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Risk of recurrent venous thromboembolism in patients with autoimmune diseases: data from the Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry

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Summary

Autoimmune disease is a risk factor for first incident venous thromboembolism (VTE). However, data on the risk of recurrent VTE in people with autoimmune disease is sparse. We explored the risk of recurrent VTE using the RIETE registry, comparing people with autoimmune disease (n = 1305) to those without (n = 50608). Overall rates were 6.5 and 5.1 recurrent VTE/100 years for patients with autoimmune disease vs controls, respectively. After adjustment for sex and unprovoked/provoked VTE yielded an adjusted hazard ratio of 1.29 (95%CI 1.03-1.62). The analysis was limited by short median follow up time (161 days overall), precluding definitive conclusions on recurrent VTE risks.

Keywords: venous thrombosis, autoimmune disease, risk factors.

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A full list of the RIETE investigators is given in the appendix.

Introduction

One of the central issues surrounding management of venous thromboembolism (VTE) is to estimate the risk of recurrent VTE. This informs whether anticoagulant treatment should be continued indefinitely or whether a limited duration is more appropriate.[1] Although much research has concentrated on the use of biomarkers for all patients with VTE, it would be important to understand how relatively highly prevalent risk factors for VTE influence recurrence risk as well. Autoimmune diseases are such a risk factor: depending on definition, prevalence of autoimmune disease is 5–9% among the general population[2] and because they are a risk factor for VTE they are expected to be over-represented in populations with VTE. A recent systematic review concluded that there is insufficient evidence to say whether autoimmune disease is associated with a higher risk of recurrent VTE, with only some moderate quality evidence available for the risk of recurrence in patients with inflammatory bowel disease and Behçet's disease.[3] Part of the issue identified is that each separate autoimmune disease is relatively rare, making this relatively small subgroups of people suffering from VTE. To gather sufficient data on recurrence risk of VTE in these single diseases, it is likely that national-scale or even multinational-scale co-operation would be needed. A different approach would be to use existing VTE registries, which would likely document comorbidities, and consider autoimmune disease as one entity despite their heterogeneity in disease presentation and severity. The Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry has extensive data during treatment, and showed no difference in occurrence of VTE and/or bleeding during this period in these patients.[4] In the present study, we analysed the risk of recurrent VTE in patients with autoimmune diseases using the RIETE registry after withdrawing treatment.

Patients and methods

The RIETE registry has been described previously.[5] In short, it is an ongoing, multicentre, international registry of consecutive patients with objectively confirmed acute VTE (ClinicalTrials.gov identifier: NCT02832245). Multiple centres enrol patients at the time that they have a VTE and extensive clinical data are collected including medication use, laboratory measurements and comorbidities. Participants are subsequently followed-up during treatment.

Participants

Patients who entered the registry with a first episode of VTE and who did not have a recurrence during anticoagulant therapy and who subsequently stopped anticoagulant therapy were included.

Data collection methods

Data in RIETE are recorded on to a computer-based case report form at each participating hospital and submitted to a centralised co-ordinating centre.

Exposure

The main exposure of interest was autoimmune disease. Within the registry, this included inflammatory bowel disease (ulcerative colitis/Crohn's disease), systemic lupus erythematosus, Behçet's disease, temporal arteritis, rheumatoid arthritis, ankylosing spondylitis, polymyalgia rheumatica and vasculitis.

Outcome

Recurrent deep vein thrombosis was adjudicated by treating physicians and is defined as a new non-compressible vein segment, or an increase of the vein diameter of >4 mm compared with last available measurement on ultrasonography. Recurrent pulmonary embolism is defined as a new ventilation-perfusion mismatch or new intraluminal filling defect on relevant imaging.[5]

Confounders

Sex and provoking factors were considered to be confounders. Provoking factors were modelled as categorical variables, with the following three categories: unprovoked (no clear provoking factor), cancer-associated (active cancer, irrespective of presence of other provoking factors) or provoked (associated with surgery in the 2 months prior to VTE, immobilised for >4 days, use of oestrogen and/or pregnancy).

