Risk factors associated with venous thromboembolism in rheumatoid arthritis in clinical practice

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Abstract

Objective

To identify classical or disease-related risk factors of venous thromboembolic events (VTE) in rheumatoid arthritis (RA) patients in clinical practice.

Methods

Cross-sectional single-centre study conducted on consecutive RA patients over a 24-month period. Electronic medical reports were used to identify the occurrence of VTE after 2018 (JAK inhibitors, JAKi, availability in France) and to collect RA disease characteristics/VTE risk factors. Multivariate logistic regression analysis was performed to identify factors independently associated with VTE.

Results

Among 469 RA patients (81% women, mean age 59±14 years), 15 had VTE (3%)-after 2018, with a mean interval of 4.5±5.6 months between the occurrence of VTE and the clinical evaluation. The strongest risk factor of VTE was the history of previous VTE with an OR of 44.74 (95% CI 8.83–226.68). We identified hospitalisation up to 3 months before the occurrence of VTE and also diabetes as other factors independently associated with the occurrence VTE, with respective OR of 6.82 (95% CI 1.60–29.11) and 11.23 (95% CI 2.21–57.01). Among RA therapies, JAKi were significantly associated with the occurrence of VTE (OR 5.54, 95% CI 1.03–29.72).

Conclusion

In this study of RA patients, history of VTE and recent hospitalisation were identified as strong risk factors of VTE. Moreover, it emphasises the importance of evaluating cardiovascular risk factors, particularly diabetes, for both arterial and venous thromboembolism risks. Finally, JAKi should be used with caution in patients with risk factors for VTE, as recommended by the Pharmacovigilance Risk Assessment Committee and the French Society of Rheumatology.

Key words

rheumatoid arthritis, venous thromboembolism, risk factors

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Introduction

Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease affecting 0.5% to 1% of the adult population worldwide. It is characterised by joint pain and swelling, leading to disability. Additionally, RA is associated with premature mortality mainly due to cardiovascular diseases, with a higher risk compared to the general population, especially among patients with persistent high disease activity (1, 2).

Besides the well-known risk of arterial cardiovascular events in RA patients, recent evidence has highlighted an increased risk of venous thromboembolism (VTE) in chronic inflammatory rheumatic diseases compared to healthy controls, and particularly in RA (3, 4). A recent meta-analysis of 10 observational studies has reported a risk of VTE in RA estimated by an odds ratio (OR) of 2.23 (95% confidence interval [CI] 1.79–2.77). The ORs for deep vein thrombosis (DVT) and pulmonary embolism (PE) were 2.25 (95%CI 1.70–2.98) and 2.15 (95%CI 1.39–3.49), respectively (5).

General VTE risk factors including age, male sex, obesity and comorbidities, such as cardiovascular risk factors, have been reported in chronic inflammatory diseases, as well as classical risk situations like hospitalisation, surgery and neoplasia (corresponding to 60% of provoked VTE) (6, 7). Importantly, inflammation is known to upregulate procoagulant factors and cause endothelial damage (8), and recent data suggested an association between RA disease activity and VTE risk (9, 10). With regards to the effects of drugs, a trend for VTE risk was identified with glucocorticoids, persistent even when disease activity has been controlled (11), and more recently with JAK inhibitors (JAKi) (9). Increased number of VTE events in randomised controlled trials of baricitinib and upadacitinib versus placebo were identified (12). Meta-analyses of phase III trials of JAKi and a post approval safety trial of tofacitinib versus tumour necrosis factor inhibitors (TNFi) both indicate a higher risk of (VTE) with JAKi (13). Moreover, a recent study has confirmed a 50–100% increased risk of VTE for JAKi used in clinical practice and demonstrated that the VTE rate with JAKi was higher than with TNFi, with other biological disease-modifying antirheumatic drugs, and in the background RA population. This study also showed that the increased VTE rate seemed to be explained by an increased rate of pulmonary embolism rather than deep venous thrombosis (10, 14).

