

Risk of Recurrent Venous Thromboembolism in Autoimmune Diseases: A Systematic Review of the Literature

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Abstract

Despite an abundance of literature on the risk of a first venous thromboembolic event (VTE) in autoimmune diseases, specific recommendations about managing VTE in autoimmune diseases are lacking. This article aimed to collect evidence on the risk of recurrent VTE in patients with autoimmune diseases. The authors searched PubMed/Embase for studies including patients with VTE and autoimmune diseases as an exposure or studies including patients with autoimmune diseases in which recurrent VTE was one of the outcomes. Eleven articles were selected from 4,739 unique abstracts. Of the 11 studies, 3 reported time-dependent rates. Two studies collected rates of recurrence in Behcet's disease, reporting a 5-year recurrence risk between 35 and 40%. However, the 5-year recurrence risk was lower than 10% in patients treated with immunosuppressant medication, while two studies suggested frequent recurrence in patients on only anticoagulant therapy. The other study reporting time-dependent incidence concerned patients with inflammatory bowel disease and index VTE. The 5-year risk of recurrent VTE was 33.4%, yielding a hazard ratio of 1.7 versus controls. All studies were retrospective and therefore risk may overestimate recurrence risk in comparison with known prospective cohort studies. There are insufficient data to make confident recommendations about the management of recurrent VTE prevention in patients with autoimmune diseases in general. The overall VTE risk profile, lower effectiveness of anticoagulants, and the observation that immunosuppression lowered risk of recurrence in patients with Behcet's disease seem to warrant immunosuppressant therapy over anticoagulation as a first consideration when preventing VTE recurrence in these patients.

Keywords

- ▶ venous thromboembolism
- ▶ autoimmune disease
- ▶ rheumatoid arthritis
- ▶ risk

There is an abundance of literature^{1–21} demonstrating that chronic inflammatory diseases are associated with an increased risk of venous thrombotic events (VTEs). Across the spectrum of autoimmune diseases, the risk is elevated threefold,¹⁹ and the relative risks seem to be higher in patients with systemic

autoimmune disease. However, to our knowledge, there are no specific recommendations about the duration of anticoagulation treatment in patients with autoimmune disease experiencing a first VTE, especially in the absence of antiphospholipid antibodies or lupus anticoagulant.²²

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To estimate the risk of recurrence in these patients, it would seem reasonable to make an analogy to another disease entity clearly linked to VTE, such as cancer.^{23–26} Patients with cancer-associated VTE are generally treated with anticoagulation indefinitely unless the risk of bleeding is exceedingly high or cure has been assumed.^{23–27} Thus, the reasoning is that hazard of recurrence is high if the underlying risk factor is still present. If we extend this reasoning to patients with VTE associated with autoimmune diseases, we can hypothesize that the hazard of recurrence must be high and will remain high, as cure in autoimmune diseases usually cannot be achieved.

However, we must also consider the observation that VTE risk in patients with autoimmune disease is related to disease activity¹³ and, therefore, assuming a constant hazard after an unprovoked VTE is problematic. This is best illustrated by the overview of standardized incidence rates (SIRs) for pulmonary embolism in patients across a broad spectrum of autoimmune diseases, as reported by Zöller et al.¹⁵ The SIRs for pulmonary embolism were persistently high in the first year of follow-up (almost all diseases analyzed had a SIR > 5) and almost uniformly declined toward < 2 after the first year of follow-up. It seems reasonable to attribute this to the fact that the proportion of patients with active disease is highest in the first year after diagnosis. Admittedly, a survivor's bias may be at play (patients who are thrombosis-free in the first year represent a selection of patients with a low VTE risk profile²⁸). Nevertheless, if the observation that VTE risk follows disease activity is true, it would be reasonable to hypothesize that patients with autoimmune diseases have no net clinical benefit from secondary thromboprophylaxis during periods of disease remission.

In summary, both competing hypotheses (patients with autoimmune risk are at a constant high versus a decreasing risk of VTE recurrence) seem equally plausible. To try to resolve this, we performed a systematic review of the medical literature to gather evidence on absolute risk of recurrent VTE in patients with autoimmune diseases, with the aim of informing recommendations for the length of anticoagulation after a first unprovoked VTE in these patients. Specifically, we sought to examine the relationship between disease activity and the risk of recurrent VTE.

Methods

We prespecified the aims of the systematic review and the initial MEDLINE search string. We did not register the protocol online.

Eligible studies were cohort and case-control studies that either enrolled patients with VTE and had autoimmune disease as one of the exposures of interest or included patients with autoimmune diseases and studied VTE as (one of the) outcome(s) of interest. Only studies that reported absolute rates of venous thrombotic complications were deemed eligible. If only relative measures were reported, the study was deemed eligible if it was possible to derive absolute rates.

The following diseases were included in the search strategy: rheumatoid arthritis, spondyloarthropathy (SpA), psoriatic arthritis, inflammatory bowel disease (IBD; Crohn's disease

and ulcerative colitis), connective tissue diseases (systemic lupus erythematosus [SLE], systemic sclerosis, mixed connective tissue disease, Sjögren's syndrome), the primary vasculitides (Takayasu arteritis, polymyalgia rheumatica, giant cell arteritis, polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis/Churg-Strauss, granulomatosis with polyangiitis/Wegener's, microscopic polyangiitis, Henoch-Schönlein purpura/IgA vasculitis, and cryoglobulinemic vasculitis), Behcet's disease, dermatomyositis, polymyositis, and sarcoidosis.

