Risk of recurrence after transient inflammation-associated venous thromboembolism

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Supporting Information

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

Method S1. Supplementary Methods and Supplementary Tables S1–S6.

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Risk of recurrence after transient inflammation-associated venous thromboembolism: similar to provoked, unprovoked or in-between?

Venous thromboembolism (VTE) is categorised as either unprovoked or provoked by an external risk factor.[1] This classification has prognostic implications, as unprovoked VTE has a high recurrence risk of 30–50% within 5 years, which is three-times higher than that of provoked VTE.[2–5] Current guidelines advise to extend anti-coagulation therapy in patients with an unprovoked first VTE. Anti-coagulation therapy is effective in the prevention of recurrent VTE, but comes at the cost of an increased bleeding risk.[6] As patients with an unprovoked VTE have heterogeneous clinical characteristics and thus varying recurrence risks, this may not outweigh the bleeding risk in every individual. Therefore, efforts should be made to identify patients who will not benefit from long-term anti-coagulation therapy, e.g. those with previously unrecognised transient risk factors. Transient inflammation is shown to be a provoking factor for VTE, but is not yet considered in clinical practice.[7–12] In the present study, we aimed to explore whether patients having a first VTE associated with transient inflammation have a lower risk of recurrent VTE.

Patients and methods

In 2019, we retrospectively reviewed a cohort of patients with a confirmed first pulmonary embolism (PE) and/or deep vein thrombosis (DVT) for recurrent VTE (www.trialregister.nl,

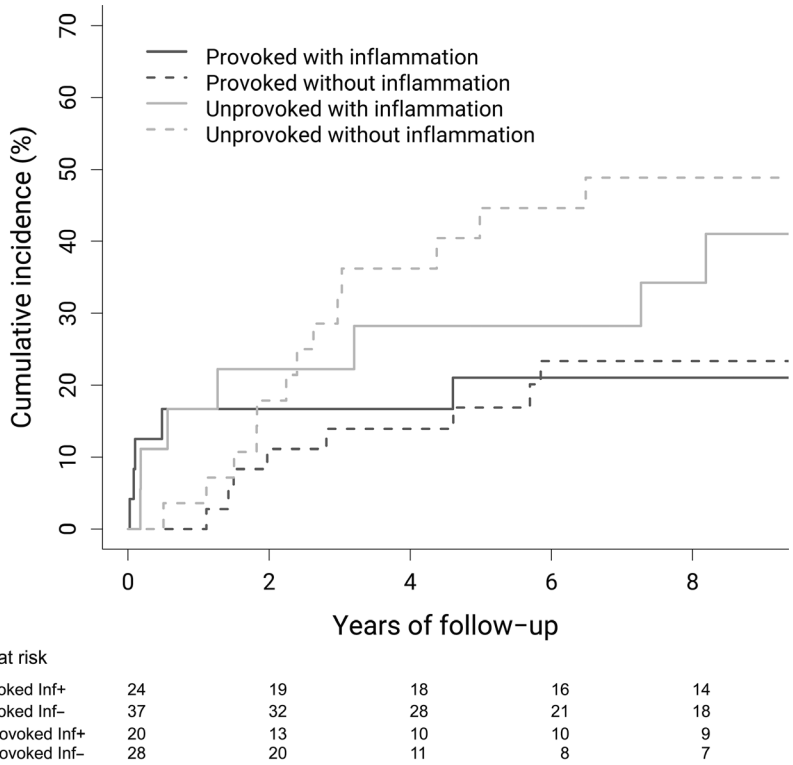

Fig 1. Cumulative incidences of recurrent VTE after inflammation-associated and not inflammation-associated index-VTE, stratified by presence of a provoking factor with non-VTE-related death as competing risk.

NL5047). These patients participated in the BEAST case-control study (2008–2010)[11] and gave informed consent for use of clinical data in accordance with the Dutch Medical Research Act.