Statistical analysis

Rates were calculated by dividing events by total years of follow-up.

Cumulative incidences were estimated accounting for competing risk of death.

Cause specific hazard estimates were estimated using Cox proportional hazards regression, adjusted estimates were arrived at by adjusting for sex and index event type (provoked/cancer associated/unprovoked).

Post hoc, the data showed a high rate of censoring, meaning that data from late follow-up would not only be an

Table I. Participants after exclusion of people with venous thromboembolism prior to registry entry or who had a recurrence during anticoagulant therapy.

	Autoimmune disease	No autoimmune disease
Patients, *N*	1305	50608
Inflammatory bowel disease, *n* (%)	275 (21)	
Systemic lupus erythematosus, *n* (%)	97 (7)	
Behçet's disease, *n* (%)	18 (1)	
Temporal arteritis, *n* (%)	74 (6)	
Other vasculitis, *n* (%)	148 (11)	
Rheumatoid arthritis	459 (35)	
Ankylosing spondylitis	42 (4)	
Polymyalgia rheumatica	225 (17)	
Clinical characteristics		
Age, years, mean (SD)	66 (17)	68 (18)
Male gender, *n* (%)	477 (36)	24391 (48)
Anti-phospholipid antibodies	11 (1)	26 (0)
Initial VTE presentation		
DVT only, *n* (%)	505 (39)	20491 (40)
Pulmonary embolism*	800 (61)	30117 (60)
VTE type		
Unprovoked	742 (57)	23021 (45)
Active cancer	143 (11)	11117 (22)
Other provoking factors	420 (32)	16470 (33)

DVT, deep venous thrombosis; SD, standard deviation; VTE, venous thromboembolism.
*With or without DVT.

implausible extrapolation of risk estimates from the initial risk set, but also there was some concern that there might be selective follow-up for participants with autoimmune disease: it was deemed more likely that these patients would have ongoing care in the hospital that participated in the registry, so there would be more information available distorting results. Therefore, a sensitivity analysis including only the early follow-up period was performed.

Results

After exclusion of RIETE participants who did not enter the registry with a first VTE and exclusion of participants who had a recurrence during use of anticoagulants, 51 913 participants remained. Of these >2% had one of the mentioned autoimmune diseases. Baseline characteristics are shown in Table I. As expected, there was a slightly higher proportion of females in the autoimmune group and a higher proportion of unprovoked index VTEs. Excluded participants with autoimmune disease had a similar sex ratio (41% male).

The median follow-up across the whole cohort was 161 days, with three-quarters being censored after 335 days, with only slightly longer follow-up for participants with autoimmune disease (median 181 days, third quartile 371 days). Rates considering all follow-up and only early follow-up are shown in Table II.

Cumulative incidence plots are shown in the supplementary appendix, showing overall cumulative incidence and cumulative incidences stratified by sex and within the unprovoked stratum. In the overall analysis, cumulative incidence rates at 1, 2 and 5 years were 5·8%, 12·5% and 26·5% for participants with autoimmune disease and 4·8%, 9·0% and 22·1% for participants without autoimmune disease. In the analysis stratified by sex, it appeared that females with autoimmune disease had a particularly higher risk of recurrent VTE as compared to other strata.

Table II also shows the results of the Cox proportional hazards regression analysis, estimating an approximately 30–40% higher hazard of recurrent VTE after adjustment for sex and type of index event. However, limiting the analysis to only the first year follow-up attenuated the association to a 20% higher hazard, with the confidence interval including a null effect. None of the models showed any evidence of violation of proportional hazards for the variable autoimmune disease. A *post hoc* subgroup analysis of the most prevalent autoimmune diseases was done to explore whether the average effect of autoimmune disease was being driven by one particular disease. This was not the case (results in the appendix).

Table II. Rates and hazard ratios of recurrent venous thromboembolism.