The comprehensive assessment of all the above risk factors, including classical risk factors, disease-dependent factors including joint and systemic inflammation as well as RA treatments has been barely studied in RA in clinical practice. Thus, the aim of this study was to assess the combined impact of classical, disease-related, and treatment-associated risk factors of VTE in RA patients in clinical practice.

Methods

Study design

This was a retrospective cross-sectional study in the Rheumatology Department of a tertiary care hospital (Cochin hospital) in Paris, France.

Study population

All consecutive patients over 18 years-old, fulfilling the 2010 ACR/EULAR classification criteria for RA (15) and attending the one-day hospitalisation unit of the department between January 1st 2021 and December 31st 2022 were identified by an analysis of the Electronic medical reports (EMR). Most patients with RA passed through the one-day hospitalisation unit at least once for comprehensive assessments, monitoring, or treatments that require a controlled clinical environment without necessitating an overnight stay. Typical reasons for RA patients to attend this unit included biologic infusions, treatment adjustments, multidisciplinary evaluations, or detailed diagnostic workups.

Setting

VTE were identified through hospital admission records, with only those occurring after 2018 – date of the first JAKi (tofacitinib and baricitinib) availability in France – being included in the analysis. For these patients, we retrospectively collected data at the closest evaluation to the occurrence of VTE, and preferably prior to the event. For

patients in the non-VTE group, which includes those who had VTE prior to 2018, data were collected during the latest evaluation (2021-2022), where disease activity, structural damage, comorbidities and other health events were assessed.

Outcomes

VTE was defined by the occurrence of deep vein thrombosis (DVT) confirmed by venous echodoppler and/or pulmonary embolism (PE) confirmed by CT scan angiography. It was either provoked VTE in presence of a major transient or persistent risk factor, or unprovoked VTE otherwise.

Data collection

Data were obtained from the review of the patients EMR. The occurrence of VTE was specifically recorded in the systematic pre-therapeutic assessment. Classical VTE risk factors were selected according to literature that reported an established association with VTE (16): history of VTE, hospitalisation for an acute illness up to 3 months before VTE occurence, surgery up to 6 months, recent travel up to 3 months (defined by immobility due to sitting >4 hours, for example prolonged car, train or air travel), history of fracture, pregnancy, active neoplasia (treatment in progress or within 6 months, palliative treatment or progressive disease) and thrombophilia. Therapies having a potential impact on the risk of VTE were also evaluated, *i.e*. oestrogen therapy (contraceptive or hormone replacement therapy), antidepressants, anticoagulants and platelet anti-aggregants.We also collected the following cardiovascular risk factors : body mass index (BMI), smoking status, high blood pressure, dyslipidaemia, diabetes and history of major adverse cardiovascular events (MACE), which include myocardial infarction, stroke and cardiovascular-related death.

The following data on RA characteristics were collected: disease duration, autoantibody status (rheumatoid factor and anti-citrullinated protein antibodies), erosions, history of articular surgery due to the disease and presence of extra-articular manifestations. Disease activity was assessed using Disease Activity Score based on evaluation of 28 joints (DAS28) (17) using Protein C reactive (CRP) level and Erythrocyte sedimentation rate (ESR). Commonly used treatments were evaluated, including oral glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate and other conventionnal synthetic disease-modifying antirheumatic drugs (csDMARDs), represented by leflunomide, salazopyrine or hydroxychloroquine, and biological or targeted synthetic DMARDs.

Statistical analysis

All data were expressed as mean values ± standard deviation (SD) or number and percentage (%) for continuous and categorical variables, respectively, unless stated otherwise. Incidence rates were expressed as events per 1000 person-years. Statistical analysis was performed using Medcalc (v. 22.016). For a two-group comparison, unpaired t-test was used for continuous variables, and the chi-square test was used to detect differences in frequency among binary variables.

To determine the association between the different factors and the occurrence of a VTE, a first univariable analysis comparing patients with/without VTE was performed (unpaired t-test was used for continuous variables, and the chi-square test was used to detect differences in frequency among binary variables). Then, to determine the independent association between the different factors and VTE, a multivariate logistic regression analysis was performed. Given the small number of events expected, to avoid overfitting related to an excessive number of covariates, four complementary models were tested, built based on their clinical relevance; and an analysis of the power of our study sample for logistic regression has also been applied based on the Van Wijngaarden-Dekker-Brent algorithm. The statistical power for logistic regression of our study sample was 0.91.

