unprovoked VTE (not triggered by trauma, surgery, or pregnancy). The primary end point was symptomatic, objectively confirmed, recurrent VTE after discontinuation of anticoagulation therapy after a first VTE. **RESULTS:** Overall, of 116 IBD patients who had a history of first VTE, 86 were unprovoked. The probability of recurrence 5 years after discontinuation of anticoagulation therapy was higher among patients with IBD than patients without IBD (33.4%; 95% confidence interval [CI]: 21.8–45.0 vs 21.7%; 95% CI: 18.8–24.6; $P = .01$). After adjustment for potential confounders, IBD was an independent risk factor of recurrence (hazard ratio = 2.5; 95% CI: 1.4–4.2; $P = .001$). **CONCLUSIONS: Patients with IBD are at an increased risk of recurrent VTE compared to patients without IBD.**

Keywords: Crohn's Disease; Ulcerative Colitis; Active Disease; Provoked Thrombosis.

Venous thromboembolism (VTE) represents a relevant cause of morbidity and mortality among patients with inflammatory bowel disease (IBD).[1–11] Compared to non-IBD subjects, patients with IBD are at a 3- to 4-fold increased risk of VTE[5,6] and are affected by VTE at a younger age.[4,5] Because VTE is more frequent among IBD patients, increased mortality rates from pulmonary embolism (PE) have been reported in retrospective studies,[3,7,8] in a meta-analysis of population-based inception cohort studies of patients with ulcerative colitis,[9] as well as in a population-based study of hospitalized IBD patients.[10] Deep venous thrombosis (DVT) of the lower and upper limbs and PE are the most common locations of VTE in IBD patients, but also unusual sites of thrombosis, including the cerebrovascular, portal, mesenteric, or retinal veins, have been described.[11] Interestingly, the increased risk of VTE seems to be a distinct feature of IBD, as it was not found in rheumatoid arthritis, exemplifying another chronic inflammatory disease, or in celiac disease, as another chronic bowel disease.[6] The underlying pathomechanism of VTE in IBD is not completely understood, but appears to be multifactorial, with acquired risk factors playing the most relevant role.[11] Active

Abbreviations used in this paper: BMI, body mass index; CI, confidence interval; DVT, deep venous thrombosis; IBD, inflammatory bowel disease; PE, pulmonary embolism; VTE, venous thromboembolism.

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disease, fistulas, and abscesses are present in the majority of IBD patients at the time of the thromboembolic event.[3,6,8,12–14] Furthermore, IBD patients are more often exposed to disease-related risk factors that may provoke VTE, including surgery, immobilization, dehydration, and central venous catheters.

The major complications of VTE are death and recurrence of thromboembolism,[15,16] which occurs in 5%–10% of non-IBD patients per year and is fatal in approximately 5%.[15] Recurrent VTE can be prevented by anticoagulant treatment,[17–19] which can cause severe or fatal bleeding.[20] Thus, choosing the optimal duration of prophylaxis for an individual patient entails balancing the risk of bleeding against the risk of recurrent VTE. In non-IBD patients, several factors associated with an increased risk of recurrence, including male sex, history of previous VTE, cancer, antiphospholipid syndrome, natural coagulation inhibitor deficiency, hyperhomocysteinemia, or high clotting factor levels have been identified.[21–28] However, in IBD patients, the recurrence rate and risk factors of recurrence are widely unknown.[6–8]

We hypothesized that IBD patients are at increased risk of recurrent VTE. Our primary objectives were to evaluate the rate and risk factors of recurrent VTE in a large cohort of IBD patients and to compare the results to recurrence rates among patients without IBD.