Studies that included only patients with secondary antiphospholipid syndrome were not deemed eligible. However, we did screen studies in which antiphospholipid syndrome was the main exposure of interest, as the data in control groups (SLE patients with VTE but no antiphospholipid antibodies) would be potentially meaningful for the topic of this review.

We initially searched MEDLINE, with no limitations on language and date. We used the search string presented in ► **Table 1**. After reviewing all abstracts and eligible studies, we decided to perform additional queries that included strings for antiphospholipid antibodies/syndrome (APS). We also performed a comparable search in Embase (additional strings in supplementary data). A librarian experienced in constructing search strings for systematic reviews assisted in constructing all search queries. The last search was performed on March 1, 2017. We screened references from the literature results for other relevant studies.

Two authors (J.F.B.-H., K.d.L.) screened the abstracts for eligibility for full-text review. Discrepancies in study selection were discussed between the two authors and a decision for full-text review was made by consensus. The same authors then read the full-text study and scored the quality of the study using the Newcastle-Ottawa scale.

If, after full-text reading, it became apparent that the study did not fulfill the eligibility criteria, the study was excluded from the final selection for data analysis and description. Overall quality of evidence was judged using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.

Statistical Analysis

We did not predefine a data analysis plan as we expected that data would present too much heterogeneity for meta-analysis, as we were interested in risk estimates in different patient groups.

Results

We screened 4,739 individual abstracts, of which 76 were selected for full-text review for final eligibility (► **Fig. 1**). Eleven articles were finally selected. A summary of the final papers reviewed is shown in ► **Table 2**.

Systemic Lupus Erythematosus

In 1980, Gladman and Urowitz²⁹ reported on 17 patients with SLE who presumably had a total of 21 attacks of venous syndrome, implying that 4 patients had recurrent venous thrombosis. Although most patients had either venograms or

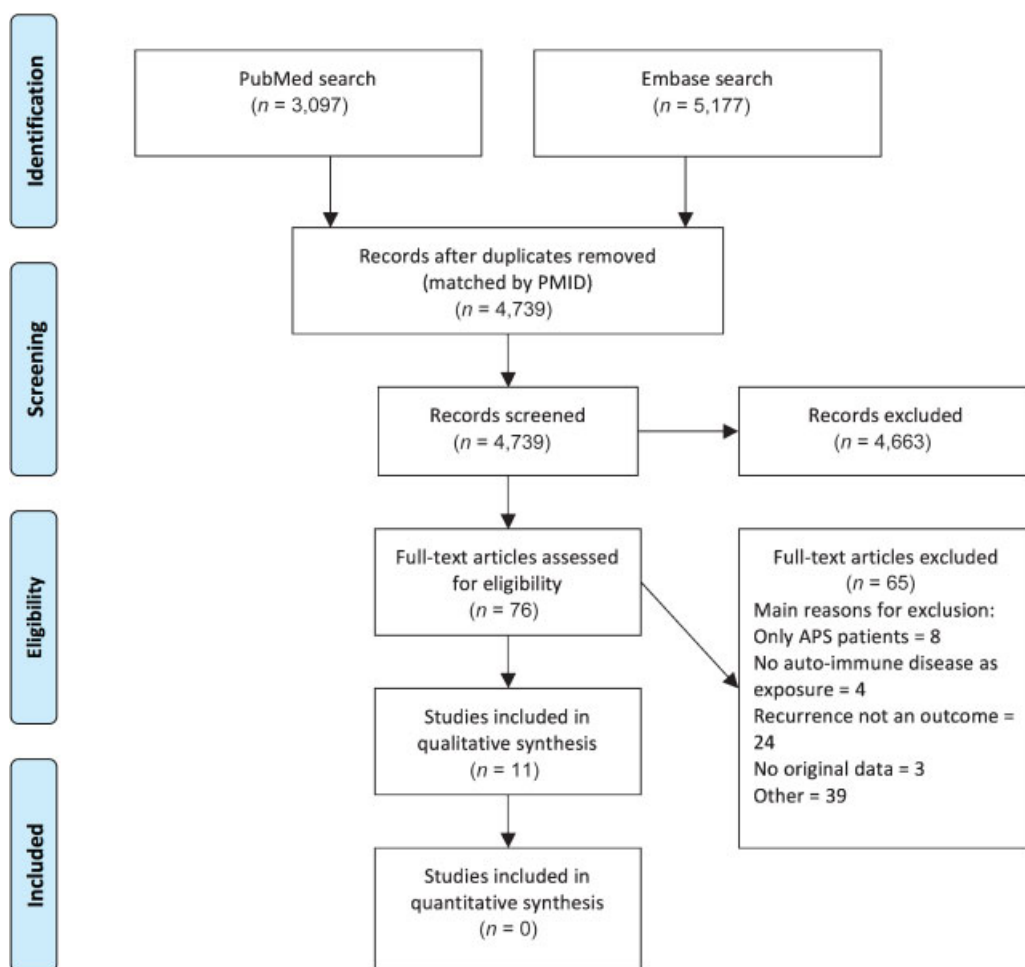


Fig. 1 PRISMA 2009 flow diagram. Other reasons for excluding were mainly that the abstract was somewhat ambiguous about the type of study, and review of full text revealed that the text was a review or a case series. Some manuscripts presented combined outcomes (thrombosis and pulmonary hemorrhage combined in people living with Behcet's disease. APS, antiphospholipid syndrome; PMID, PubMed ID number.

a perfusion scan, no mention was made of how diagnosis of recurrent ipsilateral extremity thrombosis was made, nor was it clear whether patients suffered superficial thrombophlebitis or deep vein thrombosis (DVT).

