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The Risk of Venous Thromboembolism in Patients with Rheumatoid Arthritis

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Abstract

BACKGROUND—Rheumatoid arthritis (RA) is associated with cardiovascular disease (CVD) but little is known about its association with another form of vascular disorder, venous thromboembolism (VTE).

METHODS—A retrospective cohort study was conducted using the US insurance claims. RA and non-RA patients were matched on age, sex, and index date. Incidence rates (IR) and rate ratios (RR) of VTE, defined as the composite of deep vein thrombosis (DVT) or pulmonary embolism (PE), were calculated. Cox proportional hazards models compared VTE risks between RA and non-RA patients, adjusting for VTE risk factors such as CVD, surgery, hospitalization, medications, and acute phase reactants (APR).

RESULTS—Over the mean follow-up of 2 years, the IR for VTE among RA patients was 6.1 per 1,000 person-years, 2.4 times higher (95%CI 2.1–2.8) than the rate of non-RA patients. The IRs for both DVT (RR 2.2, 95%CI 1.9–2.6) and PE (RR 2.7, 95%CI 2.2–3.5) were higher in RA compared with non-RA patients. After adjusting for risk factors of VTE, the VTE risk remained elevated in RA (hazard ratio 1.4, 95%CI 1.1–1.7) compared to non-RA patients. The result was similar after further adjustment for elevated APR (hazard ratio 1.5, 95%CI 0.3–6.5). One-third of patients who developed VTE had at least one major VTE risk factors 90 days before and after the VTE event.

CONCLUSION—Our results showed an increased risk of developing VTE for RA patients compared with non-RA patients. The risk was attenuated but remained elevated even after adjusting for various risk factors for VTE.

Keywords

rheumatoid arthritis; venous thromboembolism; pulmonary embolism; deep vein thrombosis

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Competing interests
Liu has nothing to disclose for financial support or conflict of interest

INTRODUCTION

Venous thromboembolism (VTE) which includes deep vein thrombosis (DVT) and pulmonary embolism (PE) is a major health problem and occurs in approximately 1 per 1,000 persons in the U.S.(1) The incidence increases dramatically with age. Other known risk factors for VTE are fracture of lower extremities, joint replacement surgery, major general surgery, major trauma, malignancy, heart or respiratory failure, pregnancy, history of VTE, hormone replacement therapy and oral contraceptive use, but do not traditionally include inflammatory diseases such as rheumatoid arthritis (RA).(2, 3) The link between chronic systemic inflammatory diseases, such as RA, and cardiovascular disease (CVD), including myocardial infarction and stroke, has been well documented.(4–7) Systemic inflammation may also play a important role in the development of VTE as inflammatory cytokines such as interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF) could modulate thrombotic responses by activating coagulation pathways.(8, 9) Markers of systemic inflammation, such as C-reactive protein (CRP), fibrinogen, and factor VIII, are also found at higher levels in patients with VTE, similar to atherothrombosis.(10, 11)

Recent studies report that patients with RA have a 1.5- to 6-fold increased risk of VTE, such as pulmonary embolism (PE) and deep vein thrombosis (DVT) compared to non-RA patients.(12–18) Many of these studies identified their RA cohort based on a hospital discharge diagnosis of RA which could introduce a bias to select patients with severe RA and hence may not be generalizable to typical RA patients seen in the outpatient setting.(13–16) Furthermore, no prior studies have examined the VTE risk in RA adjusting for acute phase reactant levels. The objectives of this study are 1) to examine the rate of incident VTE in a cohort of patients with RA compared with those without RA in the general population, 2) to assess the VTE risk in RA compared to non-RA adjusting for a number of known risk factors for VTE as well as baseline acute phase reactant levels, and 3) to determine the proportion of VTE cases in the presence of major VTE risk factor such as recent hospitalization, surgery and malignancy during the follow-up period.