The first model integrated classical risk factors of VTE, the second model incorporated RA characteristics and the third model focused on RA therapies. For these 3 models, all relevant identified covariates with a p-value ≤0.1 in the single variable analysis were entered in one single step their respective model. Then, a final model was designed, constructed using only variables that had a p-value ≤0.1 in at least one of the multivariable models in Table II. All variables in this model were adjusted for each other to assess their independent association with VTE. Odds ratio (OR) and 95% confidence intervals (CI) were then calculated. A p-value <0.05 was considered statistically significant.

Ethics

The protocol and the informed consent document have received Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval before initiation of the study ("Comité de Protection des Personnes" Paris Ile de France I). The study was declared to the Commission Nationale de l'Informatique et des Libertés (reference 2221678). All patients in our institution (AP-HP) are informed that their clinical data can be used for research and give their consent for the use of their data unless they provide an opposition to it. All patients notified their non-opposition to participating in this study, which was recorded in the medical source file.

Results

Study population

We included 469 RA patients during the 24-months study period, representing over a third of the source population, among which 381 were women (81%), with a mean age of 59±14 years and a mean disease duration of 16±13 years. Positive rheumatoid factor and positive anti-CCP antibodies were detected in 387 (82%) and 403 (86%) patients respectively. 293 patients (62%) had erosive disease and 73 (15%) had a history of disease-related articular surgery. Extra-articular manifestations were observed in 165 (35%) patients, the most frequent being rheumatoid nodules (30%) and interstitial lung disease (22%). The mean DAS28 was 3.1±1.2, the mean CRP level was 7.2±17.5 mg/L and the mean ESR was 27±25.6 mm/h (Table I).

Regarding the current treatment of RA, 235 patients (50%) were receiving glucocorticoids with a mean dose

of 2.9±3.6 mg per day and 282 (60%) methotrexate; 236 (50%) patients were treated by targeted biologic or synthetic DMARDs (b/tsDMARDs), including 76/236 (32%) on TNF–α inhibitors, 74/236 (31%) on rituximab, 42/236 (18%) on JAK inhibitors (21 upadacitinib, 12 baricitinib, 6 tofacitinib and 3 filgotinib), 28/236 (12%) on IL6 receptor-inhibitors and 17/236 (7%) on abatacept (Table I).

Occurrence of VTE in the study sample

In the whole population of 469 patients, we identified through the EMR 27 (6%) patients with previous or recent VTE. Fifteen of them (3%) had VTE since 2018 and underwent a rheumatological evaluation within 12 months of the event allowing us to study potential disease-related factors associated with VTE to provide a comprehensive view of VTE risk over the entire study period. The mean duration between the occurrence of VTE and the visit was 4.5±5.6 months. The rheumatological evaluation occurred before the VTE for the majority of patients. For the two patients who only had a recent evaluation shortly only after VTE, data on treatment at the time of the event were available and used. The 12 excluded patients had a history of VTE before 2018 without rheumatological assessment close to the event available and a mean time between VTE and the study visit of 17±10 years.

Among these 15 patients, we identified 9 VTE that occurred during the study period (2021-2022), including 5 DVT and 6 PE, with 2 patients presenting both conditions (Fig. 1). This represents an incidence rate of 9.59 for 1000 patient/year.

Analysis of VTE risk factors

- Classical risk factors

Among the 15 patients with VTE identified since 2018, 10 were women (66%, *vs*. 82% in patient without VTE, p=0.10), with a mean age of 64±10 years (*vs*. 59±14, p=0.10). Age over 65 years was more frequent in patients with VTE (60% *vs*. 37%, p=0.070). Six (40%) patients with VTE had a history of previous VTE (*vs*. 3%, p<0.001), including 2 still on anticoagulants, 7 (46%) were hospitalised up to 3 months before the event (*vs*. 6%, p<0.001), 4 (26%) experienced surgery up to 6 months before the event (*vs*. 2%, p<0.001), mainly orthopaedic surgeries. Moreover, the frequency of diabetes was higher in patients with VTE (40% *vs*. 9%, p<0.001) (Table I). We also observed that VTE patients were more likely overweighted, non-smokers and to have travelled up to 3 months. No difference was observed regarding neoplasia (one patient had active renal carcinoma among patients with VTE), oestrogen or antidepressant therapies. No patient had thrombophilia.

