EPIDEMIOLOGICAL SCIENCE

Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: a nationwide cohort study from Sweden

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ABSTRACT

Objective To assess the incidence of venous thromboembolism (VTE) in rheumatoid arthritis (RA) relative to individuals without RA, and to investigate the relationship between aspects of clinical disease activity in RA and the risk of VTE.

Methods We conducted a nationwide register-based cohort study 2006 through 2018 using the Swedish Rheumatology Quality Register linked to other national patient registers to identify all patients with RA with at least one registered rheumatologist visit during the study period (n=46 316 patients, 322 601 visits). The Disease Activity Score 28 erythrocyte sedimentation rate (ESR) (DAS28 ESR) and its components served as the exposure, and a VTE event within the year following the visit was the main outcome. We also included general population referents (1:5) matched on age, sex and residential area.

Results Based on 2241 incident VTE events within 1 year of each included visit, and 5301 VTE events in the general population cohort, the risk ratio for VTE in RA was 1.88 (95% CI 1.65 to 2.15). Among patients with RA, the risk (and risk ratio) increased with increasing RA disease activity, from 0.52% following visits in remission to 1.08% following visits with DAS28 ESR high disease activity, RR compared with remission=2.03, 95% CI 1.73 to 2.38. Compared with the general population, also patients with RA in DAS28 ESR remission were at elevated VTE risk.

Conclusions This study demonstrates a strong association between clinical RA disease activity measured by DAS28 ESR and the risk of VTE. RA disease activity can be used as an additional tool for VTE risk stratification in patients with RA.

Key messages

What is already known about this subject?

- Patients with rheumatoid arthritis (RA) may be at increased risk of venous thromboembolism (VTE), but how any risk increase varies with RA disease activity is not known.

What does this study add?

- In this nationwide study, there was a close to doubled risk of VTE in patients with RA compared with the general population.
- We noted strong associations between measures of RA disease activity and risk of VTE events, for example, a twofold increase in risk from Disease Activity Score 28 (DAS28) remission to DAS28 high disease activity.

How might this impact on clinical practice or future developments?

- These results may be used as a basis for clinical VTE risk stratification in patients with RA.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), are common medical concerns associated with significant morbidity and mortality.[1] Established VTE risk factors include age, immobilisation, surgery, specific drugs and comorbid conditions such as malignancy, ischaemic heart disease, chronic obstructive pulmonary disease and hospitalised infection.[2]

Several studies have demonstrated that patients with rheumatoid arthritis (RA) are, on average, at increased risk for VTE.[3–10] By contrast, few if any studies have investigated the underlying reasons for this risk increase, let alone how it varies across patient subsets. Many established VTE risk factors occur more often in patients with RA. In vitro and in vivo studies have shown that aspects of inflammation might increase VTE risk by upregulation of procoagulatory factors and through endothelial damage.[11 12] Whether and how much clinical RA disease activity is linked to VTE risk remains to be understood. Such information would be important for a better understanding of the nature of the observed overall risk increase, and might constitute an important means for risk stratification in clinical practice, and in clinical trials.

The need for a better understanding of the association between the RA phenotype and VTE risk has radically increased with the recent safety signals arising from trials of Janus kinase inhibitors (JAKi). In 2019, and based on an increased number of VTE events in patients treated with the higher dose (10 mg) in an ongoing postmarketing safety trial, the European Medicines Agency and the US Food and Drug Administration issued caution for VTE events in patients treated with tofacitinib.[13 14] It remains unclear, however, if the purported VTE risk increase with JAKi is mainly explained by the drug itself, by the underlying disease, or by other factors.

The aims of this study were therefore to (1) investigate the relationship, if any, between clinical RA disease activity and the incidence of VTE, and

(2) for contextualisation, to assess the incidence of VTE in RA patients relative to individuals without RA.

METHODS

Study design

We performed a nationwide cohort study of the association between clinical RA disease activity and VTE risk. We also compared VTE incidence in the RA population relative to matched general population referents.

Setting

Sweden has a population of around 10 million. Healthcare is publicly funded for all residents. Drug prescriptions are free of charge after an annual threshold of €220. Most patients with RA are treated by rheumatologists based at public hospitals.