METHODS

Data Source

We conducted a cohort study using the claims data from a commercial U.S. health plan which insures primarily working adults and their family members, and a small Medicare population for the period January 1, 2001 through June 30, 2008. This database contains longitudinal claims information including medical diagnoses, procedures, hospitalizations, physician visits, and pharmacy dispensing on more than 28 million fully-insured subscribers, with medical and pharmacy coverage, to 14 Blue Cross/Blue Shield health plans across the United States. Results for outpatient laboratory tests, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were available on a subset of beneficiaries. Personal identifiers were removed from the dataset before the analysis to protect subject confidentiality. Patient informed consent was not required. The study protocol was approved by the Institutional Review Board of Brigham and Women’s Hospital.

Study Cohort

Adult patients who had at least two visits seven days apart coded with the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD 9-CM) code, 714.xx, for RA were eligible for the RA cohort. The index date for the RA cohort was the date of the first dispensing of a disease-modifying anti-rheumatic drug (DMARD) after at least 12 months of continuous health plan eligibility; thus, all persons in the RA cohort were required to have had two diagnoses and at least one filled prescription for a DMARD at the start of follow-up. A previous validation study showed that RA patients can be accurately identified using a combination of diagnosis codes and DMARD prescriptions in insurance claims data.(19) Patients with one or more diagnostic codes of DVT or PE, solid tumors, hematologic malignancies, or myelodysplastic syndrome recorded in the 12-month period prior to index dates were excluded. To ensure that we only include incident cases of VTE, subjects with claims for DVT or PE, or dispensings for anticoagulants in the 12-month period prior to index dates were also excluded from both cohorts. (See Appendix 1 for the list of diagnosis codes for VTE and the name of anticoagulants that were excluded).

The non-RA cohort, defined as adults who never had a diagnosis of RA during the study period, were identified and the aforementioned exclusion criteria were applied. The index date for the non-RA cohort was the second physician visit date after at least 12 months of continuous health plan eligibility. The non-RA cohort was then matched to the RA cohort on age, sex and index date (+/− 30 days) with a 4:1 ratio to mirror the health care utilization of the RA cohort. Patients in both cohorts were followed from the index date to the first of any of the following censoring events: development of DVT, PE, loss of health plan eligibility, end of study database, or death.

Outcome Definition

The primary outcome was defined as a hospitalization for the composite endpoint of incident VTE, either PE or DVT, based on discharge diagnosis codes within the study database.(20, 21) The secondary outcome was defined more strictly with a combination of hospital discharge diagnosis codes for VTE and a prescription for anticoagulants within ten days after discharge date (Appendix 1).

Covariates

Variables potentially related to development of VTE were assessed using data from the 12 months before the index date. These variables included demographic factors (age and sex), comorbidities (hypertension, CVD, chronic obstructive pulmonary disease, diabetes, heart failure, chronic kidney disease, liver disease, malignancy, smoking, varicose vein, obesity, and history of various types of surgeries), medications (oral contraceptives and hormone replacement therapy), and health care utilization factors (the number of visits to any physicians and acute care hospitalizations, and the number of different prescription drugs). To quantify patients' comorbidities, we also calculated the Deyo-adapted Charlson Comorbidity Index based on ICD-9-CM.(22, 23) The Comorbidity Index is a summative score, based on 19 major medical conditions including myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, pulmonary, renal, hepatic disease, diabetes, ulcer, connective tissue disease, cancer, and HIV infection.

A score of 0 representsabsenceof comorbidity and a higher score indicates a greater number of comorbid conditions. Outpatient laboratory data such as levels of acute phase reactants (i.e., ESR or CRP) at baseline were available in a subgroup of the study cohort.

In patients who developed VTE during the follow-up, major clinical risk factors or provoking factors for VTE such as malignancy 90 days before and after the VTE and hospitalization and surgeries 90 days before the date of VTE events were assessed.(24)

Statistical Analyses

We compared the baseline characteristics between RA and non-RA patients. We estimated incidence rate (IR) of VTE events with 95% confidence interval (CI), calculated as the number of subjects who had a hospitalization for either DVT or PE divided by the total person-time, in both RA and non-RA cohorts. The rate ratio (RR) with 95% CI was estimated by dividing the rate of the VTE events among RA patients by that of non-RA.(25) To adjust for potential confounders, separate Cox proportional hazard models were used to compare the rate of VTE events among RA patients with those in non-RA cohort.(26) The relationship between RA and the proportion of patients free of VTE was plotted on a Kaplan-Meier curve. Additionally, we conducted subgroup analyses for the primary outcome in patients in whom we had an acute phase reactant measurement at baseline. Among these subjects, the acute phase reactant levels were used as a covariate in Cox proportional hazard models comparing the risk of a hospitalization for VTE in RA with non-RA. All analyses were done using SAS 9.2 Statistical Software (SAS Institute Inc., Cary, NC).