From 192 eligible patients in the original case-control study, 49 did not provide informed consent, in 27 anti-coagulation therapy was never discontinued and in seven follow-up data were not available, leaving 109 patients for analysis. Before imaging to prevent recall bias, ascertainment of inflammation was done at the time of the BEAST case-control study through questioning patients on the presence of upper or lower airway complaints, gastroenteritis, malaise and fever up to 4 weeks prior to referral to the emergency department.

Follow-up started at discontinuation of initial anti-coagulation therapy. The primary outcome was recurrent VTE at any site confirmed by clinical and radiological data and the use of anti-coagulation for ≥3 months. B.S.B. and J.F.B. independently performed outcome adjudication with a third reviewer (Y.I.G.V.T.) in cases of disagreement.

Analyses were stratified by presence of a classical provoking factor at the time of the index-VTE [i.e. surgery, trauma (plaster cast) immobilisation, oestrogen use, pregnancy or puerperium, travel >4 h or (treatment for) malignancy in the past 3 months]. Cumulative incidences were calculated with non-VTE-related death as a competing risk. Sex-adjusted subdistribution hazard ratios (SHR) were estimated with a Fine and Gray model (R version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria).

Results and discussion

Baseline characteristics are summarised in Table I. A total of 33 recurrences occurred in 798 person years of follow-up (median 8 years). Within unprovoked index-VTEs, the cumulative incidence of recurrence was 34·3% [95% confidence interval (CI) 13·3–56·7%] for inflammation-associated index-VTE and 48·9% (95% CI 28·2–66·7%) for not inflammation-associated index-VTE at 8 years (Fig 1). A non-significant trend was observed indicating a lower recurrence of inflammation-associated index events compared to not inflammation-associated index events (SHR 0·8, 95% CI 0·3–2·1). We did not observe a difference in recurrent VTE within provoked index-VTE [inflammation-associated 21·1% (95% CI 7·4–39·3%) vs. not inflammation-associated 23·4% (95% CI 10·7–38·8%); SHR 1·0, 95% CI 0·3–3·1 at 8 years] (Fig 1). In a pre-specified sensitivity analysis, excluding index-PE accompanied by lower airway signs, the results remained the same.

This is broadly in line with a previous study in which the recurrence risk of first VTEs preceded by antibiotic use in the primary care-setting was evaluated.[12] Compared to patients with provoked VTE not due to antibiotics as reference, otherwise unprovoked first VTE associated with antibiotics use had a similar recurrence risk as patients with a

Table I. Baseline characteristics.

Characteristic	Unprovoked		Provoked	
	Inf− (n = 28)	Inf+ (n = 20)	Inf− (n = 37)	Inf+ (n = 24)
Age at index-VTE, years, median (IQR)	62 (49–75)	58 (50–69)	41 (35–62)	49 (36–64)
Male sex, n (%)	21 (75)	15 (75)	16 (43)	11 (46)
Vital status, n (%)				
Alive	12 (43)	12 (60)	25 (68)	19 (79)
Deceased	14 (50)	4 (20)	7 (19)	4 (17)
Unknown	2 (7)	4 (20)	5 (14)	1 (4)
Type of index-VTE, n (%)				
DVT	15 (54)	11 (55)	20 (54)	12 (50)
PE	13 (46)	7 (35)	15 (41)	10 (42)
Both	0 (0)	2 (10)	2 (5)	2 (8)
Duration anti-coagulation, months, median (IQR)	7 (6–7)	7 (6–7)	7 (6–9)	7 (6–11)
Duration of follow-up, years, median (IQR)	8 (3–9)	9 (5–9)	8 (6–9)	9 (8–9)
Provoking factor, n (%)				
Surgery	NA	NA	12 (32)	4 (17)
Trauma			3 (8)	5 (21)
Immobilisation			8 (22)	4 (17)
Pregnancy/puerperium			5 (14)	0 (0)
Oestrogens			13 (35)	12 (50)
Travel >4 h			3 (8)	4 (17)
Malignancy			4 (11)	5 (21)
Inflammatory signs, n (%)				
Upper airway infection	NA	11 (55)	NA	6 (25)
Lower airway infection		5 (25)		12 (50)
Gastroenteritis		3 (15)		4 (17)
Fever		7 (35)		6 (25)
Malaise		8 (40)		8 (33)