	Events, *n*	Follow-up, years	Rate, *n*/100 years	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Total follow-up available					
No autoimmune disease	2204	42813	5 1 (4 9–5 4)	Ref.	Ref.
Autoimmune disease	77	1179	6 5 (5 2–8 1)	1 29 (1 03–1 62)	1 33 (1 06–1 67)
Only first 2 years					
No autoimmune disease	1691	33463	5 1 (4 8–5 3)	Ref.	Ref.
Autoimmune disease	64	954	6 7 (5 3–8 5)	1 34 (1 04–1 72)	1 37 (1 06–1 76)
Only first year					
No autoimmune disease	1337	25829	5 2 (4 9–5 5)	Ref.	Ref.
Autoimmune disease	44	724	6 1 (4 6–8 1)	1 18 (0 88–1 60)	1 22 (0 91–1 65)

CI, confidence interval; HR, hazard ratio.
*Adjusted for sex and unprovoked/cancer-provoked/provoked venous thromboembolism.

Discussion

The present results suggest that participants with the studied autoimmune diseases are at a higher risk of recurrent VTE than controls. This is the first study to produce such a large-scale analysis of recurrent VTE in participants with autoimmune disease. Indeed, the previous studies that included patients with a first VTE had a sample size of 116 patients (inflammatory bowel disease)[6] and 296 patients (Behçet's disease).[7]

The main limitation of the present analysis relates to the fact that the registry was not designed to assess recurrent VTE, mainly due to short follow-up times: three-quarters of participants were censored before 1 year of follow-up, questioning the validity of estimates derived after this time point. We amended analyses accordingly. At high censoring rates, a further concern is differential loss to follow-up. In this specific setting, it is plausible that, given the chronic nature of autoimmune diseases, these participants may be followed in the same centre by a rheumatologist, whilst this may not be the case for other participants without disease raising concern about detection bias. However, the direction of this bias is unclear: participants with autoimmune disease may have a both inflated numerator (events reported) and denominator (follow-up time). Limiting follow-up time to 1 year attenuated the hazard ratio, suggesting that this mainly led to an overestimation of relative risk. Therefore, although the results follow the expected direction of effect (higher risk of recurrence in people with autoimmune disease) they should be interpreted with caution.

The present study highlights the challenges in investigating the risk of recurrent VTE in subgroups of patients. On the one hand, existing dedicated recurrent VTE cohort studies [e.g. the Austrian Study on Recurrent Venous Thromboembolism (AUREC)][8] will have insufficient participants exposed to autoimmune disease for a meaningful analysis, let alone whether autoimmune disease is reliably ascertained as an exposure. In turn, within any cohort dedicated to a single autoimmune disease, we can only expect a small minority to have had a VTE. This implies that larger datasets will have to be used. Routinely collected datasets with long-term follow-up come to mind, e.g. data collected at general practitioner practices. Here, problems are likely to arise with ascertainment of the recurrent VTE outcome; validity of diagnostic codes for a recurrent VTE episode would have to be validated. We are aware of one study that collected general VTE recurrence trends using a GP records database in the UK.[9]

Finally, it is important to stress that the present study covered only a specific subset of autoimmune disease collected in RIETE. Estimates from the present study cannot be extrapolated to autoimmune diseases that have typically less systemic involvement, e.g. autoimmune thyroiditis, celiac disease or psoriasis.

In conclusion, the present study suggests a higher risk of recurrent VTE in patients with the selected autoimmune diseases, especially in women. However, several limitations preclude making confident conclusions. Future large-scale studies using routinely collected data are needed to obtain more reliable estimates.

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Author contributions

Jaime Borjas Howard designed the research, analysed the data and wrote the manuscript; Pablo Ruiz-Sada, Luciano López-Jiménez, Carme Font, Pablo Javier Marchena and Philippe Debourdeau were involved in data collection and reviewed drafts of the manuscript; Karina Meijer and Karina de Leeuw designed the research and reviewed drafts of the manuscript; Manuel Monreal supported data acquisition and analysis and reviewed drafts of the manuscript.

Conflict of interest

All the other authors declare no conflict of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Cumulative incidence of recurrent venous thromboembolism, stratified by autoimmune disease and sex.

Table SI. Subgroup analysis of recurrent venous thromboembolism in the largest autoimmune disease groups.

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