RESULTS

Cohort Selection

There were initially 92,827 subjects with at least one RA diagnosis after a 12-month-enrollment period and 920,697 subjects with no RA diagnosis at any time during the entire study period. Of the potential 44,978 RA patients with at least two diagnoses of RA at least seven days apart, 25,065 patients had at least one prescription for DMARDs. 700,647 patients with no RA had at least two physician visits after a 12-month-enrollment period. There were 6,138 patients with a history of VTE in the 12-month baseline period. After applying the exclusion criteria, we selected four non-RA patients matched to each RA patient on age, sex, and index date (+/− 30 days). Our final study cohort includes 22,143 RA patients and 88,572 non-RA patients. Figure 1 displays our cohort selection process. The mean (SD) follow-up time was 2.0 (1.6) years for RA and 2.0 (1.5) years for non-RA patients.

Patient Characteristics

Baseline characteristics of the age- and sex-matched cohorts were compared (Table 1). The mean age was 52 years and 75% were women in both cohorts. Substantial differences across almost all other baseline characteristics were observed between the cohorts, with the prevalence of comorbid conditions that may be related to VTE risks more common in RA patients than non-RA subjects. A recorded diagnosis of smoking, hypertension, CVD,

chronic obstructive pulmonary disease, and intra-abdominal surgery, hormone replacement therapy and oral contraceptive use, and health care utilization including physician visits, hospitalization, and number of prescription drugs were more commonly noted in patients with RA. The mean (SD) length of hospitalization among those who had at least one hospitalization in the baseline 365-day period was 7.2 (12.0) days for the RA cohort and 5.9 (11.1) days for the non-RA cohort. 15% of RA patients and 1% of non-RA patients had their baseline acute phase reactants measured (see Appendix 2). Thirty-seven percent of RA and 18% of non-RA patients with a baseline acute phase reactant level measurement available had elevated levels. The mean (SD) CRP level at baseline was 15.2 (28.1) milligram per liter for RA and 3.4 (6.1) milligrams per liter for non-RA patients. The mean (SD) ESR at baseline was 19.3 (21.9) millimeters per hour for RA and 10.2 (14.0) millimeters per hour for non-RA patients.

Risk of Venous Thromboembolism

During the study follow-up, 713 (0.6%) of the study population were hospitalized for VTE. Of these patients with VTE, 42.8% received a dispensing for an anticoagulant within 10 days after hospital discharge and 47.1% received a dispensing for an anticoagulant within 30 days after hospital discharge. Among those who developed VTE events during the follow-up time, the mean (SD) length of hospitalization was 13.8 (19.1) days for the RA cohort and 12.9 (18.9) days for the non-RA cohort. As shown in Table 2, the IR of the primary outcome, hospitalization for VTE among RA patients was 6.1 per 1,000 person-years and 2.4 times higher than that of non-RA patients (2.5 per 1,000 person-years). The age and sex-adjusted RR of RA was 2.2 (95 % CI, 1.9–2.6) for experiencing DVT and 2.7 (95% CI, 2.2–3.5) for PE, compared to non-RA. Similar risks were observed for the secondary outcomes, defined by both diagnosis codes and dispensings of anticoagulants.

Age and sex-adjusted hazard ratio (HR) of VTE for RA compared with non-RA was 2.5 (95% CI, 2.2–2.9). After adjusting for all the potential confounders of VTE including demographic factors, comorbidities, medications, and health care utilization characteristics (listed in Table 1), the VTE risk remained elevated in RA (HR 1.4, 95% CI, 1.1–1.7) compared to non-RA patients. The fully adjusted HR was 1.2 (95% CI, 0.9–1.5) for DVT and 1.9 (95% CI, 1.3–2.7) for PE. The HRs were very similar for the secondary definitions of VTE (Table 3). Figure 2 shows the Kaplan-Meier curves for hospitalization for VTE in RA and non-RA patients. 84.2% of VTE events in RA and 85.5% of VTE events in non-RA occurred in the first three years of follow-up.