Data sources

We identified a cohort of patients with RA from the Swedish Rheumatology Quality Register (SRQ), a large longitudinal clinical RA register operated by the Swedish Society for Rheumatology since the mid-1990s. SRQ contains longitudinal information on RA disease activity and treatment. Typically, at each outpatient visit to a rheumatologist, data are entered into SRQ by the rheumatologist, data on patient-reported outcome measures are entered by the patient. Cumulatively, SRQ holds information on around 52 000 patients with RA. We linked this RA cohort to a series of other national and population-based Swedish registers: The Swedish National Patient Register, the Prescribed Drug Register, the Cause of Death Register and the Swedish Population Register. The National Patient Register contains information, including all registered International Classification of Diseases (ICD) codes, on hospital discharges from inpatient care since 1969, and visit data from non-primary outpatient care since 2001. Since 1987, the inpatient coverage is >99%.[15] The Prescribed Drug Register contains information on all dispensations of prescribed drugs since 2005. The Cause of Death Register contains information about all deaths and causes (main and contributory ICD codes) since 1961. The Swedish Population Register contains information on residence and domicile, civil status and migration data for all inhabitants of Sweden. Individual-level data from these registers can be linked together using a unique personal identification number issued to all Swedish residents.

Study population and exposure

We identified all patients ≥18 years of age with a rheumatologist-based diagnosis of RA, and who had at least one visit registered in the SRQ during 1 January 2006 to 31 December 2017 (46 316 patients with RA who contributed data from 322 601 visits). For each visit, we obtained data on Disease Activity Score 28 ESR (hereafter DAS28) and its components (main outcome), Health Assessment Questionnaire (HAQ) and other clinical RA-variables, where available. We categorised each visit by its recorded DAS28 category; remission (0–2.6), low (2.7–3.2), intermediate (3.3–5.0) and high (>5.0) disease activity. For each unique patient, we randomly selected five referents from the Swedish Population Register (n=215 843), individually matched by sex, year of birth and residential area. Online supplemental table S1 describes the creation of the datasets.

Outcome

Through linkage to the Patient Register, the Prescribed Drug Register and the Cause of Death Register we identified incident VTE events occurring during the 365 days after each registered visit. One individual could thus contribute to more than one visit (and with more than one VTE event); each visit had its own baseline covariate status. In the main analysis, incident VTE was defined as a registration of any VTE diagnosis within the 365-day period in the Patient Register (inpatient and specialised outpatient care) or PE listed as underlying cause of death in the Cause of Death Register (online supplemental table S2 and online supplemental figure S1). We excluded visits for which the patient had a registered VTE event within the prior year, since VTE during this time was considered a prevalent VTE. Patients with a more distant history of VTE were included. If death (other than from PE) or emigration occurred during the 1-year follow-up that visit was excluded. For the general population referents, the 1-year follow-up period for assessment of incident VTE events started at the same date as the rheumatologist visit for their corresponding patient with RA.

Statistical analyses

We calculated the cumulative 1-year incidence for VTE in the RA population, by each DAS28 category, and in the general population referents. Risk ratios for the association between each DAS28 category and VTE risk, and for the RA population versus the general population referents, were calculated using log-binomial regression. We used robust cluster SEs to account for the correlated data structure in which one individual could contribute more than one visit. Models were adjusted for age at visit, via a restricted cubic spline with 3 df, sex and calendar year of visit (categorised 2006–2009, 2010–2013, 2014–2017). To test the robustness of our findings in relation to the definition of VTE, the length of the time window and the selection of rheumatologist visits, we performed a series of sensitivity analyses, as summarised in online supplemental table S2. We also performed multiple imputation (MI) using chained equations with 30 imputations to impute missing DAS28 category (17% of all visits); multinomial regression was used for MI which included the VTE outcome, indicators for PE/DVT, age, sex and year. All analyses were performed using Stata V.16.[16]

RESULTS

Table 1 displays characteristics at each rheumatologist-visit for the entire RA population, overall and separately according to the DAS28 category at the visit (percentage missing for each variable presented in online supplemental table S3). Comparing patient characteristics by DAS28 category, we noted even distribution regarding RA treatment and socioeconomic characteristics, but a slightly increased prevalence of comorbidities at visits with high DAS28 disease activity (vs remission). Online supplemental table S3 displays characteristics at the first and last visit.