A study by Alarcón-Segovia et al³⁰ in 1989 analyzed 500 consecutive patients with SLE for antiphospholipid antibodies and antiphospholipid syndrome characteristics (i.e., obstetric complications, VTE, hemolysis, thrombocytopenia). Mean follow-up was 7.7 months. Only anticardiolipin antibodies were tested. Of these 500 patients, 43 (8.6%) had venous events. Of these latter, 20 patients were seronegative for anticardiolipin antibodies using a cutoff of the mean plus

2 standard deviations, while 28 were seronegative using a cutoff of the mean plus 5 standard deviations. Fourteen (32%) of these 43 patients had recurrent venous events. Only one patient with a recurrent venous event was seronegative for anticardiolipin antibodies at 2 standard deviations from the mean. Three of the patients with recurrent venous events were seronegative for anticardiolipin antibodies at 5 standard deviations from the mean.

Thus, when seronegativity was defined as never having a test result above 2 standard deviations from the mean, 1 in 20 (5%) patients suffered a recurrent venous event. When seronegativity was defined as never resulting above 5 standard

Table 1 Main MEDLINE search string

"Autoimmune Diseases"[Mesh] OR autoimmun*[tw] OR auto-immun*[tw] OR "Spondylarthritis"[Mesh] OR "Inflammatory Bowel Diseases"[Mesh] OR "Connective Tissue Diseases"[Mesh] OR "Vasculitis"[Mesh] OR "Myositis"[Mesh] OR "Sarcoidosis"[Mesh] OR vasculiti*[tw] OR henoc*[tw] OR psoria*[tw] OR rheuma*[tw] OR arthriti*[tw] OR sarcoidos*[tw] OR polyarter*[tw] OR polyang*[tw] OR churg*[tw] OR Wegener[tw] OR cryoglob*[tw] OR dermatomyo*[tw] OR polymyo*[tw] OR ibd[tw] OR inflammatory bowel[tw] OR sjogren*[tw] OR spondyl*[tw] OR lupus[tw] OR sclerosis[tw] OR takayasu*[tw] OR polymyalgia*[tw] OR behcet*[tw]) AND ("Thromboembolism"[Mesh:noexp] OR "Thrombosis"[Mesh:noexp] OR "Pulmonary Embolism"[Mesh] OR "Venous Thromboembolism"[Mesh] OR "Venous Thrombosis"[Mesh] OR thrombot*[tw] OR thrombos*[tw] OR thromboembol*[tw] OR embol*[tw]) AND ("Recurrence"[Mesh] OR recurr*[tw] OR reoccur*[tw]) NOT "Case Reports"[Publication Type]

Table 2 Summary of results from studies arranged by disease classification

Disease type	Study type	Proportion of patients with VTE recurrence	Cumulative incidence (5 y)	NOS score	Main limitation(s)
SLE, negative/unknown APS serology					
Gladman and Urowitz ²⁹	RC	23% (4/17)	N/A	2	Unclear definition for VTE in general/no follow-up times
Alarcón-Segovia et al ³⁰	RC				
Negative for ACL at 2 SD		5% (1/20)	N/A	3	1. Lacking classification of VTE (phlebitis/proximal VTE)
Negative for ACL at 5 SD		11% (3/28)	N/A		2. Lacking data on how VTE was treated
Ren et al ³¹	RC	25% (51/201) (OR vs. non-SLE: 1.48)	N/A	4	Only DVT, unclear treatment/definition of recurrent VTE
Brouwer et al ³²	CS and RC ^a	Overall patients without APS: 2/9 (22%)	N/A	4	
		Patients with unprovoked index VTE: 0/4 (0%)			
Behcet's disease					
Ahn et al ³³	RC	Only AC: 75% (3/4) Pooled patients with immunosuppression: 9% (3/33)	N/A	4	1. No follow-up time 2. Small subgroups 3. Only DVT of the legs
Desbois et al ³⁴	RC	34% (100/296)	CR est.: 36.5%	5	
Tascilar et al ³⁵	RC	35% (312/882)	1-KM est.: 38.4%	4	~10% index and recurrent events not VTE
Yaşar et al ³⁶	RC	25% (24/96)	N/A	4	
Inflammatory bowel disease					
Solem et al ³⁷	RC	10.3% (10/98)		2	
Novacek et al ³⁸	RC (IDB) vs. PC (control)	Unprovoked index event: 26/86 Provoked index event: 8/30	1-KM: 33.4%	9	
Unselected patients with autoimmune disease					
Cosmi et al ³⁹	PC	10% (3/30)	N/A	6	Definition of autoimmune disease lacking