Among 713 patients who developed incident VTE, 57% of RA and 60% of non-RA patients had a hospitalization, surgery or a new diagnosis of malignancy, which are considered major VTE risk factors or provoking factors 90 days before the VTE event and a diagnosis of malignancy 90 days after the time of the VTE event. (Table 4) About one-third of those with incident VTE had at least one antecedent major risk factor in the 90 days prior to VTE events.

Subgroup Analyses on Laboratory Data

In a subgroup of patients (N=4, 153) with the baseline acute phase reactant levels available, a total of 22 (0.5%) hospitalizations for VTE occurred. The multivariable HR for VTE associated with RA was 1.7 (95% CI, 0.5–5.9) adjusted for age, sex, and elevated acute phase reactants. After adjusting for age, sex, Comorbidity index and elevated acute phase reactants, the multivariable HR was 1.3 (95% CI, 0.4–4.4). The fully adjusted model that further adjusted for elevated acute phase reactants showed the HR of 1.5 (95% CI, 0.3–6.5) associated with RA.

DISCUSSION

The link between RA and VTE is not yet clearly understood, it has been thought that hypercoagulability is induced by active systemic inflammation and production of cytokines such as TNF–alpha and IL-1. These inflammatory cytokines can lead to endothelial dysfunction, down-regulation of protein C and inhibition of fibrinolysis.(8, 9, 27) It is also possible that patients with RA have more risk factors of VTE such as acute hospitalization, surgical procedures, physical inactivity, and other cardiovascular comorbidities compared to non-RA. This study found that the occurrence of hospitalization for VTE in patients with both RA and non-RA is uncommon, but the risk of incident VTE is increased by 40% in patients with RA compared to non-RA in a fully adjusted analysis accounting for more than 20 different potential confounders. The result remain consistent even after adjusting for elevated acute phase reactants, albeit not statistically significant due the small number of events in this subgroup.

It is well-known that VTE is associated with a number of risk factors such as lower extremity fracture, joint replacement surgery, major general surgery, major trauma, spinal cord injury, congestive heart failure, hormone replacement therapy and oral contraceptive use, and older age.(2) It is also known that nearly all patients who develop VTE have at least one recognized clinical factor associated with VTE, and the risk of VTE increases as the number of VTE risk factors increases.(2, 28, 29) In the present study, 57% of RA and 60% of non-RA patients who developed VTE during the follow-up time had at least one major VTE risk factor, such as a recent hospitalization, surgery, or a diagnosis of malignancy 90 days before or a diagnosis of malignancy 90 days after the date of VTE events.

Several strengths of this study are worth noting. First, we examined a large cohort of RA and non-RA patients in a population that is representative of the U.S. commercially-insured population. Second, although we mainly relied on diagnosis codes for RA and VTE which could potentially lead to exposure and outcome misclassification, both the ICD diagnosis codes for RA and VTE have been validated and used in a number of studies. (19, 20) Moreover, event rates observed in this study are consistent with prior studies: the IR of VTE in non-RA patients, 1 to 2 per 1,000 person-years, is consistent with prior studies,(1, 17,18, 30, 31) and the IR in RA patients was 6 per 1,000 person-years, similar to a previously reported IR which used medical records to define the outcome.(12) Third, we conducted a subgroup analysis of patients with baseline CRP or ESR levels measured and noted a consistently elevated risk of VTE, albeit not statistically significant due to a smaller size of the subgroup, between the RA and non-RA cohorts.