Table I. Comparison of VTE patients at the visit closest to the event and non-VTE patients at their latest evaluation (2021-2022).

	Total (n=469)	VTE # (n=15)	No VTE # (n=454)
Age (years), mean ± SD	59±14	64±10	59±14
Age ≥ 65 years, n (%)	179 (38)	9 (60)	170 (37)
Female sex, n (%)	381 (81)	10 (66)	371 (82)
BMI, kg/m^2, mean ± SD	25.7±5.5	28.1±5.2	25.5±5.5
Smokers, n (%)	79 (17)	0	79 (17)
Diabetes, n (%)	48 (10)	6 (40)	42 (9) ***
High blood pressure, n (%)	124 (26)	5 (33)	119 (26)
Dyslipidaemia, n (%)	89 (19)	4 (26)	85 (18)
History of MACE, n (%)	23 (5)	0	23 (5)
Disease duration (years), mean ± SD	15.6±12.8	17±13	15.5±13
Positive anti-CCP antibodies, n (%)	403 (86)	14 (93)	389 (85)
Positive rheumatoid factor, n (%)	387 (82)	14 (93)	373 (82)
Erosions, n (%)	293 (62)	11 (73)	282 (62)
Extra-articular manifestations, n (%)	165 (35)	9 (60)	156 (34) *
History of articular surgery, n (%)	73 (16)	4 (26)	69 (15)
DAS28 CRP, mean ± SD	3.1±1.2	3.1±1.5	3.1±1.2
CRP (mg/L), mean ± SD	7.2±17.5	17.3±33	6.8±16.7 *
ESR (mm H1), mean ± SD	27±25.6	34.4±34.5	27±25
Current glucocorticoids use, n (%)	235 (50)	11 (73)	224 (49)
Glucocorticoids dose (mg/day), mean ± SD	2.9±3.6	3.7±2.8	2.8±3.6
Current methotrexate use, n (%)	282 (60)	7 (47)	275 (61)
Methotrexate dose (mg/week), mean ± SD	17±5.3	14.3±6.2	17.1±5.1 *
Other csDMARDs	42 (9)	5 (33)	37 (8) ***
Current targeted biologic or synthetic treatment, n (%) ##	236 (50)	10 (66)	226 (50)
TNF-a inhibitors, n (%)	76 (16)	1 (6)	75 (16)
Rituximab, n (%)	74 (16)	5 (33)	69 (15)
JAK inhibitors, n (%)	42 (9)	3 (20)	39 (8)
Upadacitinib, n	21	2	19
Baricitinib, n	12	1	11
Tofacitinib, n	6	0	6
Filgotinib, n	3	0	3
Tocilizumab and sarilumab, n (%)	28 (6)	1 (6)	27 (6)
Abatacept, n (%)	17 (4)	0	17 (4)
History of VTE, n (%)	18 (4)	6 (40)	12 (3) ***
Hospitalisation up to 3 months, n (%)	36 (8)	7 (46)	29 (6) ***
Surgery up to 6 months, n (%)	13 (3)	4 (26)	9 (2) ***
Recent travel up to 3 months, n (%)	6 (1)	1 (6)	5 (1)
Active neoplasia, n (%)	12 (3)	1 (6)	11 (2)
History of fracture, n (%)	125 (27)	5 (33)	120 (26)
Oestrogen therapies, n (%)	31 (7)	1 (7)	30 (7)
Antidepressant therapies, n (%)	41 (9)	1 (7)	40 (9)

BMI: body mass index; MACE: major adverse cardiovascular events; VTE: venous thromboembolic events; CCP: cyclic citrullinated peptide; DAS: disease activity score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; TNF: tumour necrosis factor; JAK: Janus Kinase; SD: standard deviation

Patient characteristics at the visit closest to the VTE event for patients with VTE, and at the latest evaluation for patients without VTE.