Abbreviations: AC, anticoagulation; ACL, anticardiolipin antibodies; APS, antiphospholipid antibodies; CR, competing risk; CS, cross-sectional; DVT, deep vein thrombosis; Est., estimate; IBD, inflammatory bowel disease (Crohn's and ulcerative colitis); KM, Kaplan-Meier; N/A, not available; NOS, Newcastle-Ottawa scale; OR, odds ratio; PC, prospective cohort; RC, retrospective cohort; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

^aLaboratory data were collected cross-sectionally; clinical data were retrospective.

deviations from the mean, 3 of 28 (14%) patients suffered a recurrent venous event. This study is limited in that it did not measure lupus anticoagulant, state definitions of VTE diagnosis, or define persistently elevated antiphospholipid antibodies as a criterion for positivity. There was limited follow-up and, even with short follow-up, it did not describe how patients were treated for these venous events.

A 2013 report by Ren et al³¹ analyzed SLE as a risk factor for recurrent DVT of the lower extremity in 1,124 patients. Pulmonary embolism was not an outcome of interest. The exact classification criteria used to diagnose SLE were not stated. A total of 206 patients with SLE had a DVT, of which 51 had a recurrence. Follow-up times were not mentioned. Compared with the whole cohort, SLE carried a relative risk of recurrence of 1.48 in the univariate analysis. The adjusted odds ratio was 1.42 in the multivariate analysis, with a 95% confidence interval (CI) ranging from 0.97 to 2.09. This study was limited in that it appears that not all patients were treated with anticoagulation for their first VTE; some were treated with thrombolysis or surgery only.

Brouwer et al³² described 15 patients with venous thrombosis and SLE. Eight of these 15 patients had an unprovoked VTE. Four of these 15 patients had a positive test for lupus anticoagulant. Three of the 15 patients tested positive for anticardiolipin antibodies. It was not mentioned whether patients had overlapping antibody positivity. We were able to access data from this article, as it was published by our own center. Two out of nine patients (22%) without antiphospholipid antibodies had a recurrent VTE; both patients with recurrence had a VTE provoked by pregnancy as a first event. It was not possible to calculate time-dependent incidence, as the dates of discontinuation of anticoagulation were unreliable.

Behcet's Disease

We found four studies reporting recurrence of VTEs in Behcet's disease.

In 2007, Ahn et al³³ reported on recurrence of DVT in the legs in 37 patients with venous thrombosis associated with Behcet's disease. There were five recurrences (13.5%) in total. Mean follow-up was 50 months after initial VTE diagnosis,

translating into a manually calculated crude incidence rate of 3.2/100 patient-years. Patients who suffered a VTE associated with Behcet's disease were divided into three groups: a group of 4 patients treated only with anticoagulation (beyond 6 months); a group of 16 treated only with immunosuppression (after a 6-month course of anticoagulation), and a group of 17 treated with both anticoagulation and immunosuppression. Of the four patients who received only anticoagulation, three (75%) had a recurrent VTE. Two of these recurrences occurred during anticoagulant treatment. Whether the patient without a recurrence was continuing anticoagulation was not mentioned. Two patients (12.5%) in the immunosuppression group suffered a recurrence. No data were provided on the follow-up duration. Only one patient (6%) in the combination therapy group suffered a recurrence, again with no mention of follow-up years.

This study presented a cumulative incidence (<10% 5-year) in patients mainly treated with immunosuppression, and a questionable efficacy of anticoagulant treatment. This finding is further strengthened by a study from Desbois et al³⁴ published in 2012. Overall, the authors presented a 36.5% 5-year rate of VTE recurrence in patients with Behcet's disease. Of note, patients treated with immunosuppressive drugs yielded a hazard ratio of 0.27 (95% CI, 0.14–0.52) for recurrent VTE in multivariate analysis. Personal communication with the corresponding author confirmed that, in these patients, the long-term cumulative incidence (>5 years follow-up) of recurrent VTE did not exceed 10%. However, it was not indicated whether ongoing anticoagulant treatment was a factor influencing the rate of recurrence in these patients.

Another report on VTE in Behcet's disease was published by Tascilar et al in 2014.³⁵ In this study, vascular involvement (including arterial aneurysms) was evaluated in a cohort of 5,970 patients with Behcet's disease. A total of 882 patients had at least one vascular event; 856 (97%) of these were events of the venous vasculature. Of these 856 events, some were defined as pulmonary involvement, but it was not stated whether these were pulmonary emboli or aneurysmatic disease processes. A total of 312 patients had a recurrent vascular event. It was not possible to deduce which of these were a VTE as a first event. Overall, 5-year Kaplan–Meier estimates for recurrent vascular disease was 38.4%. Eighty percent of the recurrent events were thrombotic events; so, the 5-year rate of thrombotic recurrence is presumably in the range of 25 to 35%.

Finally, an article published in 2010 by Yasar et al³⁶ consisted of a cohort of 402 patients with Behcet's disease. Of these, 96 had suffered a VTE, of which 24 (25%) had more than one event. The study did not mention for how long patients were followed up.