Finally, unlike most published studies that examined the risk of VTE in RA patients based on hospital diagnosis of RA,(13–16) our study cohort was mainly selected based on outpatient RA diagnoses (94%) to be representative of RA patients seen in an ambulatory setting. Our results are also consistent with findings from a recently published cohort study using data from the U.K outpatient medical records.(17) Acute medical hospitalization is a known risk factor for VTE regardless of RA diagnosis.(32) Furthermore, very active RA requiring acute hospitalization could be a potential confounder for the association between RA and VTE. A Swedish study based on patients admitted to hospital for an autoimmune disease reported that PE is a serious problem in this population and the standardized incidence ratio for RA was 6.0 (95% CI 5.6–6.4) in the first year after hospital admission.(16) Another Swedish population-based study also showed a higher rate of VTE in the first year following hospitalization in both RA patients (13.1 per 1,000 person-years) and the general population (2.4 per 1,000 person-years).(18) In a study from the U.S., the adjusted RR of VTE in hospitalized RA patients who did not have an orthopaedic surgery was 2.0 (95% CI 2.0–2.0) compared to non-RA patients.(13) Similarly, a Danish population-based study showed that the adjusted RR for VTE was 1.2 (95% CI 1.0–1.3) among patients with a history of hospitalization for RA.(15)

There are, however, limitations to our study. First, this cohort study is likely subject to residual confounding by body mass index, immobility, severity of heart failure or chronic obstructive pulmonary disease, hereditary hypercoagulable conditions, and other unmeasured risk factors including RA disease severity as well as surveillance bias.(2, 33) A previous U.S. population-based study of 464 RA and 464 non-RA patients, however, reported that there was no significant association between VTE risk and RA disease activity such as presence of rheumatoid factor, presence of joint erosions or destructive changes, or rheumatoid nodules.(12) We assessed a prior diagnosis of VTE, use of anticoagulants and a number of variables potentially related to a future VTE event using the data from the 12 months prior to the index date, but this time period might not be long enough to capture all the information on preexisting diagnosis of VTE and/or potential confounders. We also used multivariable Cox models that were simultaneously adjusted for more than 20 risk factors of VTE, the Comorbidity Index and health care utilization patterns to minimize the effect of such confounders.

Second, we relied on prescription dispensing records in the database to determine patients' drug exposures including anticoagulants. This may not be the most accurate way to verify individuals' daily drug exposures, but it is considered one of the best ways to ascertain drug exposure status in non-experimental settings.(34) Lastly, this study was not designed to address a potential role of DMARDs including TNF-α inhibitors in the risk of incident VTE among RA patients. There is limited data suggesting an increased risk of VTE associated with use of DMARDs.(12, 35, 36) The exact effects of DMARDs, either traditional or biologic DMARDs, on the risk of VTE in RA should be further studied, given the large degree of potential for confounding by indication.

Third, because our primary outcomes were based on a hospital discharge diagnosis of VTE, not an admission diagnosis, some of the VTE cases might have occurred during the

hospitalization for a different reason. In this study, mild cases of VTE treated in the outpatient setting were not included.

In conclusion, our results showed an increased risk of incident VTE, both DVT and PE, for RA patients compared with non-RA patients. The risk was attenuated but remained elevated after adjusting for known risk factors for VTE such as CVD, surgery, hospitalization, and medications and elevated acute phase reactants levels. Future research is needed whether treatment with DMARDs could modify the risk of VTE in patients with RA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Significance and Innovation

- Incident VTE occurred in 6 per 1,000 RA patient-years, 2.4 times higher than the rate of age, sex, index date-matched patients without RA.
- There was a 40% increased risk of developing VTE in RA patients compared with non-RA patients after adjusting for baseline VTE risk factors.
- One-third of patients who developed VTE had at least one major VTE risk factors such as acute hospitalization, surgery and malignancy diagnosis 90 days before and after the VTE event.