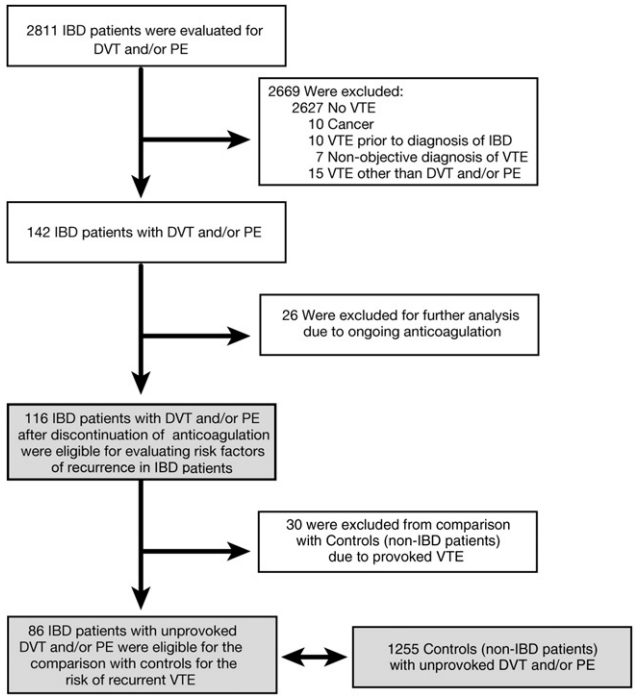

Figure 1. Flowchart of patients with inflammatory bowel disease (IBD) included and excluded in the study. DVT, deep venous thrombosis; IBD, inflammatory bowel disease; PE, pulmonary embolism; VTE, venous thromboembolism.

Methods

Study Design

The study was performed as a cohort study that included 2 cohorts. One cohort consisted of IBD patients with first VTE. This cohort was used to evaluate the rate and risk factors of recurrent VTE in IBD patients. The second cohort consisted of control patients with first VTE but without IBD. This cohort was used together with the first cohort for the comparison of recurrence rates of VTE between IBD and non-IBD patients. The acquisition of both cohorts will be described in detail here.[29]

IBD Patients

This part of the study was designed as a multicenter cohort study with 14 participating Austrian centers specializing in the treatment of patients with IBD. Data of IBD patients attending outpatient clinics of these referral centers who were older than 18 years with an established diagnosis of IBD (based on clinical, endoscopic, histological, and radiological criteria according to European Crohn's and Colitis Organisation (ECCO) guidelines),[30,31] were retrospectively evaluated for a history of VTE that had occurred after diagnosis of IBD. Only patients with DVT of the lower and upper limbs and/or PE were included in the analysis for recurrence of VTE because other types of thromboses might have different rates of thrombosis recurrence. DVT and PE had to be objectively confirmed by compression ultrasound or venography and by spiral computed tomography or ventilation/perfusion lung scanning, respectively.[32,33] Between June 1, 2006 and December 31, 2008, 2811 consecutive IBD patients were evaluated. One thousand four hundred and nineteen (50.5%) patients were female; 1802 (64.1%) had Crohn's disease, 945 (33.6%) had ulcerative colitis, and 64 (2.3%) had indeterminate colitis. A flowchart for patients included and excluded in the study is presented in Figure 1. Patients were excluded for VTE before diagnosis of IBD (n = 10), cancer (n = 10), a VTE not confirmed by objective imaging techniques (n = 7), or VTE other than DVT and/or PE, including thrombosis of the portal vein (n = 4), superior mesenteric vein (n = 2), splenic vein (n = 1), internal jugular vein (n = 1), or sinus vein (n = 7). Patients with both DVT and PE were categorized as having PE. VTEs occurring secondary to trauma, surgery, or pregnancy were classified as "provoked VTEs," all other VTE were classified as "unprovoked VTEs." All patients were treated with standard heparin or low-molecular-weight heparin at therapeutic dosages for the acute event.

IBD- and VTE-related data were collected from a standardized questionnaire provided to the patient by the treating physician or via telephone interview by the study coordinator (AS). The information of the patient was double-checked by reviewing patient charts and missing data were added. The study coordinator visited each study center at least once and the patients' records were