Inflammatory Bowel Disease

The first report mentioning recurrent thrombosis in a cohort study was published by Solem et al,³⁷ in 2003. In a cohort of 98 patients with IBD and VTE (59 patients with ulcerative colitis and 39 with Crohn's disease), there were a total of 10 (10%) recurrences. Median follow-up after diagnosis of the first VTE was 1.8 years.

In 2010, Novacek et al³⁸ published the only study that analyzed VTE recurrence in patients with chronic IBD compared with a general cohort of patients with unprovoked VTE. Of note, this cohort defined VTE associated with oral contraceptives as unprovoked. Finally, 86 IBD patients with unprovoked VTE were compared with 1,255 controls with unprovoked VTE. Twenty-seven of 86 (31%) patients with IBD and an unprovoked index VTE reportedly had a recurrent VTE, yielding a 5-year Kaplan–Meier recurrent VTE estimate of 33.4%. In the control group, 204 of 1,255 (16.3%) patients with an unprovoked index VTE reportedly had a recurrent VTE, yielding a 5-year Kaplan–Meier VTE recurrence estimate of 21.7%. In a univariate Cox regression analysis, IBD yielded an HR of 1.7 (95% CI, 1.1–2.5) compared with controls. In the multivariate analysis, IBD yielded an adjusted HR of 2.5 after correction for age, factor V Leiden, prothrombin mutation, high factor VIII, duration of anticoagulation, and body mass index. This report mentions that half of the VTEs were associated with disease activity both at the index event and at recurrence.

Six (17%) of the recurrences in IBD patients were associated with a surgical procedure. Moreover, in four of these cases, no medical thromboprophylaxis was given.

Unselected Patients with Autoimmune Disease

An article by Cosmi et al³⁹ in 2010 incorporated comorbidities as a risk factor for recurrent VTE. In this cohort of 619 patients with idiopathic VTE, 30 reportedly had an autoimmune disease. The article does not report on the recurrence of VTE in this subgroup. However, the authors were willing to share some data on these patients. Three (10%) of these 30 patients with autoimmune disease had a recurrent VTE. Diagnosis of autoimmune disease was based on questionnaires at enrolment and not on diagnostic criteria. The mentioned diagnoses were as follows: eight patients had rheumatoid arthritis, five had polymyalgia rheumatica, one had ankylosing spondylitis, three had autoimmune thyroiditis, one had Crohn's disease, and the remainder had a chronic inflammatory disease not otherwise specified.

Discussion

In this systematic review, we gathered evidence on the risk of recurrent VTE in autoimmune diseases outside of the setting of antiphospholipid syndrome. Most studies were limited in that they did not report risk as a function of time. There were only two studies^{34,38} that presented time-dependent incidences of recurrent VTE. One study³⁵ reported recurrence of vascular events in Behcet's disease and stated that VTE represented a majority of the events in this spectrum (>85%). All of the reviewed studies were retrospective and therefore might have overestimated recurrent VTE by ascertainment bias, which is especially a problem when assessing recurrent VTE in an anatomical location that was previously affected by a first VTE.

At a glance, all studies show that the absolute risk of recurrent VTE ranges between 30 and 40% at 5 years, which is just under the rate seen in unselected male patients with a

first idiopathic VTE in patient level meta-analysis (just above 40%).^{40,41} Assuming an annual major bleeding rate of less than 3%,^{23,42} with indefinite anticoagulant therapy, it would seem that indefinite anticoagulant therapy would be warranted in these patients.

However, the studies by Novacek et al³⁸ and Desbois et al³⁴ lead us to speculate whether extended and, more specifically, life-long anticoagulation would in fact constitute the best approach. Desbois et al's study showed a 0.27 HR associated with immunosuppressive treatment. Novacek et al's study also suggests, albeit less convincingly, that recurrence risk is driven by disease activity, as 50% of patients had their VTEs (both first and recurrent) during periods of disease activity. This does suggest that optimal management of the autoimmune disease itself may be a reasonable approach compared with life-long anticoagulant therapy.

However, the apparent elegance of consistency in the rate of recurrence between IBD and Behcet's is arguably a red herring, as there are reasons for arguing that VTE in Behcet's is a disease entity separate from VTE in other disease processes. First of all, the studies in this review consistently show a cumulative incidence of a *first* VTE after the diagnosis of Behcet's of 10% in the first year and up to 30% in 5 years, an incidence surpassed only by certain high-risk malignancies.⁴³ This rate suggests that the disease inherently leads to venous thrombosis, which is plausible as vasculitis/venulitis⁴⁴ is seen as the main pathologic process in Behcet's disease. Also, the distribution of the sites involved in venous thrombosis (5–10% caval vein thrombosis, 5% portal/mesenteric/Budd Chiari syndrome, frequent reports of intracardiac thrombosis) is different from that in other VTE risk groups. Furthermore, recurrence rates were not different between males and females in the study by Desbois et al,³⁴ while a higher risk of recurrence for men is consistently shown in patients with otherwise unprovoked VTE,^{40,41} and was also reported in the study by Novacek et al.³⁸ Also, Desbois et al³⁴ noted in a personal communication that they did not distinguish between provoked and unprovoked index VTE; so, the high recurrence risk seems to be independent of any underlying transient risk factors besides the disease itself.