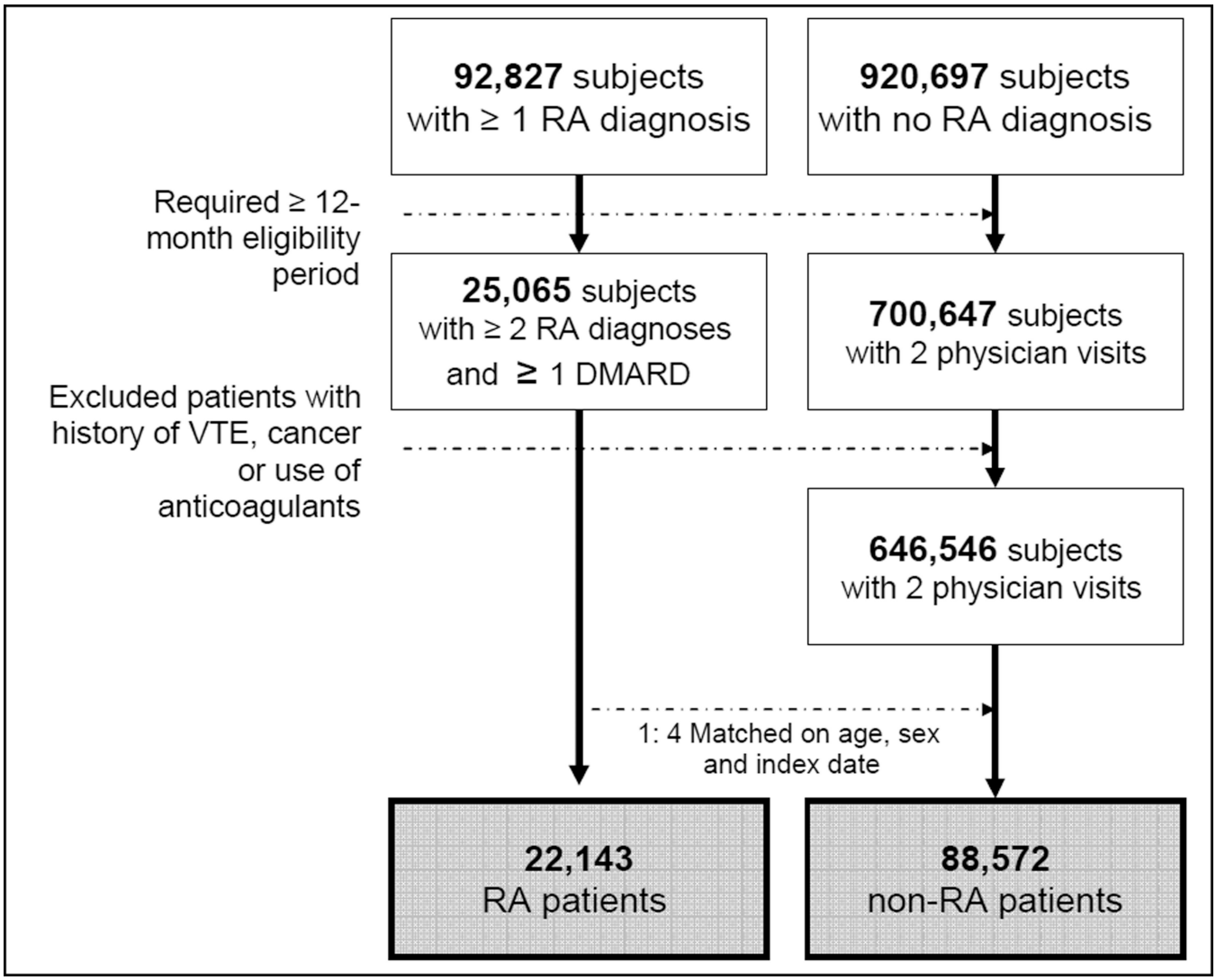