Inf−, non-inflammation-associated; Inf+, inflammation-associated; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis.

provoked index-VTE (HR 1·1, 95% CI 0·7–1·7).[12] In turn, antibiotic use did not influence the recurrence risk within patients with index-VTEs associated with another provoking factor (HR 0·9, 95% CI 0·6–1·3).[12] However, our present incidences of recurrent VTE were overall higher in comparison with theirs, possibly as a result of non-responder bias. Patients who had a recurrence might have been more willing to participate in this study than those who did not due to the retrospective nature of this study.

Strikingly, the median time to recurrence in our present study was shorter for inflammation-associated index-VTE, irrespective of the presence of a provoking factor, at 0·5[interquartile range (IQR) 0·2–3·6] years *versus* 2·4 (IQR 1·5–4·4) years. An explanation might be in the studies of Clayton *et al.*[7] and Smeeth *et al.*[10], which evaluated respiratory and urinary tract infection as risk factors. In both studies, the risk of a first VTE was at its highest 1 month after the infection and gradually decreased thereafter. However, after 1 year the elevated risks had not returned to baseline level. This might imply that anti-coagulation was discontinued in a period that coagulation activation from inflammation is still present.

Strengths of the present study are the availability of a long follow-up and the establishment of inflammatory signs before final diagnosis of the index-VTE was made. A limitation is the small sample size. However, in the current treatment paradigm with long-term anti-coagulation therapy for unprovoked VTE, we can only use existing databases to evaluate the influence of new provoking factors on risk of recurrence.

The present study suggests that transient inflammation might be considered as a provoking factor for VTE, but not to the same extent as classical provoking factors (e.g. surgery, oestrogens), as the recurrence risk of otherwise unprovoked but inflammation-associated first VTE still exceeds the threshold to justify extended anti-coagulation therapy. However, transient inflammation could optimise (existing) prediction models for recurrent VTE and may be of importance in patients with a low baseline risk of recurrence (e.g. young women without comorbidities).

Competing interests

Karina Meijer received research support from Bayer, Sanquin and Pfizer; speaker fees from Bayer, Sanquin, Boehringer Ingelheim, BMS and Aspen; consulting fees from UniQure (all fees go to the institution). Bibie Soerajja Bhoelan, Jaime

F. Borjas Howard and Ynse Ieuwe Gerardus Vladimir Tichelaar have no competing interests.

Author contributions

Bibie Soerajja Bhoelan, Jaime F. Borjas Howard, Ynse Ieuwe Gerardus Vladimir Tichelaar and Karina Meijer contributed to the design of the study and data interpretation. Data collection, analysis and drafting of the manuscript were performed by Bibie Soerajja Bhoelan. Jaime F. Borjas Howard, Ynse Ieuwe Gerardus Vladimir Tichelaar, and Karina Meijer revised the manuscript.

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Supporting Information

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Data S1. Detailed description of the methods.

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ROR1 is an accurate and reliable marker of minimal residual disease in chronic lymphocytic leukaemia

The receptor tyrosine kinase-like orphan receptor-1 (ROR1) is an evolutionary conserved type I surface membrane protein that is expressed during embryogenesis.[1–3] Like most adult cells, normal B cells do not express ROR1. On the contrary, chronic lymphocytic leukaemia (CLL) cells express high levels of ROR1.[4,5] These properties make ROR1 an attractive target for the treatment of CLL. Indeed, a humanized monoclonal antibody, cirmtuzumab, which targets ROR1 and inhibits ROR1-signaling *in vitro* has been developed.[6] A phase I study of cirmtuzumab in patients with CLL has demonstrated that this antibody can also inhibit ROR1-signaling *in vivo*, suppressing leukaemia cell activation of r-GTPases and phosphorylation of HS1.[7]

Monitoring of minimal residual disease (MRD) plays an increasing role in the management of CLL, particularly with the new therapeutic combinations.[8] In this study, we have