Moreover, the data on the effects of therapy also suggest that thrombosis in Behcet's disease presents a distinct disease pattern. The observation that immunosuppressive therapy lowered the risk of recurrence to below 10% in the study by Desbois et al³⁴ at 5 years was satisfying, as we set out to discover relationships between disease activity and thrombotic risk. Nevertheless, we must seriously consider that the treatment effect found is disease specific and cannot be extrapolated to other patients with chronic inflammatory disease. This is reinforced by some of the discussed data,^{33,34} especially from Ahn et al,³³ suggesting that anticoagulation treatment alone is not very effective in patients with Behcet's, which is in stark contrast to the generally assumed efficacy of anticoagulant treatment for VTE prevention (risk reductions of 80–90%).⁴⁵ Therefore, it is very unlikely that the observations from patients with Behcet's disease are generalizable to patients who suffer from VTE in association with other autoimmune diseases.

Conversely, the study by Novacek et al³⁸ in patients with IBD presents recurrence risk patterns that are more compatible with recurrence risks in VTE patients without autoimmune disease: age and sex had associations with a higher VTE risk, and hazard in the first year after discontinuing anticoagulation was higher than in the years thereafter. However, the study presents some caveats. In particular, VTE associated with hormonal factors and distal DVT were included in the definition of unprovoked VTE. This presents a methodological shortcoming in retrospect, as robust data showing that VTE associated with estrogen use is associated with a low recurrence risk became available after this study was published.^{40,46} Nevertheless, the control cohort had a slightly higher proportion of index distal DVT and events associated with hormonal factors, as well as a slightly higher proportion of women. Furthermore, the IBD cohort was analyzed retrospectively with patients recruited at 14 IBD centers, whereas the control cohort consisted of prospectively followed-up patients recruited at 4 centers with expertise in diagnosis and management of VTE. Therefore, there is substantial risk of misdiagnosis of events in the IBD cohort. In summary, we must conclude that the risk of recurrent VTE in IBD is probably overestimated, but it is difficult to appreciate by how much.

Considering all of the aforementioned data, and the fact that the literature provides only useful data for two diseases, we must conclude that there are insufficient data to make confident recommendations about whether or not anticoagulation should be continued indefinitely in patients with autoimmune diseases and a first otherwise unprovoked VTE. We simply need more data on the recurrence rate in patients with autoimmune diseases, particularly diseases other than IBD and Behcet's disease. This is expressed in the GRADE summary of evidence table (►Table 3). We judged the estimates from studies which did perform survival analysis to have serious, but not very serious, bias in ascertaining recurrence rate. In general, due to heterogeneity of follow-up times, there were no clear signs that the studies were inconsistent with each other. We judged that there was serious indirectness of the evidence, as presentation of a proportion of patients with recurrent event can only lead to rough extrapolations of a rate. Furthermore, as outlined previously, the external validity of data on Behcet's disease for patients with other autoimmune diseases are questionable. We did not downgrade judgment on precision as the number of recurrent events in total is large (521 events), but we cannot pool these due to the way these events were analyzed.

Returning to the question of what decision should be made in a patient with autoimmune diseases and an unprovoked VTE, the data do still suggest that analyzing prognosis in patients with a VTE during disease flare versus those without merits further study. To further elucidate net clinical benefit, we would ideally also want to know rates of major bleeding with anticoagulation in these patients, as many patients with autoimmune disease have indications for medications that enhance bleeding (i.e., nonsteroidal anti-inflammatory drugs, corticosteroids),⁴⁷ and patients with systemic autoimmune disease have organ involvement that

Table 3 GRADE assessment of overall quality of evidence

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patients with autoimmune disease	Patients without autoimmune disease	Relative (95% CI)	Absolute (95% CI)		
Recurrent VTE												
11	Observational studies	Serious ^a	Not serious	Serious ^b	Not serious	None	Pooling not meaningful	Pooling not meaningful	N/A	N/A	⊕ Very low	Critical

Abbreviations: CI, confidence interval; N/A, not available; VTE, venous thromboembolism.

^aRetrospective ascertainment of recurrent VTE may overestimate recurrent VTE rate, especially if compared with prospective rates.

^bOnly a minority of studies measured rates (recurrent VTE/time unit) or did a Kaplan–Meier/competitive risk analysis. The evidence from Behcet's disease has questionable external validity for VTE in other autoimmune diseases.

predisposes to bleeding (renal/liver dysfunction). If major bleeding rates are high (>3% annual major bleeding), then long-term anticoagulation may lack net clinical benefit.²³

When data are lacking, how should a clinician approach the question of how long to administer anticoagulation in a patient with autoimmune disease and an otherwise unprovoked VTE? Recent guidance from the Scientific and Standardization Committee of the International Society on Thrombosis Haemostasis may be helpful in this individual decision-making process:⁴⁸ if the provoking factor is persistent (ongoing disease activity), then the recurrence hazard might be even higher than in patients with otherwise unprovoked VTE, and anticoagulation should be continued unless bleeding risks are high. In turn, if the provoking risk factor has subsided (the patient is in stable remission after having a VTE during a disease flare), then the recurrence hazard might be low. Consequently, withdrawal of anticoagulation may be considered. In other words, a patient who had an index VTE during a disease flare should be on anticoagulation until disease remission—earlier interruption should only be considered if the bleeding risk is considered high. When/if stable disease remission has been achieved, discontinuation of anticoagulation may be discussed with the patient.