Table 2 presents the number of VTE events and cumulative incidences of VTE for the entire RA population, by each DAS28 category, and for their general population referents, overall and by VTE subtype, sex and age. In the RA population, 2241 visits in 1360 unique individuals were followed by a VTE within 1 year. Of these, 1408 were DVT events and 833 were PE events.

The overall cumulative 1-year incidence of VTE was 0.71% in the RA population (ie, across all DAS28 categories) and 0.36% among their general population referents, corresponding to an adjusted risk ratio of VTE in RA of 1.88 (95% CI 1.65 to 2.15). In both populations, the incidence of DVT was about twice as that of PE. The cumulative incidence of VTE was higher in males, and increased with increasing age.

Table 1 Characteristics at each rheumatologist visit for entire study population and stratified by DAS28 category, in Swedish patients with RA registered in the Swedish Rheumatology Quality register from 2006 until 2017

		DAS28 category			
	RA population	Remission	Low	Intermediate	High
Observations (n)	322 601	97 347	43 756	94 611	33 217
Individuals (n)	46 316	29 264	22 637	31 611	17 385
Age at visit, median (IQR)	63 (52–71)	62 (50–70)	64 (54–72)	63 (53–71)	63 (53–71)
Females (%)	74	67	75	78	78
RA duration, median (IQR)	8.7 (3.2–17.6)	8.1 (3.2–15.9)	9.8 (3.8–19.1)	9.3 (3.2–18.7)	7.0 (1.5–16.2)
Clinical RA data					
DAS28ESR, median (IQR)	3.1 (2.2–4.3)	1.9 (1.5–2.3)	2.9 (2.8–3.1)	4.0 (3.6–4.5)	5.8 (5.4–6.3)
DAS28CRP, median (IQR)	2.9 (2.0–3.9)	1.9 (1.6–2.2)	2.6 (2.3–3.0)	3.7 (3.2–4.2)	5.3 (4.9–5.9)
CRP, median (IQR)	5.0 (2.0–10.0)	3.0 (1.0–5.0)	4.9 (2.0–8.0)	5.4 (3.0–12.0)	16.0 (7.0–36.0)
ESR, median (IQR)	14.0 (8.0–26.0)	8.0 (4.0–13.0)	14.0 (8.0–24.0)	20.0 (12.0–31.0)	36.0 (23.0–55.0)
HAQ, median (IQR)	0.8 (0.3–1.3)	0.3 (0.0–0.8)	0.8 (0.3–1.1)	1.0 (0.6–1.4)	1.4 (1.0–1.9)
Swollen joint count, median (IQR)	1.0 (0.0–3.0)	0.0 (0.0–0.0)	0.0 (0.0–2.0)	2.0 (1.0–4.0)	8.0 (5.0–11.0)
Tender joint count, median (IQR)	1.0 (0.0–4.0)	0.0 (0.0–0.0)	1.0 (0.0–2.0)	3.0 (1.0–5.0)	10.0 (6.0–14.0)
VAS global, median (IQR)	33.0 (14.0–57.0)	13.0 (4.0–28.0)	30.0 (15.0–48.0)	47.0 (29.0–64.0)	70.0 (54.0–81.0)
VAS pain, median (IQR)	32.0 (13.0–57.0)	13.0 (4.0–28.0)	28.0 (14.0–47.0)	45.0 (28.0–64.0)	69.0 (52.0–80.0)
Seropositive, (%)	77	75	78	78	77
Seronegative, unknown (%)	24	25	23	22	23
Smoker (%)	56	55	58	58	58
Comorbidities*					
ACS (%)	2	2	3	3	3
Other cardiac disease (%)	26	22	27	28	30
VTE (%)	1	1	1	1	2
Chronic kidney disease (%)	1	1	1	1	2
Cancer (in past 10 years) (%)	4	3	4	4	5
COPD (%)	15	12	15	16	17
Diabetes (%)	9	7	9	10	12
Surgery (%)†	3	3	4	4	4
No of hospitalisations, median (IQR)	6 (3–12)	5 (2–9)	6 (3–12)	7 (4–14)	8 (4–15)
No of specialist care visits, median (IQR)	33 (18–60)	29 (16–51)	34 (19–60)	35 (18–63)	32 (15–61)
Treatments‡					
Methotrexate (%)	69	74	71	68	64
Other csDMARD (%)	18	16	18	20	19
TNFi (%)	33	33	35	33	31
Other b/tsDMARD (%)	12	10	10	13	17
No previous biologics, median (IQR)	1 (1–3)	1 (1–2)	1 (1–3)	1 (1–3)	1 (1–3)
NSAID/ASA (%)	59	54	58	63	69
Anticoagulant§ (%)	8	6	8	8	9
Oral oestrogen¶ (%)	14	13	15	15	14
Socioeconomic charcateristics					
Married/cohabiting partner (%)	53	55	53	52	51
Disability pension in previous year (%)	2	2	2	2	2
Sick leave in previous year (%)	12	12	12	13	12