Refers to treatment status at the time of VTE event (stable treatment between the pre- and post-event visits).

* p<0.05 *vs*. VTE; *** p <0.001 *vs*. VTE.

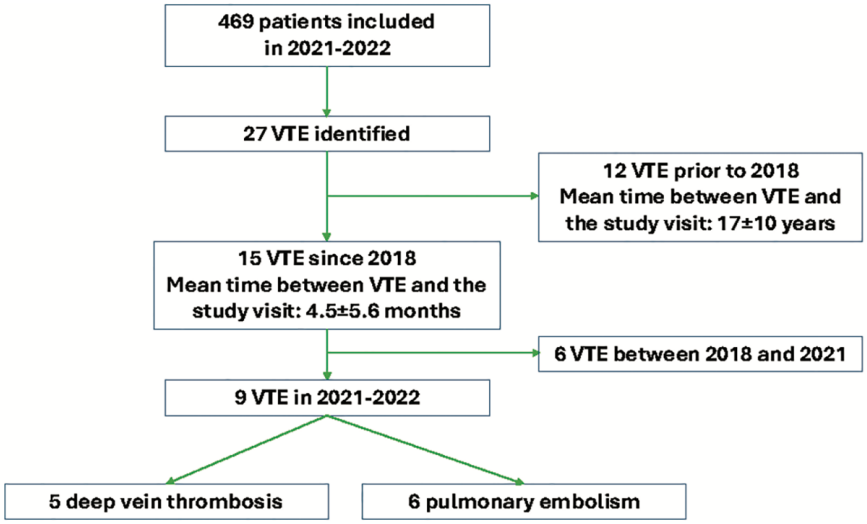

Fig. 1. Flowchart illustrating the analysis of VTE occurence in the study sample.

Table II. Association between classical risk factors, RA specific risk factors, therapies and the occurrence of VTE.

Covariates	Univariate *p*-value	Adjusted Odds ratio (95% CI)	Adjusted *p*-value
Model 1: classical risk factors			
Age ≥65 years	0.07	1.09 (0.25-4.91)	0.901
Male sex	0.12	2.32 (0.42-12.78)	0.332
BMI ≥30	0.072	1.57 (0.34-7.19)	0.560
Smoking	0.081	0.33 (0.06-1.90)	0.216
Diabetes	<0.001	**9.74 (1.82-52.22)**	**0.008**
History of VTE	<0.001	**40.75 (7.95-208.82)**	**<0.001**
Hospitalisation up to 3 months	<0.001	**6.58 (1.33-32.50)**	**0.021**
Surgery up to 6 months	<0.001	2.92 (0.46-18.66)	0.256
Travel up to 3 months	0.076	4.17 (0.17-100.11)	0.378
Model 2: RA specific risk factors			
Age	0.10	1.03 (0.98-1.07)	0.172
Male sex	0.10	2.02 (0.66-6.19)	0.218
Extra-articular manifestations	0.038	2.58 (0.89-7.50)	0.081
CRP level >10 mg/L	0.022	1.02 (0.27-3.78)	0.976
Model 3: RA therapies			
Glucocorticoids	0.068	2.61 (0.77-8.93)	0.215
Other csDMARDs	<0.001	**4.81 (1.50-15.47)**	**0.008**
JAK inhibitors	0.099	**4.43 (1.19-16.42)**	**0.026**
Rituximab	0.059	**3.77 (1.01-14.01)**	**0.047**

BMI: body mass index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; CI: confidence interval.
Each model adjusts for all variables included in its respective category, and identified with a *p*-value ≤0.1 in the single variable analysis. Odds ratios (ORs) are adjusted estimates and not derived from univariate analyses.