Addendum

J.F.B.-H. was responsible for the study idea and design, performed the literature search and review, and wrote the manuscript. K.d.L. was responsible for study design, performed literature search and review, and reviewed the manuscript. A.R. was responsible for study design and reviewed the manuscript. K.M. was responsible for study idea and design, supervised writing of the manuscript, and reviewed the manuscript. Y.I.G.V.T. was responsible for study idea and supervision of manuscript writing process and reviewed the manuscript.

Conflict of Interest

None.

References

- 1 Carruthers EC, Choi HK, Sayre EC, Aviña-Zubieta JA. Risk of deep venous thrombosis and pulmonary embolism in individuals with polymyositis and dermatomyositis: a general population-based study. *Ann Rheum Dis* 2016;75(01):110–116
- 2 Chung WS, Lin CL, Chang SN, Lu CC, Kao CH. Systemic lupus erythematosus increases the risks of deep vein thrombosis and pulmonary embolism: a nationwide cohort study. *J Thromb Haemost* 2014;12(04):452–458
- 3 Peeters PJ, Bazelier MT, Uitdehaag BM, Leufkens HG, De Bruin ML, de Vries F. The risk of venous thromboembolism in patients with multiple sclerosis: the Clinical Practice Research Datalink. *J Thromb Haemost* 2014;12(04):444–451
- 4 Selva-O'Callaghan A, Fernández-Luque A, Martínez-Gómez X, Labirua-Iturburu A, Vilardell-Tarrés M. Venous thromboembolism in patients with dermatomyositis and polymyositis. *Clin Exp Rheumatol* 2011;29(05):846–849
- 5 Ungprasert P, Sanguankee A. Risk of venous thromboembolism in patients with idiopathic inflammatory myositis: a systematic review and meta-analysis. *Rheumatol Int* 2014;34(10):1455–1458