*Registered within the last 5 years unless otherwise stated.
†Surgery (musculoskeletal, gynaecological, gastrointestinal or cardiovascular) within 90 days before visit.
‡RA treatments: at time of visit. Other treatments: Registered within the last year.
§Collected anticoagulant drug from pharmacy within 1 year before VTE event.
¶Oral contraceptive w oestrogen *or* hormone replacement therapy.
ACS, acute coronary syndrome; b/tsDMARD, biological or targeted synthetic disease-modifying antirheumatic drug; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; DAS28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire; HAQ, Health Assessment Questionnaire; NSAID/ASA, non-steroidal anti-inflammatory drug/acetylsalicylic acid; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhabitor; VAS, visual analogue scale; VTE, venous thromboembolism.

Within the RA population, we noted a strong association between RA disease activity and the 1-year cumulative incidence of VTE, table 2 and figure 1. The 1-year incidence of VTE events increased from 0.52% following visits in DAS28 remission, via 0.63% and 0.80% for low and moderate DAS28, respectively, to 1.08% following visit with a DAS28 above 5.1, which corresponded to an adjusted risk ratio of VTE with high DAS28 RA disease activity (vs remission) of 2.03 (95% CI 1.73 to 2.38).

When contrasting the DAS28 categories to the general population referents, the adjusted risk ratio of VTE was 1.34 (95% CI 1.13 to 1.58) for patients in DAS28 remission, and 2.74 (95% CI 2.31 to 3.25) for those with high DAS28 (table 2).

Figure 2 displays the association between DAS28 and VTE stratified by VTE type (DVT vs PE), by personal history of VTE (yes vs no), by smoking status (smoker vs non-smoker) and by C reactive protein (CRP) level (<5 vs ≥5) at the visit. For each

Table 2 Cumulative incidence and risk ratio of VTE during 1-year follow-up after rheumatologist visit in Swedish patients with RA versus matched general population referents (1:5), and in DAS28 categories