- RA risk factors

Patients with VTE were more likely to exhibit extra-articular manifestations (60% *vs*. 34%, *p*=0.038), mostly intestitial lung disease (55% *vs*. 22%, *p*=0.020) and rheumatoid nodules (55% *vs*. 30%, *p*=0.11). C-reactive protein (CRP) levels were higher in patients with VTE (17.3±33 mg/L *vs*. 6.8±16.7 mg/L, *p*=0.022). At the time of VTE event, they also were more frequently treated with another csDMARD instead of methotrexate (33% *vs*. 8%, *p*<0.001), tended to receive more glucocorticoids (73% *vs*. 49%, *p*=0.068), rituximab (33% *vs*. 15%, *p*=0.059) and JAK inhibitors (20% *vs*. 8%, *p*=0.099) (Table I).

- Multivariate models

In order to identify the risk factors independently associated with the risk of VTE, we performed multivariate logistic regression analyses using four models. Each model was adjusted for all variables included in it, resulting in adjusted OR (Table II).

In the first model, we focused on the classical risk factor of VTE, and integrated variables with a *p*-value ≤0.1 in univariate analysis. Variables identified as independently associated to VTE were history of VTE with an OR of 40.75 (95% CI 7.95–208.82, *p*<0.001), diabetes with an OR of 9.74 (95% CI 1.82–52.22, *p*=0.008) and hospitalisation up to 3 months (OR 6.58, 95% CI 1.33–32.50, *p*=0.021) (Table II). We performed a sensitivity analysis adding into the model history of fractures, which was not associated with VTE in univariate analysis but is a well-known VTE risk factors. This addition did not change the previously observed results.

In the second model, dedicated to RA characteristics, we did not identify any variable independently associated with the occurrence of VTE, and in particular extra-articular manifestations (OR 2.58, 95% CI 0.89–7.50, *p*=0.081) or CRP levels (OR 1.02, 95% CI 0.27–3.78, *p*=0.976) (Table II).

In the third model, we assessed the impact of RA treatment on the risk of VTE. We highlight that exposure to other csDMARDs than methotrexate was independently associated to VTE with an OR of 4.81 (95% CI 1.50–15.47, *p*=0.008), as well as JAKi with an OR of 4.43 (95% CI 1.19–16.42, *p*=0.026), and treatment by rituximab (OR 3.77, 95% CI 1.01–14.01, *p*=0.047) (Table II).

In our final logistic regression model (Table III), including independent risk factors identified in the previous models, the strongest risk factor independently associated with the occurrence of VTE was the history of previous VTE with an OR of 44.74 (95% CI 8.83–226.68, *p*<0.001). We also identified an hospitalisation up to 3 months before the occurrence of VTE and diabetes as other factors that remained independently associated with VTE in this model, with respective OR of 6.82 (95% CI 1.60–29.11, *p*=0.009) and 11.23 (95% CI 2.21–57.01, *p*=0.003). Among RA therapies, JAK inhibitors remained significantly associated with the occurrence of VTE with an OR of

5.54 (95% CI 1.03-29.72, p=0.046) (Table III).

Table III. Association between independent risk factors identified in previous models and the occurrence of VTE.

Variable	Adjusted Odds ratio (95% CI)	Adjusted p-value
History of previous VTE	44.74 (8.83-226.68)	<0.001
Hospitalisation up to 3 months	6.82 (1.60-29.11)	0.009
Diabetes	11.23 (2.21-57.01)	0.003
Extra-articular manifestations	1.74 (0.43-7.01)	0.436
Other csDMARDs	4.71 (0.94-23.67)	0.060
JAK inhibitors	5.54 (1.03-29.72)	0.046
Rituximab	2.38 (0.43-13.24)	0.321

The final model was constructed using only variables identified as having a p-value ≤0.1 in at least one of the multivariable logistic regression models from Table II. These included history of VTE, hospitalisation up to 3 months, diabetes, other csDMARDs, JAK inhibitors, and rituximab. All variables in this model were adjusted for each other.