- 6 Ungprasert P, Sanguankeo A, Upala S, Suksaranjit P. Psoriasis and risk of venous thromboembolism: a systematic review and meta-analysis. *QJM* 2014;107(10):793–797
- 7 Ungprasert P, Srivali N, Kittanamongkolchai W. Risk of venous thromboembolism in patients with Sjögren's syndrome: a systematic review and meta-analysis. *Clin Exp Rheumatol* 2015;33(05):746–750
- 8 Ungprasert P, Srivali N, Kittanamongkolchai W. Systemic sclerosis and risk of venous thromboembolism: a systematic review and meta-analysis. *Mod Rheumatol* 2015;25(06):893–897
- 9 Ungprasert P, Srivali N, Spanuchart I, Thongprayoon C, Knight EL. Risk of venous thromboembolism in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Clin Rheumatol* 2014;33(03):297–304
- 10 Ungprasert P, Srivali N, Wijarnpreecha K, Thongprayoon C. Sarcoidosis and risk of venous thromboembolism: a systematic review and meta-analysis. *Sarcoidosis Vasc Diffuse Lung Dis* 2015;32(03):182–187
- 11 Ungprasert P, Tanratana P, Srivali N. Autoimmune hemolytic anemia and venous thromboembolism: a systematic review and meta-analysis. *Thromb Res* 2015;136(05):1013–1017
- 12 Ungprasert P, Wijarnpreecha K, Tanratana P. Risk of venous thromboembolism in patients with celiac disease: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016;31(07):1240–1245
- 13 Tichelaar YI, Kluin-Nelemans HJ, Meijer K. Infections and inflammatory diseases as risk factors for venous thrombosis. A systematic review. *Thromb Haemost* 2012;107(05):827–837
- 14 Zöller B, Li X, Sundquist J, Sundquist K. Autoimmune diseases and venous thromboembolism: a review of the literature. *Am J Cardiovasc Dis* 2012;2(03):171–183
- 15 Zöller B, Li X, Sundquist J, Sundquist K. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. *Lancet* 2012;379(9812):244–249
- 16 Aviña-Zubieta JA, Bhole VM, Amiri N, Sayre EC, Choi HK. The risk of deep venous thrombosis and pulmonary embolism in giant cell arteritis: a general population-based study. *Ann Rheum Dis* 2016;75(01):148–154
- 17 Aviña-Zubieta JA, Vostretsova K, De Vera MA, Sayre EC, Choi HK. The risk of pulmonary embolism and deep venous thrombosis in systemic lupus erythematosus: a general population-based study. *Semin Arthritis Rheum* 2015;45(02):195–201
- 18 Choi HK, Rho Y-H, Zhu Y, Cea-Soriano L, Aviña-Zubieta JA, Zhang Y. The risk of pulmonary embolism and deep vein thrombosis in rheumatoid arthritis: a UK population-based outpatient cohort study. *Ann Rheum Dis* 2013;72(07):1182–1187
- 19 Lee JJ, Pope JE. A meta-analysis of the risk of venous thromboembolism in inflammatory rheumatic diseases. *Arthritis Res Ther* 2014;16(05):435
- 20 Schoenfeld SR, Choi HK, Sayre EC, Aviña-Zubieta JA. Risk of pulmonary embolism and deep venous thrombosis in systemic sclerosis: a general population-based study. *Arthritis Care Res (Hoboken)* 2016;68(02):246–253
- 21 Murthy SK, Nguyen GC. Venous thromboembolism in inflammatory bowel disease: an epidemiological review. *Am J Gastroenterol* 2011;106(04):713–718
- 22 Garcia D, Akl EA, Carr R, Kearon C. Antiphospholipid antibodies and the risk of recurrence after a first episode of venous thromboembolism: a systematic review. *Blood* 2013;122(05):817–824
- 23 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149(02):315–352
- 24 Lyman GH, Bohlke K, Khorana AA, et al; American Society of Clinical Oncology. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline update 2014. *J Clin Oncol* 2015;33(06):654–656
- 25 Lee AY, Levine MN, Baker RI, et al; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;349(02):146–153
- 26 Lee AY, Kamphuisen PW, Meyer G, et al; CATCH Investigators. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA* 2015;314(07):677–686
- 27 van der Hulle T, den Exter PL, van den Hoven P, et al. Cohort study on the management of cancer-associated venous thromboembolism aimed at the safety of stopping anticoagulant therapy in patients cured of cancer. *Chest* 2016;149(05):1245–1251
- 28 Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999;353(9159):1167–1173
- 29 Gladman DD, Urowitz MB. Venous syndromes and pulmonary embolism in systemic lupus erythematosus. *Ann Rheum Dis* 1980;39(04):340–343
- 30 Alarcón-Segovia D, Delezé M, Oria CV, et al. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of 500 consecutive patients. *Medicine (Baltimore)* 1989;68(06):353–365
- 31 Ren W, Li Z, Fu Z, Fu Q. Analysis of risk factors for recurrence of deep venous thrombosis in lower extremities. *Med Sci Monit* 2014;20:199–204
- 32 Brouwer JL, Bijl M, Veeger NJ, Kluin-Nelemans HC, van der Meer J. The contribution of inherited and acquired thrombophilic defects, alone or combined with antiphospholipid antibodies, to venous and arterial thromboembolism in patients with systemic lupus erythematosus. *Blood* 2004;104(01):143–148
- 33 Ahn JK, Lee YS, Jeon CH, Koh EM, Cha HS. Treatment of venous thrombosis associated with Behçet's disease: immunosuppressive therapy alone versus immunosuppressive therapy plus anticoagulation. *Clin Rheumatol* 2008;27(02):201–205
- 34 Desbois AC, Wechsler B, Resche-Rigon M, et al. Immunosuppressants reduce venous thrombosis relapse in Behçet's disease. *Arthritis Rheum* 2012;64(08):2753–2760
- 35 Tascilar K, Melikoglu M, Ugurlu S, Sut N, Caglar E, Yazici H. Vascular involvement in Behçet's syndrome: a retrospective analysis of associations and the time course. *Rheumatology (Oxford)* 2014;53(11):2018–2022
- 36 Yaşar NŞ, Salgür F, Cansu DÜ, Kaşifoğlu T, Korkmaz C. Combined thrombophilic factors increase the risk of recurrent thrombotic events in Behçet's disease. *Clin Rheumatol* 2010;29(12):1367–1372
- 37 Solem CA, Loftus EV, Tremaine WJ, Sandborn WJ. Venous thromboembolism in inflammatory bowel disease. *Am J Gastroenterol* 2004;99(01):97–101
- 38 Novacek G, Weltermann A, Sobala A, et al. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. *Gastroenterology* 2010;139(03):779–787, 787.e1
- 39 Cosmi B, Legnani C, Tosetto A, et al; PROLONG Investigators; FCSA, Italian Federation of Anticoagulation Clinics. Comorbidities, alone and in combination with D-dimer, as risk factors for recurrence after a first episode of unprovoked venous thromboembolism in the extended follow-up of the PROLONG study. *Thromb Haemost* 2010;103(06):1152–1160
- 40 Douketis J, Tosetto A, Marcucci M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. *BMJ* 2011;342:d813
- 41 Rodger MA, Scarvelis D, Kahn SR, et al. Long-term risk of venous thrombosis after stopping anticoagulants for a first unprovoked event: a multi-national cohort. *Thromb Res* 2016;143:152–158

- 42 Ay C, Posch F, Kaider A, Zielinski C, Pabinger I. Estimating risk of venous thromboembolism in patients with cancer in the presence of competing mortality. *J Thromb Haemost* 2015;13(03):390–397
- 43 Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;65(01):1–11
- 44 Klok FA, Kooiman J, Huisman MV, Konstantinides S, Lankeit M. Predicting anticoagulant-related bleeding in patients with venous thromboembolism: a clinically oriented review. *Eur Respir J* 2015; 45(01):201–210
- 45 Schulman S, Kearon C, Kakkar AK, et al; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013;368(08):709–718
- 46 Eischer L, Eichinger S, Kyrle PA. The risk of recurrence in women with venous thromboembolism while using estrogens: a prospective cohort study. *J Thromb Haemost* 2014;12(05): 635–640
- 47 Davidson BL, Verheijen S, Lensing AW, et al. Bleeding risk of patients with acute venous thromboembolism taking nonsteroidal anti-inflammatory drugs or aspirin. *JAMA Intern Med* 2014; 174(06):947–953
- 48 Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA; Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost* 2016; 14(07):1480–1483