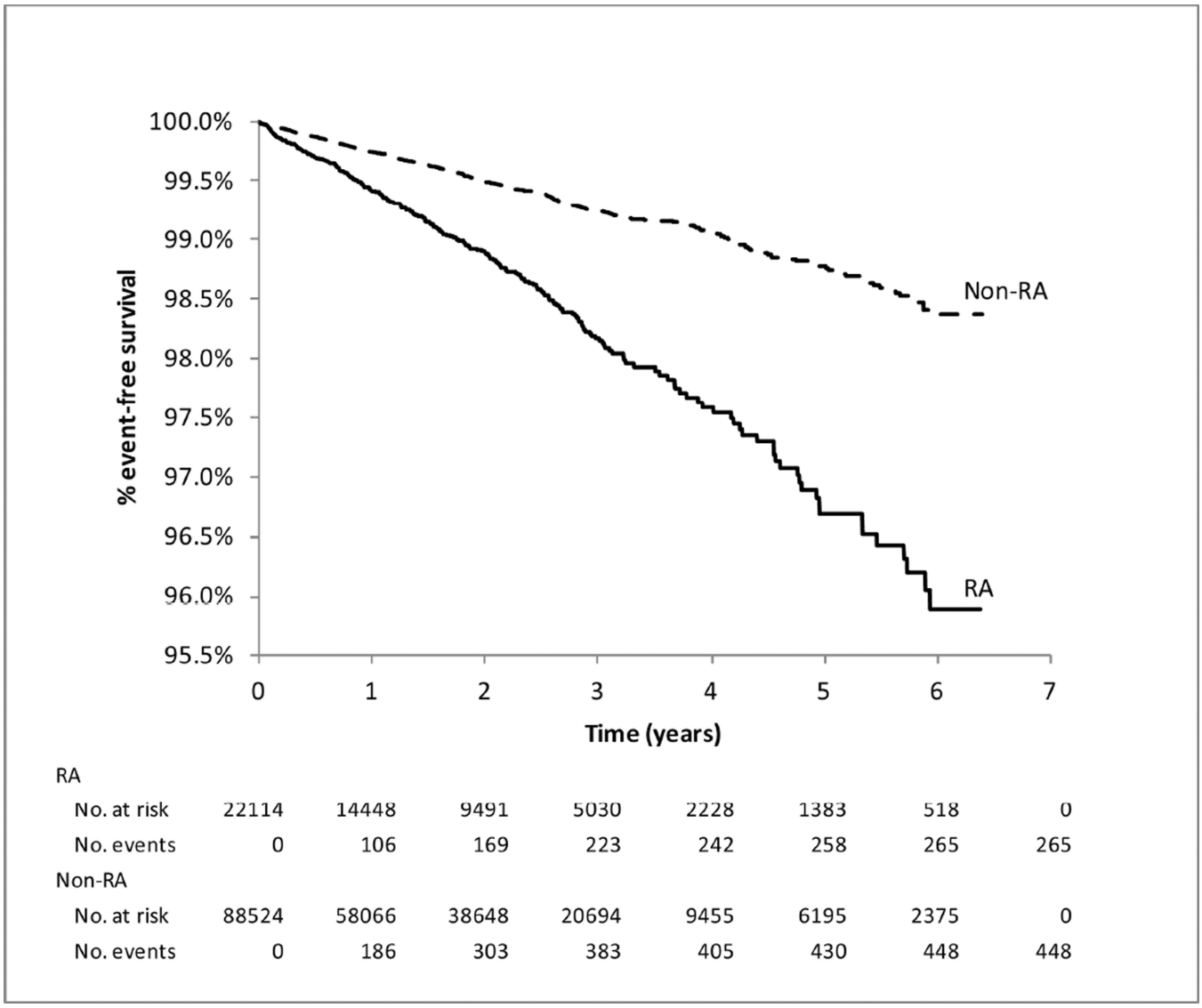