reviewed for accuracy and completeness by 2 investigators (GN and AS). IBD-related parameters of interest included type of IBD, age at diagnosis, disease extent and behavior, intestinal IBD-related surgery, medication, smoking habits, disease activity, and fistula and abscess at the time of the first and recurrent thromboembolic event. Extent of IBD and disease behavior were classified according to the Montreal classification.[34] Active Crohn's disease at the time of first and recurrent VTE was defined by a Harvey–Bradshaw Index of >4[35] and active ulcerative colitis was defined by a simple clinical colitis activity index of ≥ 2.5.[36–38] IBD-related surgery was defined as bowel resection only. A smoker was defined as a patient who smoked at least 7 cigarettes weekly for at least 1 year.[39] VTE-related parameters, such as type of the first and recurrent thrombosis, age at time of the thromboembolic event, time when anticoagulation was discontinued, observation time (time from end of anticoagulation to recurrent VTE or end of follow up, respectively), body mass index (BMI; calculated as body weight in kilograms divided by body height in meters squared), oral contraceptive use at the time of VTE, and results of a laboratory thrombophilia workup, if available, were collected in a standardized file for information about the VTE in accordance with control patients. Data about type and exact location of thrombosis, age at VTE, provocative factors, and laboratory results were collected retrospectively from chart review. In case of equivocal diagnosis of first or recurrent venous thrombosis, all relevant medical charts were reviewed by an independent expert who was unaware of all other patient's characteristics, and who adjudicated on the final diagnosis of VTE. The information about time when anticoagulation was discontinued and oral contraceptive use was provided by the patient.

The day of discontinuation of anticoagulant therapy was defined as the day of start of observation time. The study was approved by all responsible local Ethics Committees. All patients gave informed consent.

Control Patients

The cohort of control patients consisted of patients with a first VTE but without evidence of IBD. These patients attended the outpatient clinics of 4 participating thrombosis centers in Vienna, Austria, and were included consecutively from July 1992 to May 2008 in the Austrian Study on Recurrent Thromboembolism (AUREC), which is an ongoing, prospective cohort study. The design of the study has been published in detail previously.[22] Briefly, patients older than 18 years were eligible if they had been treated with oral anticoagulants for at least 3 months after a first episode of VTE. VTE had to be objectively confirmed by compression ultrasound or venography and by spiral computed tomography or ventilation/perfusion lung scanning.[32,33] Patients with both DVT and PE were categorized as having PE. Patients were excluded for the following reasons: VTE provoked by surgery, trauma, or pregnancy; deficiency of antithrombin, protein C, or protein S; presence of a lupus anticoagulant or cancer; or a requirement for long-term antithrombotic treatment (including aspirin) for reasons other than venous thrombosis (eg, atrial fibrillation). Patients entered the study on the day of discontinuation of oral anticoagulant therapy (start of observation time) and were followed-up in regular intervals.

Study End Point

The primary end point in both patients with and without IBD was recurrence of symptomatic DVT and/or PE after discontinuation of anticoagulation. Recurrent VTE had to be confirmed by venography, compression ultrasound, ventilation-perfusion lung scanning, spiral computed tomography of the lung, or autopsy. Patients with both DVT and PE at recurrence were categorized as having PE.

Laboratory Analyses

Venous blood was obtained in fasting state after anticoagulant treatment had been stopped for at least 2 weeks. Routine laboratory methods were used to identify antithrombin, protein C, and protein S. Screening for factor V Leiden and factor II G20210A was carried out on genomic DNA.[40,41] Factor VIII was measured by 1-step clotting assays with the use of factor VIII–deficient plasma obtained from Immuno Baxter (Baxter Healthcare, Vienna, Austria) and a fully automated coagulation analyzer (CA 6000; Sysmex, Kobe, Japan). Presence of lupus anticoagulant was established on the basis of the criteria of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis.[42]

Statistical Analysis

SPSS 15.0.1 software (SPSS Inc, Chicago, IL) was used for statistical analysis. Data are presented as numbers, percentages, and median values with interquartile range, respectively. Differences between groups were analyzed using the χ^2 test for categorical data and the Mann-Whitney *U* test for continuous data. Survival time methods were used to analyze the time to recurrent VTE among patients with a subsequent episode (uncensored observations) or duration of follow-up among patients without recurrence (censored observations). Data on patients who were lost to follow-up or who died were censored at the time of the last follow-up. The probability of recurrence of VTE was estimated according to the method of Kaplan and Meier.[43] Cox proportional hazard regression analysis was used to explore the effects of potential confounders on risk of recurrent VTE. Data were adjusted for age, sex, duration of anticoagulation, high BMI (>25), presence of factor V Leiden or the prothrombin G20210A mutation, and high factor VIII

levels (>234 IU/dL).[26] Patients with missing data were not included in the regression model. Validity of the proportional hazards assumption was tested by plotting a log-minus-log survival plot. In IBD patients, a Cox proportional hazard regression analysis was also used to evaluate the impact of predictors of recurrent VTE. Those risk factors with P values <.1 in the univariate analysis were included into the multivariate model. The results were expressed as hazard ratios with corresponding 95% confidence interval (CI). P values <.05 were considered as statistically significant.