	No of VTE events (cumulative incidence, %)					
	Within RA, between DAS28 categories					
	Remission	Low	Intermediate	High	Entire RA pop*	Gen pop
Type						
Any	496 (0.52)	271 (0.63)	743 (0.80)	350 (1.08)	2241 (0.71)	5301 (0.36)
DVT	346 (0.36)	170 (0.40)	467 (0.50)	196 (0.61)	1408 (0.45)	3303 (0.22)
PE	150 (0.16)	101 (0.24)	276 (0.30)	154 (0.48)	833 (0.26)	1998 (0.14)
Sex						
Male	188 (0.60)	71 (0.66)	190 (0.94)	78 (1.10)	664 (0.80)	1631 (0.43)
Female	308 (0.47)	200 (0.62)	553 (0.76)	272 (1.08)	1577 (0.68)	3670 (0.34)
Age						
18–49	37 (0.16)	23 (0.30)	54 (0.31)	24 (0.39)	174 (0.27)	419 (0.13)
50–74	332 (0.54)	174 (0.62)	450 (0.74)	215 (1.01)	1386 (0.68)	3541 (0.37)
75-	127 (1.06)	74 (1.03)	239 (1.65)	111 (2.27)	681 (1.44)	1341 (0.71)
	Risk ratios (95% CI)†					
	Within RA, between DAS28 categories					
	Remission	Low	Intermediate	High		
Unadjusted	1 (ref)	1.22 (1.05 to 1.43)	1.56 (1.37 to 1.76)	2.10 (1.79 to 2.46)		
Adjusted	1 (ref)	1.12 (0.96 to 1.31)	1.48 (1.30 to 1.68)	2.03 (1.73 to 2.38)		
	RA population (including DAS28 categories) versus general population					
	Remission	Low	Intermediate	High	Entire RA pop	Gen pop
Unadjusted	1.43 (1.28 to 1.59)	1.75 (1.52 to 2.01)	2.23 (2.02 to 2.45)	3.00 (2.62 to 3.43)	1.96 (1.83 to 2.11)	1 (ref)
Adjusted	1.34 (1.13 to 1.58)	1.51 (1.25 to 1.82)	1.99 (1.72 to 2.31)	2.74 (2.31 to 3.25)	1.88 (1.65 to 2.15)	1 (ref)

Patients and referents followed from first visit registered after 2006 until 2018.
*Includes VTE events following a visit with missing DAS28 value (n=381, 17% of all VTE events).
†Risk ratios adjusted for age, sex and calendar year.
DAS28, Disease Activity Score 28; DVT, deep vein thrombosis; PE, pulmonary embolism; RA, rheumatoid arthritis; VTE, venous thromboembolism.

of these analyses, we noted a pattern of increasing risk and risk ratios for VTE with increasing DAS28 similar to that of the main analysis. For instance, the risk ratio for PE was 3.06 (CI 2.36 to 3.97) for high DAS28 (vs remission), and the corresponding risk ratio for DVT was 1.59 (1.30–1.95). Importantly, although the risk ratios were largely similar across subgroups, the corresponding absolute 1-year risks varied across these patient subsets.

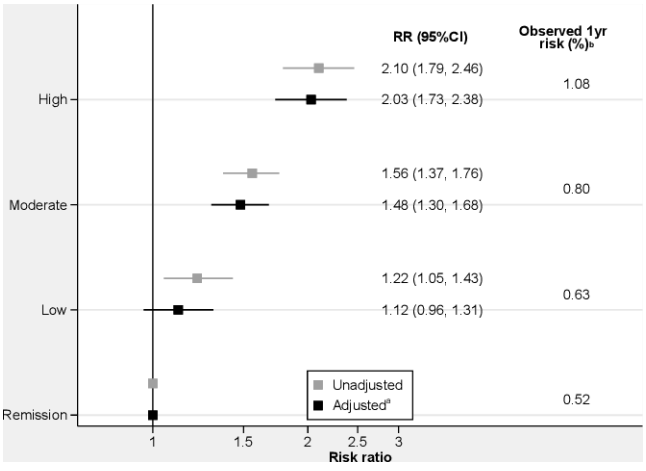

Figure 1 Risk ratios and absolute 1-year risks for the association between DAS28 and the risk of VTE within 1 year among Swedish patients with RA from 2006 until 2018. [a]Adjusted for age (restricted cubic spline), sex and calendar year of the visit year (categorised 2006–2009, 2010–2013, 2014–2017). [b]Absolute 1-year risks are calculated from observed data. DAS28, Disease Activity Score 28; RA, rheumatoid arthritis; VTE, venous thromboembolism.

For instance, among individuals with high DAS28 disease activity, the 1year risk for VTE was 7.8% for individuals with a history of VTE compared with 1.0% for individuals without previous VTE. Risk ratios and 1-year risks for VTE were relatively similar across strata as defined by RA serostatus, RA disease duration, sex and oral glucocorticoids (online supplemental figure S2 and online supplemental table S5).

