Risk of Venous Thromboembolism in Patients With Rheumatoid Arthritis and Association With Disease Duration and Hospitalization

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Context Recent reports suggest that rheumatoid arthritis (RA) may be a risk factor for venous thromboembolism (VTE), particularly in conjunction with hospitalization. Using hospitalization data to identify RA and VTE may identify patients when they are at elevated risk for other reasons, obscuring the incompletely understood underlying association between RA and VTE and leading to inappropriate institution or timing of interventions.

Objective To estimate risks for VTE in patients with RA, including the relation of these risks to disease duration and hospitalization.

Design, Setting, and Patients Prospective, population-based cohort study of 1 prevalent RA cohort (n=37 856), 1 incident RA cohort (n=7904), and matched general population comparison cohorts, all from Sweden, with follow-up from 1997 through 2010.

Main Outcome Measure First-time VTE.

Results Patients with prevalent RA were at greater risk of VTE than the general population (rate, 5.9 [95% CI, 5.1-6.6] vs 2.8 [95% CI, 2.6-3.1] per 1000 person-years (adjusted hazard ratio [HR], 2.0 [95% CI, 1.9-2.2]; $P<.001$). By the time of RA symptom onset, there was no statistically significant association between a history of VTE and RA (odds ratio, 1.2 [95% CI, 1.0-1.4]; $P=.08$; 150 events in the RA cohort vs 587 in the comparison cohort). Counting from RA diagnosis, an increased rate in the RA cohort vs the comparison cohort (3.8 [95% CI, 2.5-5.2] vs 2.4 [95% CI, 1.9-2.9] per 1000 person-years; HR, 1.6 [95% CI, 1.1-2.5]; $P=.02$) was detected within the first year and did not increase further during the first decade. Although rates for VTE following hospitalization were higher, the 1-year rate of VTE per 1000 person-years was not higher in the RA cohort than in the comparison cohort after hospital discharge (11.8 [95% CI, 8.6-15.1] vs 13.1 [11.3-14.8]; HR, 1.0 [95% CI, 0.7-1.4]; $P=.90$). The rates of VTE increased with age but were largely similar across sex and rheumatoid factor status, as were the HRs for VTE across age, sex, and rheumatoid factor status.

Conclusions Compared with the general population, Swedish patients with RA had an elevated risk for VTE that was stable over the first 10 years after diagnosis. Although hospitalization was a risk factor for VTE the first year after discharge, the excess risk was not greater in patients with RA than in the general population.

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ACUTE INFLAMMATION PROmotes a hypercoagulable state that may increase the risk of deep vein thrombosis (DVT) and pulmonary embolism.[1] In chronic inflammatory disease such as rheumatoid arthritis (RA), procoagulatory factors are up-regulated.[2,3] Few studies have assessed how this theoretical inflammation-induced risk of venous thromboembolism (VTE) translates into risk for clinical events in patients with RA.[4-9]

In the methodologically most rigorous study to date,[4] increased risks for VTE in RA were suggested, although small numbers precluded firm conclusions regarding the need for increased clinical vigilance and intervention (and, if intervention is warranted, when and among whom).

In a recent study[8] based on hospitalization data a worrisome 6-fold, then declining, risk of pulmonary embolism was reported in hospitalized patients with RA compared with the general population. It was suggested that the risk might decline over time because of anti-inflammatory treatment[8,10] and that thromboprophylaxis should be considered in patients with RA admitted to the hospital. Because that study identified patient groups but not comparison groups through hospitalization data, and because hospitalization is associated with VTE, reported risks may reflect circumstances unrelated to the inflammatory disease but associated with VTE. This may lead to false conclusions regarding the underlying biology of VTE in RA and the timing of risk development and

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possibly to unnecessary medical hazards related to inappropriate clinical intervention.

The aims of this study were therefore to assess the overall occurrence and relative risks of VTE in patients with RA in a population-based RA sample (in relation to RA onset and disease duration as well as in conjunction with hospitalization) and to assess whether risks were particularly high in specific patient subgroups.