For sample size calculation, we assumed, from previously published data of the Austrian Study on Recurrent Thromboembolism, a recurrence rate of unprovoked VTE of about 8% in non-IBD patients at 30 months.[22,26] Furthermore, from our own previous study, we knew that 21% of IBD patients with a previous thromboembolism had at least 1 recurrent VTE. Based on these assumptions, we primarily calculated that we needed 112 patients in each group. Because the ongoing Austrian Study on Recurrent Thromboembolism study includes >1200 non-IBD patients currently, which is 10-fold higher than the number needed for the present study, we further calculated that a smaller-sized IBD group of 62 patients would even suffice to detect a difference between the 2 groups at an α error of .05 and a β error of .8.[44]

Results

Patient Characteristics

One hundred and forty-two patients with DVT and/or PE after diagnosis of IBD were identified. Twenty-six patients were excluded because of ongoing anticoagulation, leaving 116 patients for further analysis. Table 1 shows the baseline characteristics of these patients. Anticoagulation was discontinued after a median time of 6.0 (interquartile range, 3.2−8.3) months. Median observation time after discontinuation of anticoagulation was 41.8 (interquartile range, 9.7−86.8) months. In 30 (25.9%) patients, VTE was provoked by surgery or trauma.

Risk Factors of Recurrence in IBD Patients

For evaluation of risk factors for recurrent VTE in IBD patients, those 116 patients who had discontinued anticoagulation after first DVT and/or PE were included. Thirty-five of these 116 (30.2%; recurrence rate 6.14% per patient year) IBD patients had recurrent VTE (22 DVT and 13 PE). Twenty-five patients had Crohn's disease and 10 had ulcerative colitis. According to Kaplan–Meier estimates, the cumulative probability of recurrence at 5 years after discontinuation of anticoagulation was 29.2% (95% CI: 19.8%–38.6%).

VTE recurred in 8 of 30 (26.7%; 4.72% per patient year) patients with a first provoked VTE and in 27 of 86 (31.4%; 6.73% per patient year) patients with a first unprovoked VTE. According to Kaplan–Meier estimates, the probabil-

Table 1. Baseline Characteristics of 116 Inflammatory Bowel Disease Patients With a First Venous Thromboembolism (Deep Venous Thrombosis and/or Pulmonary Embolism) Who Stopped Anticoagulation

Characteristic	
Age at first VTE (*y*), median (IQR)	42.1 (33.2–55.2)
Female, n (%)	64 (55.2)
VTE provoked by surgery/trauma, n (%)	30 (25.9)
Location of VTE, n (%)	
Proximal leg veins	49 (42.2)
Distal leg veins	17 (14.7)
Arm veins[a]	4 (3.4)
Pulmonary embolism	46 (39.7)
Duration of anticoagulation (*mo*), median (IQR)	6 (3.2–8.3)
Observation time (*mo*), median (IQR)	41.8 (9.7–90.5)
Smokers at VTE, n (%)	38 (34.2)
Missing, n	5
OC use at VTE, n (%)	20 (32.3)
Missing, n	2
BMI ≤25, n (%)	72 (63.2)
Missing, n	2
Factor V Leiden, n (%)	14 (16.7)
Missing, n	32
Factor II G20210A, n (%)	2 (2.5)
Missing, n	37
High factor VIII, n (%)	10 (17.9)
Missing, n	60
Characteristics of IBD, n (%)	
Active disease at first VTE	55 (54.5)
Missing, n	15
Crohn's disease, n (%)	77 (66.4)
Internal fistula/abscess at first VTE, n	7
Perianal fistula/abscess at first VTE, n	10
Location, n (%)	
L1	18 (23.4)
L2	9 (11.7)
L3	31 (40.3)
+L4	19 (24.7)
Behavior, n (%)	
B1	17 (22.1)
B2	33 (42.9)
B3	27 (35.1)
Perianal disease, n (%)	29 (37.7)
CD-related surgery, n (%)	46 (59.7)
Ulcerative colitis, n (%)	39 (33.6)
Disease extent, n (%)	
Proctitis	3 (7.7)
Left-sided colitis	11 (28.2)
Extensive colitis	25 (64.1)
Previous surgery	1 (2.6)
Medication at first VTE, n (%)	
5-Aminosalicylic acid	63 (60)
Corticosteroids	47 (44.8)
Azathioprine/6-MP	19 (18.1)
Methotrexate	1 (1)
Infliximab	1 (1)
Missing, n	11