Discussion

In this cohort of RA patients, a history of previous VTE, recent hospitalisation, diabetes and treatment with JAKi were associated with the occurrence of VTE. Our study identified an incidence of VTE of 9.59/1000 patients-year, which was slightly higher than reported in other studies. For example, Molander *et al*. reported an incidence rate of 7.1/1000 patients-year, Bacani *et al*. 7.4/1000 patients-year and Kim *et al*. 6/1000 patients year (6, 10, 18). This discrepancy may be explained by the methodology for data collection, and by the fact that patients in our cohort were older and more likely to have cardiovascular comorbidities as compared to other studies. Indeed, as a tertiary care hospital, our patients may display more severe disease or complex comorbidities compared to average RA population, especially for those followed in one-day hospitalisation compared to outpatients.

We have identified general and disease-related risk factors associated with the occurrence of venous thromboembolic events in RA patients in clinical practice. The strongest independent risk factor of VTE in RA patients was the history of VTE. In the literature, it is defined as a major risk factor of VTE (characterised by an odds ratio above 10), with around 30% of patients experiencing recurrence of VTE within 10 years (4, 19). A recent study investigated risk factors of VTE in ORAL Surveillance, a trial comparing the safety of tofacitinib compared to TNF inhibitors in RA patients aged over 50 years with at least one additional cardiovascular risk factor. They identified prior VTE, morbid obesity (BMI ≥35 kg/m^2), age over 65 years, and history of chronic lung disease, as baseline and persistent risk factors for VTE (20). In our study, patients with VTE were more frequently older and overweighted than patients without VTE. Yet, these factors did not appear to be independently associated after logistic regression, potentially due to limited statistical power resulting from the small number of events.

As well established, patients who had been hospitalised for an acute illness within 3 months before the event, also presented an increased risk of VTE (21, 22).

Interestingly, in agreement with Yoshimura *et al*., we found a positive association between diabetes and VTE risk in RA patients (23). In the past few years, it has been shown that arterial and venous thromboembolic events shared common risk factors. Two meta-analyses have shown a 1.4 fold increased risk of VTE in diabetic patients (24, 25), and 2019 ESC Guidelines on acute pulmonary embolism include diabetes mellitus as a weak risk factor of VTE, defined by an OR <2, on the same level as obesity and increasing age (16). Our data collection was limited to the presence of diabetes, without information concerning blood glucose levels. However, poorly controlled diabetes is common among RA patients, and pejorative outcomes, including systemic activity and bone erosions, have been linked to glycaemic control in early and established RA (26, 27). This added to the combination of low grade inflammation, hypercoagulability and endothelial dysfunction described in diabetic patients may explain the heightened risk of VTE (28-30).

Regarding RA-related risk factors, several studies suggested that disease activity is associated to the occurrence of VTE (9, 10, 20, 31). Here, despite higher CRP levels in VTE patients at the time of the event, neither CRP levels nor disease activity, assessed by DAS28, showed significant independent associations with the risk of VTE. This lack of evidence may be attributed to the fact that this cohort consisted of patients from programmed one day hospitalisation with low disease activity. Indeed, most RA flare-ups occur on an outpatient basis and are reported by patients during the visit, that took place a few weeks or even months away from the event; it is possible that the number of swollen or painful joints, as well as the CRP levels, and therefore DAS28, were higher at time of event than during the visit. There is much evidence that proinflammatory state in chronic diseases is associated with an increased risk of VTE, even more during diseases flare-ups characterised by acute inflammation (32-34). Some studies even observed a linear association between CRP levels and VTE risk (35). Furthermore, several biological studies have demonstrated the prothrombotic properties of CRP, by participating to endothelial inflammation and platelet function enhancement (36).

Additionally, among VTE patients, extra-articular manifestations were twice as frequent; however, this association lost significance after adjustment. Extra-articular manifestations of RA are related to a more severe disease and increased mortality (37, 38). Liang *et al*. notably demonstrated that severe extra-articular manifestations represented an independent risk factor for the development of non-cardiac vascular diseases, including venous thromboembolic events (39).

