INTRODUCTION

Venous thromboembolic events are a relevant cause of morbidity and mortality in patients with inflammatory bowel disease (IBD).1-10 The risk of venous thromboembolism (VTE) among IBD patients is 2- to 4-fold increased compared to non-IBD subjects.3,4,8,9 The reason for that finding is not completely understood, but acquired risk factors such as active disease, fistulas, and abscesses appear to play the most relevant role.4,9-11 Surgery, immobilization, dehydration, and central venous catheters can in addition raise the risk of VTE.10,11 Regardless of such disease-related factors the risk of VTE increases with age.12 Deep venous thrombosis (DVT) of the lower and upper limbs and pulmonary emboli (PE) are the most common locations of VTE in the general population as well as in IBD patients.10-12 Unusual sites of thrombosis include cerebrovascular, portal, mesenteric, or retinal veins.10,11

RECURRENT VTE

The major complications of VTE are death and recurrence,13,14 which occurs in 5%-10% of non-IBD patients per year and is fatal in approximately 5%.13 Standard treatment of acute VTE is heparin followed by vitamin K antagonists for several months.15 This anticoagulant treatment can prevent recurrent VTE,15-18 but can cause severe or fatal bleeding.19 Thus, in an individual patient the risk of recurrent VTE should be balanced against the risk of bleeding.15 Several clinical and laboratory risk factors for recurrent VTE have been described. However, prediction of recurrence in an individual patient still remains a challenge.15 This risk is especially high in patients with unprovoked first VTE (without temporary risk factors such as surgery, trauma, or pregnancy).15 Men have a higher risk then women.15,20 Female hormone intake is not only a risk factor for first VTE but also for recurrence among women who continue hormone intake after first thrombosis.15 The risk of recurrent VTE is also predicted by the location of first VTE and is highest in patients with proximal DVT and PE.15 Patients with cancer have a high risk of recurrence, despite the use of anticoagulation treatment.15 Further risk factors...
are multiple episodes of thrombosis in the history, overweight, residual vein thrombosis and antiphospholipid syndrome. These clinical features as well as the most important laboratory parameters associated with increased risk of recurrent VTE are listed in Table 1. However, the relevance of laboratory screening for thrombophilia seems to be limited. Amongst others due to the fact that one third of patients with recurrent unprovoked VTE have normal test results and a negative finding from thrombophilia testing could therefore lead to a false sense of safety for patients. In a large prospective cohort study patients with a first unprovoked VTE only patient’s sex, thrombosis location, and concentration of D-dimer were related to increased risk of recurrence. On the basis of these variables the individual risk of recurrent VTE can be estimated by the use of an online risk calculator. However, this prediction model needs to be validated.

### THE RISK OF RECURRENT VTE IN PATIENTS WITH IBD

In IBD patients the recurrence rate of VTE and risk factors of recurrence have been widely unknown. In a recently published large cohort study we could show that IBD is an independent risk factor for recurrent VTE and, thus, IBD patients are at high risk of recurrent thrombosis after a first venous thromboembolic event. We evaluated 2811 patients with IBD (recruited from outpatients clinics at 14 Austrian referral centers) and found 116 patients with a history of DVT and/or PE. The primary end point was objectively confirmed recurrence of symptomatic DVT and/or PE after discontinuation of anticoagulation. 35 of the 116 IBD patients with first VTE (30%; recurrence rate 6% per patient year) had recurrence (22 DVT and 13 PE). The cumulative probability of recurrence at 5 years after discontinuation was 29%. This was lower in those 30 patients with first VTE provoked by surgery or trauma (17%) and higher in 86 patients with first unprovoked VTE (33.4%). In a multivariate model, only male sex and age at first VTE were associated with a significantly increased risk of recurrent VTE.

Recurrence rates of IBD patients were compared with the results of 1255 prospectively followed non-IBD patients with a first unprovoked VTE. Compared to controls, patients with IBD tended to be younger, had a shorter duration of anticoagulation, and more often a thrombosis of the proximal leg veins. The probability of recurrence after 5 years was higher among IBD patients with unprovoked first VTE (33%) than among patients without IBD (22%). After adjustment for potential confounders, IBD was an independent risk factor of recurrent VTE (hazard ratio = 2.5; 95% CI: 1.4-4.2; P = 0.001).

### DISCUSSION

How should we try to prevent recurrent venous thromboembolism in IBD patients? Recurrence of VTE can be almost wholly prevented by anticoagulant therapy, but at the price of an increased bleeding risk. Thus, assessment of the risk of recurrence is important to balance the recurrence risk and the risk of bleeding during anticoagulation. In non-IBD patients with VTE

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SECONDARY TO A TRANSIENT RISK FACTOR SUCH AS SURGERY OR TRAUMA, DISCONTINUATION OF ANTICOAGULATION AFTER THREE MONTHS IS RECOMMENDED DUE TO THE LOW RECURRENCE RISK. IN CONTRAST, ANTICOAGULATION FOR MORE THAN THREE MONTHS SHOULD BE CONSIDERED IN NON-IBD PATIENTS WITH VTE IN THE ABSENCE OF A PROVOKING FACTOR SINCE THE RISK OF FATAL RECURRENT VTE OUTWEIGHS THE RISK OF FATAL BLEEDING. IN OUR RECENTLY PUBLISHED COHORT STUDY WE COULD SHOW THAT IBD IS AN INDEPENDENT RISK FACTOR FOR RECURRENT VTE. Thus, the risk of recurrence in IBD patients with unprovoked VTE was even significantly higher than in non-IBD patients (33% after 5 years). These IBD patients, therefore, should be particularly considered for prolonged anticoagulation (>3 months) after a first VTE. However, bleeding is a common symptom during acute flares of IBD independent from anticoagulation treatment. The risk of bleedings during vitamin K antagonist treatment is unknown in IBD patients and might be higher than in non-IBD patients. Thus, more data on the bleeding risk during anticoagulation are needed to estimate the benefit of prolonged anticoagulant treatment in IBD patients. However, it is likely that IBD is a varying thrombosis risk factor dependent on the clinical situation such as acute flares. For example, half of the IBD patients had active disease at the time of recurrent VTE. Thromboprophylactic regimens during flares of active disease should especially be considered for IBD patients with a history of VTE. The association between active disease and VTE has been reported recently in a cohort study. The relative risk at the time of flare was higher during ambulatory periods than during hospitalised periods. However, the absolute risk of VTE was highest in hospitalised patients with active disease. Beside inflammatory activity, also fistulas and abscesses as well as surgery, immobilisation, dehydration and central venous catheters can enhance the risk for thrombosis (Table 2). Effective therapy of active IBD and complications, therefore, might also help to reduce the risk for thrombosis.

Table 2.
Clinical IBD-related features associated with increased risk of venous thrombosis (maybe also associated with increased risk of recurrent thrombosis)

- Acute flare
- Fistulas/abscess
- Surgery
- Hospitalisation
- Immobilisation
- Dehydration
- Central venous catheter

Table 3.
Core messages about IBD and venous thromboembolism (VTE)

- IBD is a risk factor for first and recurrent VTE.
- Inflammation appears to be the most relevant clinical IBD-related feature associated with increased risk of VTE.
- Thromboprophylaxis during flares of active disease should especially be considered for IBD patients with a history of VTE as well as for those who are hospitalised.
- IBD patients with first unprovoked VTE should be considered for prolonged (>3 months) anticoagulation.
- The risk of bleeding might be increased in IBD patients during anticoagulation treatment.

References
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