NOTE. The number of missing data is given if data were not completely available. The calculation of percentages was referred to available data. BMI, body mass index (calculated as kg/m^2); CD, Crohn's disease; DVT, deep vein thrombosis; IQR, interquartile range; 6-MP, 6-mercaptopurine; OC, oral contraceptive; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]None of the arm vein thrombosis was associated with a central venous line.

Table 2. Impact of Potential Risk Factors on the Recurrence of Venous Thromboembolism in 116 Inflammatory Bowel Disease Patients With First Deep Vein Thrombosis and/or Pulmonary Embolism

	Hazard ratio (95% CI)			
	Univariate	*P* value	Multivariate	*P* value
Age at first VTE	1.02 (1.001–1.05)	.044	1.03 (1.002–1.05)	.031
Male sex	2.8 (1.4–5.6)	.003	3.0 (1.5–6.0)	.003
Distal DVT vs	Ref.			
Proximal DVT	1.7 (0.6–5.2)	.32	—	
Pulmonary embolism	1.4 (0.5–4.5)	.53	—	
Unprovoked first VTE	1.4 (0.6–3.1)	.38	—	
Factor V Leiden	1.8 (0.8–4.0)	.16	—	
Prothrombin G20210 mutation	3.1 (0.4–23.5)	.27	—	
High factor VIII	0.7 (0.2–2.2)	.57	—	
Duration of anticoagulation	1.02 (0.98–1.06)	.39	—	
BMI >25	1.5 (0.8–3.0)	.25	—	
CD vs UC	1.1 (0.5–2.3)	.77	—	

NOTE. A Cox proportional hazards model was used. Those variables with a *P* value <.1 in the univariate analysis were included in the multivariate model. BMI, body mass index (calculated as kg/m^2); CD, Crohn's disease; CI, confidence interval; DVT, deep vein thrombosis; IBD, inflammatory bowel disease; PE, pulmonary embolism; UC, ulcerative colitis; VTE, venous thromboembolism.

ity of recurrence after 5 years was 17.4% (95% CI: 1.7%–33.1%) among IBD patients with provoked first VTE and was 33.4% (95% CI: 21.8%–45.0%) among patients with unprovoked VTE ($P = .40$). The majority of recurrent events were unprovoked, as only 6 of 35 patients (17.1%) had recurrence provoked by surgery or trauma. However, 4 of these patients did not receive thromboprophylaxis. Nineteen (54.3%) patients had active disease at the time of recurrent VTE.

To evaluate risk factors of recurrent VTE in IBD patients, we entered potential risk factors of recurrence as displayed in Table 2 into a Cox proportional hazards model. In a multivariate model, only male sex (hazard ratio = 3.0; 95% CI: 1.5–6.0; $P = .003$) and age at first VTE (hazard ratio = 1.03; 95% CI: 1.002–1.05; $P = .031$) were associated with a significantly increased risk of recurrent VTE. Unprovoked first VTE, factor V Leiden, location of VTE (proximal DVT and PE vs distal DVT), type of IBD (Crohn's disease vs ulcerative colitis), BMI, duration of anticoagulation, or high factor VIII were not independent predictors of the recurrence risk.