Table 3 presents the association between individual DAS28 components and VTE risk, and the association between HAQ and VTE risk. The pattern for each DAS28 component, as well as HAQ, was largely similar to that of the main analysis.

Online supplemental table S6 presents the predicted 1-year risk of VTE in RA, from log binomial models, by age and gender. The risks varied from 0.2% to 0.4% (remission vs high DAS28) in the 40-year-old women, to the corresponding 1.1%–2.2% in the 80-year-old men.

In sensitivity analyses that altered the VTE definition, the width of the time windows, changed various definitions of our study population, and using imputed DAS28 values, results were similar to our main analysis (online supplemental figures S3, S4 and tables S7, S8).

DISCUSSION

Main findings

In this large nationwide study, to our knowledge the first to specifically investigate the association between measures of RA disease activity and VTE risk, we found a strong association between RA disease activity as measured by DAS28, as well as by its components and by HAQ, and the risk of VTE during the following year. The increase in risk with high DAS28 was twice as high for PE as for DVT. We also noted that compared with the

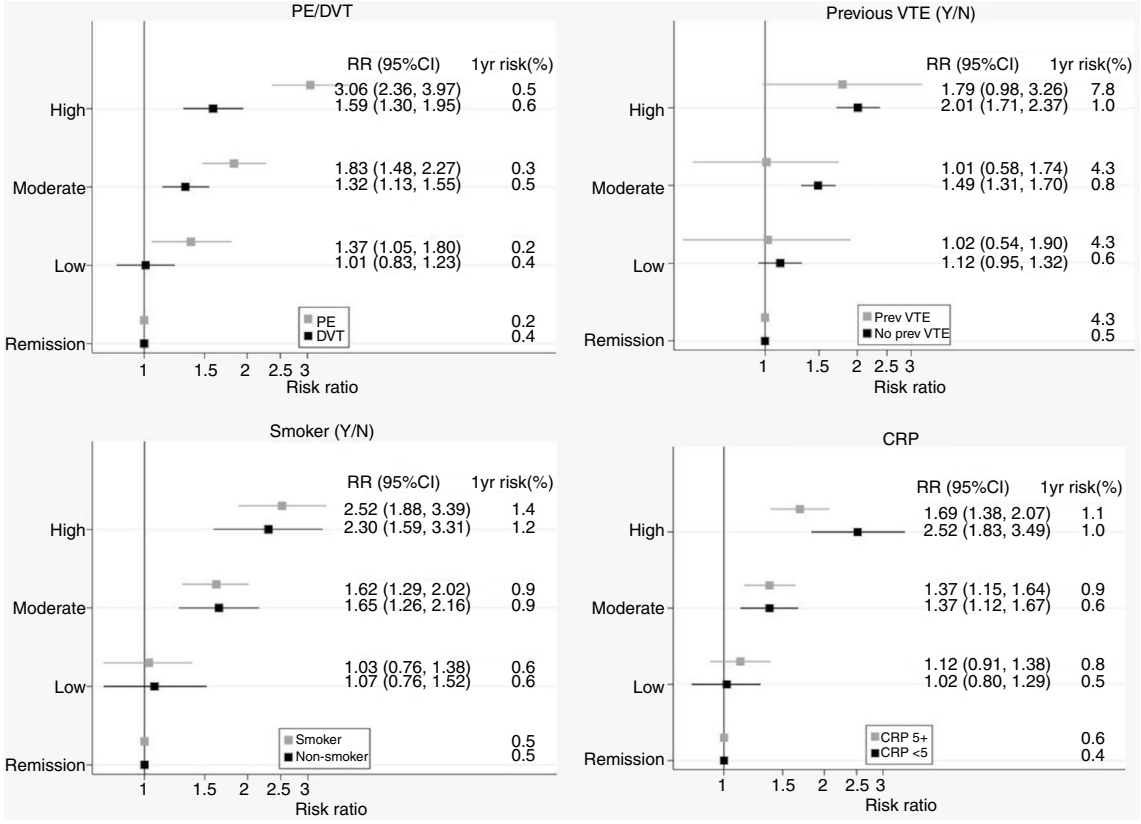

Figure 2 Risk ratios and absolute 1-year risks[a] for the association between DAS28 and VTE by specified stratification within 1 year among Swedish patients with RA. [a]Observed 1-year risk and adjusted risk ratios from log-binomial regression models adjusted for age (restricted cubic spline), sex and calendar year of the visit year (categorised 2006–2009, 2010–2013, 2014–2017). Absolute 1-year risks are calculated from observed data. CRP, C reactive protein; DAS28, Disease Activity Score 28; PE, pulmonary embolism; RA, rheumatoid arthritis; VTE, venous thromboembolism.