Regarding the risk of VTE and the treatment of RA, we identified an independent association between JAKi and the

occurrence of VTE. This finding aligns with recent research upon JAKi in RA patients, the main one being the ORAL Surveillance study, which specifically highlighted potential increased risks of major adverse cardiovascular events (MACE) and VTE in RA patients treated with tofacitinib, in a population aged over 50 with at least one cardiovascular risk factor (13). Interestingly, the majority of patients with VTE in our study fulfilled the ORAL Surveillance inclusion criteria, with obesity and diabetes being the most represented cardiovascular risk factors. Subsequent studies have further supported this association, also with baricitinib (40, 41), but yet the underlying mechanisms contributing to the increased VTE risk with JAKi have not been fully elucidated. On the other hand, two other studies found no significant difference in the risk of VTE when comparing respectively baricitinib or tofacitinib (42) and upadacitinib (43) with a TNF inhibitor (adalimumab). Moreover, a large Korean study also reported that JAKi did not increase the overall risk of cardiovascular diseases, including VTE, compared with bDMARDs and csDMARDs (44). Although the small sample size may have led to inflated OR values and certain data could have been relevant for adjustment, these results emphasise the importance of careful consideration and monitoring when prescribing JAK inhibitors to RA patients, especially those with a history of VTE or significant cardiovascular risks, as recommended by the EMA pharmacovigilance risk assessment committee (PRAC) and the French Society of Rheumatology (45).

Although this risk was attenuated when included in our final model, patients exposed to csDMARDs other than methotrexate were at higher risk of VTE. This finding is consistent with Bacani *et al*., who suggested that exposure to another csDMARD than methotrexate or hydroxychloroquine represented a time-dependent risk factor for VTE, but to a lesser extent than exposure to a biologic agent (18). Data concerning csDMARDs and VTE risk remain limited, most studies having compared b/tsDMARDs with csDMARDs, rather than directly comparing csDMARDs between each other. However, no safety signals have been associated with either leflunomide or sulfasalazine (4, 46).

Likewise, in the VTE group, patients received rituximab treatment twice as frequently, even though this correlation did not maintain significance in our final model. According to recommendations, rituximab is prescribed as a second-line treatment of severe and active RA after failure of at least one bDMARD including one TNFi (47). In our study population, most of patients treated on rituximab had an erosive disease and extra-articular manifestations, with an even higher prevalence in the VTE group, suggesting a more severe disease. In clinical practice, JAKi are also usually prescribed after several lines of treatments in patients with refractory and potentially severe RA, suggesting that beyond the effect of the treatment on the risk of VTE, this higher risk could be attributed to the severity of the disease.

Finally, exposure to glucocorticoids has been linked to a 2- to 3-fold increased risk of VTE, in various studies. This risk appears to be influenced by factors such as current or former use, duration of exposure, and cumulative dose (9, 31, 48, 49). Even though patients were more likely to receive glucocorticoids in VTE group, our data collection was limited to assessing current use and dose, and no significant association was observed.

Our study assessed real-life data regarding the risk of VTE in consecutive patients who were carefully assessed and phenotyped in a tertiary centre with a long-lasting experience in RA evaluation and care. However, our study is limited by its retrospective design and the relatively small number of events. It should be noted that the time-point of evaluation was generally more recent for non-VTE than for VTE patients, and this difference may have biased the OR estimates due to changes in the prevalence of certain risk factors during the study period. Furthermore, only patients who were alive and had at least one one-day hospitalisation between 2021 and 2022 were included, which may have led to the exclusion of some fatal VTEs occurring prior to their next hospital admission. This selective inclusion could result in an underestimation of VTE incidence and limits our data on risk factors associated with severe or fatal VTEs. Our study sample included mainly patients with established RA with low disease activity and may not be extrapolated to all RA patients. The inclusion of RA patients followed in hospital may have resulted in a selection bias. Since this study is cross-sectional, any pathogenic link should be taken very cautiously, with possibility of confounders and lack of evidence for causal associations.

To sum up, we identified history of VTE as the strongest risk factor of the occurrence of VTE. Our results suggest a specific warning on recent hospitalisation as precipitating event to VTE. They also underline the need of assessing cardiovascular risk factors, notably diabetes, in RA patients both for arterial and venous risk of thromboembolism. As recommended by the PRAC JAKi should be used with caution in patients with risk factors for VTE.

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