Risk of Recurrent VTE in Patients With and Without IBD

We compared the risk of recurrent VTE in IBD and non-IBD patients. As the patients without IBD had only unprovoked VTE, we only included 86 IBD patients with unprovoked first VTE in this comparison. Table 3 shows the characteristics of patients with unprovoked VTE with and without IBD. Compared to controls, patients with IBD tended to be younger, had a lower BMI, a shorter duration of anticoagulation, more often a thrombosis of the proximal leg veins, and higher factor VIII levels. Carriers of factor V Leiden tended to be less frequent among IBD patients than among controls. No difference between both groups was seen with regard to male-to-female ratio, proportion of smokers, or oral contraceptive users at the time of the first VTE.

VTE recurred in 27 of 86 (31.4%; 6.73% per patient year) IBD patients with a first unprovoked VTE and in 204 (16.3%; 4.63% per patient year) of the 1255 non-IBD patients. According to Kaplan–Meier estimates, the probability of recurrence after 5 years was 33.4% (95% CI: 21.8%–45.0%) among IBD patients with unprovoked first VTE and 21.7% (95% CI: 18.8%–24.6%) among patients without IBD ($P = .01$) (Figure 2).

When IBD was analyzed as a categorical variable in a Cox proportional-hazards model, the relative risk of recurrence compared to non-IBD patients was 1.7 (95% CI: 1.1–2.5; $P = .01$). After adjustment for age, sex, factor V Leiden, prothrombin G20210A mutation, high factor VIII, duration of anticoagulation, and BMI, the association between IBD and risk of recurrence was even higher, with a relative risk of 2.5 (95% CI: 1.4–4.2; $P = .001$) (see also Supplementary Table 1).

Discussion

Our study shows that IBD patients are at high risk of recurrent thrombosis after a first VTE. Five years after discontinuation of anticoagulant treatment, the probability of recurrence was 29%. This rate was higher than in other studies of IBD patients, in which recurrence rates ranged between 13% and 21%.[6–8] However, results of these former studies had been limited by small patient numbers and methodological shortcomings, including lack of objective diagnosis of first and recurrent VTE and of a defined observation time.

We identified 2 factors associated with the risk of recurrence in IBD patients. Male sex was a strong predictor and conferred a 3-fold risk increased risk as compared with women. This result is in good agreement with find-

Table 3. Characteristics of Patients With and Without Inflammatory Bowel Disease and a First Unprovoked Venous Thromboembolism

	IBD patients (n = 86)	Non-IBD patients (n = 1255)	*P* value
Age (*y*), median (IQR)	43.9 (35.6–56.2)	48.2 (36.7–60.8)	.09
Female, n (%)	44 (51.2)	672 (53.5)	.74
Location of first VTE, n (%)			.03
Proximal leg veins	42 (48.8)	417 (33.2)	
Distal leg veins	10 (11.6)	218 (17.4)	
Axillary veins	1 (1.2)	16 (1.3)	
Pulmonary embolism	33 (38.4)	604 (48.1)	
Duration of anticoagulation (*mo*), median (IQR)	6.1 (3.4–8.5)	6.5 (6–7.9)	.002
Observation time (*mo*), median (IQR)	37.2 (8.2–84.1)	29.1 (10.5–61.6)	.29
Smoker at the time of first VTE, n (%)	27 (32.5)	377 (31.2)	.81
Missing, n	3	45	
OC intake at the time of first VTE, n (%)	13 (31)	288 (43.2)	.15
Missing, n	2	5	
BMI ≥25, n (%)	33 (38.8)	770 (62.6)	.001
Missing, n	1	25	
Factor V Leiden, n (%)	10 (16.1)	325 (26.1)	.10
Missing, n	24	11	
Factor II G20210A, n (%)	1 (1.7)	75 (6)	.25
Missing, n	27	12	
High factor VIII, n (%)	8 (18.6)	93 (7.8)	.02
Missing, n	43	62	

NOTE. Number of missing data is given if data were not completely available. The calculation of percentages was referred to available data. BMI, body mass index (calculated as kg/m^2); IBD, inflammatory bowel disease; OC, oral contraceptive; VTE, venous thromboembolism.