Figure 1. Selection of the study cohort

The final study cohort included 22,143 RA patients and 88,572 non-RA patients matched on age, sex and index date.

RA: rheumatoid arthritis, DMARD: disease-modifying antirheumatic drug, VTE: venous thromboembolism



RA								
No. at risk	22114	14448	9491	5030	2228	1383	518	0
No. events	0	106	169	223	242	258	265	265
Non-RA								
No. at risk	88524	58066	38648	20694	9455	6195	2375	0
No. events	0	186	303	383	405	430	448	448

Figure 2. Kaplan–Meier survival curves for hospitalization for VTE in patients with and without rheumatoid arthritis (RA)

Number of subjects at risk and events were stratified by time since the index date.

Table 1

Baseline characteristics of the study cohort in 12 months prior to the index date

	Rheumatoid arthritis (N=22,143)	Non-rheumatoid arthritis (N=88,572)
	N (%) or mean ± SD	
Follow-up period, years	2 (1.5)	2 (1.5)
Demographic		
Age*, years	52.2 ± 12	52.2 ± 12
Female*	16,513 (75)	66,052 (75)
Comorbidities		
Comorbidity Index	1.2 ± 0.8	0.2 ± 0.6
Diabetes	1,132 (5)	3,827 (4)
Obesity	531 (2)	1,809 (2)
Smoking	1,446 (7)	3,614 (4)
Varicose vein	180 (1)	494 (1)
Chronic kidney disease	333 (2)	651 (1)
Liver disease	604 (3)	1,370 (2)
Hypertension	6,747 (30)	20,880 (24)
Cardiovascular disease	1,496 (7)	4,222 (5)
Stroke	658 (3)	1,841 (2)
COPD	2,754 (12)	6,467 (7)
Heart failure	410 (2)	915 (1)
Pregnancy	253 (1)	1,531 (2)
Hormone replacement therapy	3,304 (15)	10,234 (12)
Oral contraceptives	1,805 (8)	6,416 (7)
Oral steroids	11,730 (53)	5,948 (7)
Surgery, musculoskeletal	1,095 (5)	1,389 (7)
Surgery, cardiovascular	501 (2)	1,120 (1)
Surgery, intra-abdominal	1,465 (7)	3,481 (4)
Health care utilization		
No. of total physician visits	10.4 ± 7.6	3.8 ± 4.4
No. of hospitalizations	0.2 ± 0.7	0.1 ± 0.5
No. of prescription drug	10.3 ± 6.4	4.4 ± 4.6
Laboratory data		
APR levels available	3,313 (15)	840 (1)
Elevated APR levels[a]	1,210 (37)	149 (18)

*matched

SD: standard deviation, COPD: chronic obstructive pulmonary disease, APR: acute phase reactant

[a] the proportion was calculated among the subjects with APR levels available

Table 2

Incidence rates and rate ratios (RR) of VTE (per 1,000 person-years), age, sex, and index date matched

	Rheumatoid arthritis (N=22,143)			Non-rheumatoid arthritis (N=88,572)			
	Cases (n)	Person years	Rates (95% CI)	Cases (n)	Person-years	Rates (95% CI)	RR (95% CI)
Primary definition							
VTE (DVT or PE)	265	43,278	6.1 (5.4–6.9)	448	176,866	2.5(2.3–2.8)	2.4(2.1–2.8)
DVT	197	43,371	4.5 (4.0–5.2)	364	177,018	2.1 (1.9–2.3)	2.2 (1.9–2.6)
PE	111	43,490	2.6 (2.1–3.1)	164	177,276	0.9 (0.8–1.1)	2.7 (2.2–3.5)
Secondary definition							
VTE (DVT or PE)	115	43,462	2.7 (2.2–3.2)	190	177,209	1.1 (0.9–1.2)	2.5 (2.0–3.1)
DVT	80	43,514	1.8 (1.5–2.3)	156	177,284	0.9 (0.8–1.0)	2.1 (1.6–2.7)
PE	61	43,551	1.4 (1.1–1.8)	84	177,380	0.5 (0.4–0.6)	3.0 (2.1–4.1)

VTE: venous thromboembolism, DVT: deep vein thrombosis, PE: pulmonary embolism, CI: confidence interval
Primary definition: based on a discharge diagnosis
Secondary definition: based on a discharge diagnosis and a dispensing of anticoagulants within 10 days after the discharge date

Table 3

Fully adjusted hazard ratios (HRs)* and 95% confidence intervals (CIs) for VTE in rheumatoid arthritis compared to non-rheumatoid arthritis

	Rheumatoid arthritis
Primary definition	
VTE (DVT or PE)	1.4 (1.1–1.7)
DVT	1.2 (0.9–1.5)
PE	1.9 (1.3–2.7)
Secondary definition	
VTE (DVT or PE)	1.7 (1.2–2.3)
DVT	1.2 (0.8–1.7)
PE	2.5 (1.6–4.2)

*Adjusted for age, sex, Comorbidity Index, comorbid conditions, medications and health care utilization patterns listed in Table 1

Table 4

Presence (%) of major risk factors for VTE among patients with incident VTE (n=713) during the follow-up period

	Rheumatoid arthritis (n=265)	Non-rheumatoid arthritis (n=448)
	Percentages	
90 days before the outcome		
Hospitalization	29	32
Any surgery	38	42
Malignancy	30	19
90 days after the outcome		
Malignancy	11	19
90 days before and after the outcome		
Provoked VTE*	57	60

* Provoked VTE was defined as occurring in the presence of known malignancy 90 days before and after the VTE, acute hospitalization and surgery 90 days before the VTE.(24)