general population, even patients in DAS28 remission were at elevated VTE risk.

Few previous studies have investigated the relationship between characteristics in RA and VTE risk. One study on patients with RA (n=253 875) from a US claims database reported an increased incidence of inpatient VTE events in patients switching biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) treatment compared with patients remaining on a first b/tsDMARD or only conventional synthetic DMARD.[17] One might speculate that patients who switch b/tsDMARD on average have a higher disease activity than those who do not. If so, then the finding of an increased incidence of VTE among switchers of b/tsDMARD could be congruent with our findings, even if switching b/tsDMARD may occur for many other reasons than uncontrolled disease activity. Regarding RA disease activity and its role in coagulation, a cross-sectional study of 85 patients with RA reported an association between the rotational thromboelastometry (ROTEM) functional evaluation of the clotting cascade in whole blood, and DAS28.[18] However, in that study, the clinical correlation between the ROTEM analyses and incidence of clinical VTE was not studied.

Our results including stratifications and sensitivity analyses indicated a remarkable consistency in the pattern of association between RA disease activity and VTE risk. The risk ratios for the association between DAS28 and VTE were almost identical for patients with and without a history of VTE, demonstrating that the association between DAS28 and VTE risk is not confined to the patients with this history. At the same time, the absolute risk differences were much higher in patients with a history of VTE (8% vs 1% risk with high DAS28), indicating that the clinical significance of high RA disease activity is much larger in this patient subset, and that VTE risk stratification is especially important in this group of patients. By contrast, when stratified by CRP (<5 vs ≥5), the associations between increasing DAS28 and VTE risk were similar, as were the absolute 1-year risks in highly active RA (1.0% vs 1.1%), underscoring that the main result of this study is not necessarily driven by inflammation itself. Elevated CRP is known to cause pro-thrombotic activity and play a role in the pathogenesis of arterial thromboembolic events, although true causality with respect to VTE has not been established.[19] We also noted an association between HAQ and VTE risk, underscoring the known association between functional status/ mobility and VTE risk. Our stratification on smoking (yes vs no) showed no difference in either RR or absolute 1-year risk, but the limited access to smoking data in our population should be considered.

Important to keep in mind, this study investigated VTE risk in a 12 (and 6, respectively) month window after the visit, and therefore, does not claim that the VTE risk is particularly high at any specific time point in this window. Also, we set out to investigate the association between indices of RA disease activity and VTE risk, not risks with individual DMARDs or treatment strategies.

In keeping with our main aim of studying the association between DAS28 and VTE, we adjusted for age, sex and calendar period but not for other risk factors. Our study population mainly comprised prevalent RA, therefore, at the time point of each visit it is not possible to fully distinguish comorbidities and other covariates that might be true confounders from such that are consequential to the RA disease and potential mediators of

Table 3 Cumulative incidence and risk ratios (95% CI) for the components of DAS28 and HAQ