ings in non-IBD patients with VTE.[22,23] Interestingly, no explanation for the sex difference with regard to recurrence risk has yet been found. In IBD patients, age at first VTE was also significantly associated with an increased risk of recurrence. This is in contrast to findings in non-IBD patients, in whom the risk of recurrence is independent of age.[45] Other factors, including location of first VTE; absence or presence of transient risk factors, such as surgery or trauma at first VTE; factor V Leiden; or obesity, were not independent predictors of the recurrence risk in IBD patients in our model.[46,47] However, because of the limited number of IBD patients and hence low power, an association between these factors and recurrence risk cannot be excluded. With regard to IBD-specific factors, type of IBD at the time of the first VTE was not related to recurrence risk. Coagulation factor VIII, which is a strong predictor of recurrence in non-IBD patients,[26] was also not associated with recurrence risk in IBD patients. Factor VIII is an acute-phase protein and, thus, frequently increased in patients with IBD. However, according to the current pathophysiologic concept, only consistently elevated plasma VIII levels, which can be genetically determined, confer an increased thrombotic risk.[26]

Our study was the first to compare VTE recurrence rates of patients with IBD to those without IBD. Control patients without IBD had unprovoked VTE only and, for adequate comparison, we analyzed IBD patients with provoked and unprovoked VTE separately. The risk of recurrence in IBD patients with unprovoked VTE was significantly higher than in non-IBD patients (probability of recurrence after 5 years was 33% vs 22%). Notably, risk of recurrence in IBD patients with VTE provoked by surgery was substantial (17% after 5 years) and was similar to non-IBD patients with unprovoked thrombosis.

Six patients with IBD had recurrence after surgery or trauma, but only 2 patients received heparin thromboprophylaxis at that time. Patients with IBD with a history of VTE are at a particularly high thrombotic risk, and adequate thromboprophylaxis should be provided to these patients. Furthermore, half of the IBD patients had active disease at the time of recurrent VTE. Thromboprophylactic regimens during flares of active disease should be established for IBD patients with a history of VTE.

Patients with and without IBD differed with regard to the presence of important thrombotic risk factors. IBD patients tended to be younger, had a lower BMI, more often a proximal DVT, and higher factor VIII levels. Furthermore, IBD patients tended to be less frequent carriers of factor V Leiden. However, IBD was an independent risk factor of recurrence, as in the multivariate analysis the risk remained significantly increased (hazard ratio = 2.5) even after adjustment for these factors. Thus, the increased recurrence risk in IBD patients is most likely a result of IBD-specific factors, disease-related inflammation appearing to play the most relevant role. The inflammatory state in IBD patients has been related to several alterations of the coagulation system and a hypercoagulable state.[11] For example, markers of hemostatic system activation such as prothrombin fragment

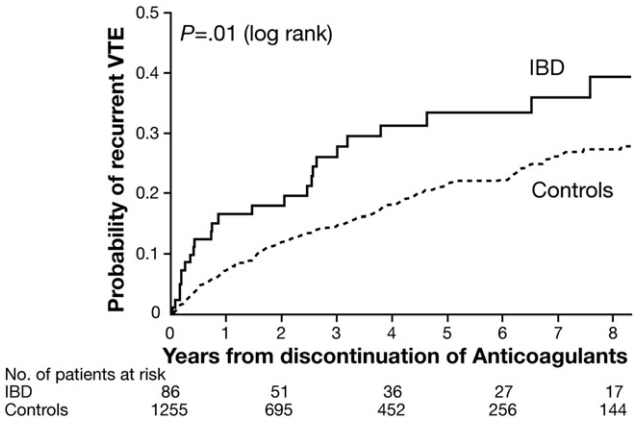

Figure 2. Kaplan–Meier estimates of recurrent venous thromboembolism (VTE) after a first unprovoked venous thromboembolism in patients with inflammatory bowel disease (IBD) and without IBD (Controls).

1 + 2 and thrombin-antithrombin complex are increased and fibrinolytic activity is reduced, particularly in IBD patients with active disease.[11] Furthermore, platelets circulate in an activated state in IBD and may also contribute to the increased risk of VTE.[48] The association between inflammation and venous thrombotic events has been confirmed very recently in a large cohort study of non-IBD patients, which indicated that a high level of C-reactive protein and therefore inflammation may be a risk factor for VTE.[49]

Some limitations of our study warrant comment. First, the data collection was different between both cohorts. For IBD patients, data collection was performed before the study (retrospective) and for non-IBD patients, data collection was performed after the start of the study (prospective). Because of the retrospective design in the IBD cohort, we may have missed some patients with VTE and recurrent VTE, respectively, which could reduce the rate of recurrent VTE in IBD patients. Second, IBD patients with more severe and complicated disease are more likely to be treated in referral centers. This can cause a selection bias. Because our data were collected from patients of such centers, it is possible that we included patients with more severe disease and that the generalizability of our findings to population-based results is limited. But one has to keep in mind that the non-IBD patients were treated in thrombosis referral centers. Third, although the present study is one of the largest cohorts, the number of IBD patients with thrombotic events is limited. Fourth, thrombophilia screening has not been performed in all patients, so we have incomplete information. Patients with IBD and a natural inhibitor deficiency or lupus anticoagulant were not excluded, but these were exclusion criteria in our study on patients without IBD. We believe that confounding with regard to recurrence in IBD patients is unlikely because the prevalence of these defects in the cohort of IBD patients was very low (<1%). Recommendations with regard to duration of anticoagulation after the first VTE was left to the discretion of the treating physician. Indeed, 30 patients could not have been included because they were on long-term anticoagulation. It could be surmised that these patients were regarded at particular high-risk and recurrence rates in our study would have been even higher if these patients would have been off anticoagulation and included in our study. Thromboprophylaxis in high-risk situation of VTE was performed according to national and international guidelines and did not follow a protocol that was specific for the study.

What are the clinical implications of our findings? Patients with IBD and VTE are at high risk of recurrent VTE. Recurrence can be prevented by anticoagulant therapy, although at the price of increased bleeding risk. Deciding on the optimal duration of anticoagulation entails balancing the risk of recurrence and risk of bleeding during anticoagulation. In non-IBD patients, discontinuation of anticoagulation after 3 months is recommended for patients with VTE secondary to a transient risk factor, such as surgery or trauma.[19] In these patients, the recurrence risk is low. In contrast, prolonged anticoagulation (longer than 3 months) should be considered in non-IBD patients with VTE in the absence of a provoking factor because the risk of fatal recurrent VTE outweighs the risk of fatal bleeding.[19] This is especially true in patients with proximal DVT or PE (recurrence risk about 30% after 5 years).[19] In our cohort, risk of recurrence in IBD patients with unprovoked VTE was even significantly higher than in non-IBD patients (33.4% after 5 years). Thus, these patients should be particularly considered for prolonged anticoagulation after a first VTE. However, it needs to be stressed that risk of bleeding during vitamin K antagonist treatment is unknown in IBD patients and might be higher than in non-IBD patients. Thus, although heparin has been reported to have a low rate of bleeding complications in clinical trials in which it was used as treatment of active ulcerative colitis,[50] more data on the bleeding risk during anticoagulation are needed to estimate the benefit of prolonged anticoagulant treatment in IBD patients. In case of prolonged anticoagulation in an individual IBD patient, risk-to-benefit ratio of continuing such treatment should be reassessed at periodical intervals.[19] Furthermore, it is noteworthy that half of the IBD patients had active disease at the time of recurrent VTE. Thromboprophylactic regimens during flares of active disease should be considered especially for IBD patients with a history of VTE. The association between active disease and VTE has been reported recently in a cohort study.[14] Effective therapy for active IBD, therefore, might also help to reduce thrombotic risk.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of

Gastroenterology at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2010.05.026.

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Reprint requests

Address requests for reprints to: Gottfried Novacek, MD, Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Waehringer Guertel 18-20, A-1090 Vienna, Austria. e-mail: gottfried.novacek@meduniwien.ac.at; fax: +43 (1) 40400 4735.

Conflicts of interest

The authors disclose no conflicts.

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Supplementary Table 1. Number of IBD and Non-IBD Patients Diagnosed With First Venous Thromboembolism in Different Time Periods

	IBD patients (n = 86)		Non-IBD patients (n = 1255)	
Time period	n	%	n	%
<1995	15	17.4	134	10.7
1995–1999	19	22.1	338	26.9
2000–2004	30	34.9	512	40.8
≥2005	22	25.6	271	21.6

NOTE. Time point of first VTE was not different between IBD and non-IBD patients (χ^2 test; $P = .15$).
IBD, inflammatory bowel disease.