	No of VTE events (cumulative incidence, %)	Risk ratio* (95% CI) Unadjusted	Risk ratio (95% CI) Adjusted
Swollen joint count			
0	811 (0.59)	1 (ref)	1 (ref)
1–2	532 (0.72)	1.24 (1.10 to 1.39)	1.27 (1.13 to 1.43)
3–28	817 (0.87)	1.49 (1.33 to 1.67)	1.55 (1.38 to 1.74)
Tender joint count			
0	772 (0.61)	1 (ref)	1 (ref)
1–3	688 (0.74)	1.22 (1.10 to 1.36)	1.29 (1.16 to 1.44)
4–28	699 (0.82)	1.35 (1.19 to 1.52)	1.52 (1.35 to 1.72)
ESR			
0–10	589 (0.55)	1 (ref)	1 (ref)
11–21	595 (0.70)	1.28 (1.12 to 1.45)	1.11 (0.97 to 1.26)
22–488	833 (0.88)	1.61 (1.41 to 1.83)	1.24 (1.09 to 1.43)
Patient global health			
0–20	564 (0.55)	1 (ref)	1 (ref)
21–49	609 (0.65)	1.17 (1.03 to 1.32)	1.12 (0.99 to 1.27)
50–100	896 (0.92)	1.66 (1.47 to 1.89)	1.65 (1.46 to 1.87)
HAQ			
0–0.38	519 (0.53)	1 (ref)	1 (ref)
0.39–1.00	569 (0.63)	1.17 (1.01 to 1.35)	1.10 (0.95 to 1.27)
1.01–3.00	879 (0.95)	1.77 (1.55 to 2.04)	1.48 (1.29 to 1.71)

*Risk ratios estimated from separate unadjusted and adjusted (age, sex and calendar year of the visit year) log-binomial regression models where each of the separate exposures were categorised according to their tertiles.
DAS28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire; VTE, venous thromboembolism.

the very association under study. Our results, therefore, accurately reflect clinical risks and relative risks for VTE in RA and how these vary across RA disease activity and patient subsets, but do not directly inform on the relative importance of different components of this risk, for example, the relative contribution of different established VTE risk factors on this association. While directly applicable to clinical practice and amenable for use for clinical risk stratification, the results of our study, therefore, do not necessarily reflect any direct causality between each aspect of RA disease activity and VTE risk.

Limitations

Using a clinical register for identifying VTE events has benefits but could potentially result in underdiagnosis or overdiagnosis, and patients with RA are at risk for musculoskeletal conditions that could be misdiagnosed as DVTs. We, therefore, investigated a series of alternative definitions of VTE, including or not also anticoagulant treatment, and also considered DVT and PE events separately. Since the results demonstrated a pattern remarkably consistent with our main analysis, we find it unlikely that misclassification of VTEs had any significant effect on our results. Using DAS28 as a measure of disease activity is also a potential source of misclassification of true RA disease activity, since any concomitant condition causing elevated ESR, such as malignancies, will contribute to the DAS28 score. However, since the risk ratios for ESR and VTE risk were, if anything, lower than those for other individual DAS28 components, such misclassification of ESR is unlikely to be a source of significant bias in our study. We had somewhat limited data on smoking, and for certain other variables of interest, such as body mass index and immobility, information was not available.

Strengths

Using the SRQ to identify our RA cohort, we were able to include around 90% of all Swedish patients with RA treated by rheumatologists, which reduces the potential for selection bias and increases the generalisability of our findings. We linked these data to other nationwide registers based on prospectively recorded data of high internal validity and coverage for information on other variables, thereby reducing selection and information bias, and enabling comparisons both within RA and vs the general population. Our study demonstrated risk ratios of around 2.0 for VTE (DVT as well as PE) in RA compared with the general population. These results are similar to previous reports. For instance, in a previous study from our group, from 1997 to 2006 (ie, before the start of our study period) we noted HRs of around 2.[3] A UK study of a prevalent RA population (n=9589) from 1986 to 2010, reported RRs of around 2.2 for VTE, DVT and PE.[8] This consistency further speaks to the generalisability of the results regarding the association between RA disease activity and VTE risk.

CONCLUSION

In conclusion, we found evidence of a strong association, with clinically relevant differences in absolute risks, between RA disease activity measured by DAS28 and the subsequent risk of VTE, which may be used for clinical risk stratification. Also, patients in remission are at increased risk vs the general population. The absolute risk increase with disease activity highlights the need for proper VTE risk assessment in patients with RA, especially for those with a history of VTE or other known risk factors. Our findings also suggest that patients with active RA, such as those typically recruited to phase III trials, are at particular elevated risk for VTE.

Correction notice This article has been corrected since it published Online First. Table 2 has been increased in size for clarity.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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