METHODS

Setting

In Sweden, patients with RA are treated by rheumatologists. There is universal access to publicly funded health care, including inpatient, nonprimary outpatient, and primary care, for all residents. Using the unique personal identification number issued to all Swedish residents,[11] data from national and virtually complete administrative or clinical registers on demographics, morbidity, and mortality can be linked together. Population registers allow for unbiased identification of general population comparison groups and enable prospective assessments of morbidity and mortality independently of RA disease status.

Study Population

Prevalent RA Cohort. Using the outpatient component of the National Patient Register, initiated in 2001 and including outpatient visits in nonprimary care, we identified a cohort of individuals with 2 or more visits to a rheumatology or internal medicine clinic with a diagnosis of RA between January 2005 and December 2009 (n = 39 372; *International Classification of Diseases, Tenth Revision* [*ICD-10*][12] codes used to identify RA are reported in the eAppendix available at http://www.jama.com). Treatment patterns in Swedish patients with prevalent RA have been described in more detail elsewhere.[13]

An index date was assigned to all individuals, representing the date of the second nonprimary care outpatient visit listing an *ICD-10* code of RA between January 2005 and December 31, 2009 (regardless of number of visits before 2005). At least 2 visits were required to increase the specificity of the RA diagnosis. This cohort should reflect the average level of (any) risk increase in patients with RA receiving follow-up routine rheumatology care.

Table 1. Characteristics of the Cohorts of Patients With Rheumatoid Arthritis (RA) and Matched Individuals From the General Population After Excluding Individuals With VTE Events Before Index Date

Characteristic	Prevalent RA		Incident RA	
	Patients (n = 37 856)	General Population (n = 169 921)	Patients (n = 7904)	General Population (n = 37 350)
Sex, No. (%)				
Women	27 305 (72)	122 332 (72)	5420 (69)	25 436 (68)
Men	10 551 (28)	47 589 (28)	2484 (31)	11 914 (32)
Rheumatoid factor–positive at index date, No. (%)	30 682 (81)	NA	5296 (67)	NA
Age at index date, mean (SD), y	61 (14)	60 (14)	57 (15)	57 (15)
Age, No. (%), y				
16-52	9116 (24)	44 219 (26)	2595 (33)	12 572 (34)
53-62	9931 (26)	46 447 (27)	2133 (27)	10 088 (27)
63-71	9061 (24)	40 909 (24)	1657 (21)	7691 (21)
72-94	9748 (26)	38 346 (23)	1519 (19)	6999 (19)
Age at first VTE, mean (SD), y	70 (12)	70 (11)	70 (12)	70 (12)
Duration of RA at index date, median (IQR)[a]	5 (2-12)	NA	170 (112-244)	NA
Follow-up, median (IQR), y	4.3 (2.7-5.3)	4.4 (2.9-5.3)	5.8 (3.4-9.0)	5.8 (3.3-9.0)

Abbreviations: IQR, interquartile range; NA, not applicable; VTE, venous thromboembolism.
[a] Duration of RA was calculated as time (years) since first-ever registration of RA in the National Patient Register in the prevalent cohort and time (days) since first symptom of RA in the incident cohort.

Incident RA Cohort. The Swedish Rheumatology Quality Register was initiated in 1995 and includes patients with RA 16 years or older and fulfilling the 1987 American College of Rheumatology criteria for RA.[14] At diagnosis, patients are entered into the register with information on age, sex, rheumatoid factor status, date of first symptom of RA, date of RA diagnosis, and personal identification number. For this study, we identified all individuals (n = 8077) diagnosed with RA between January 1997 and December 31, 2009, within 12 months of first symptoms of RA, using date of RA diagnosis as index date. The incident cohort specifically allowed the assessment of risks as a function of time since clinical onset of RA.

Comparison Cohorts for the Incident and Prevalent RA Cohorts. For each unique patient, we randomly selected up to 5 individuals from the Swedish Population Register (which includes all Swedish residents), matched on sex, year of birth, and residential area. Each individual from the general population was assigned the same index date as the corresponding patient with RA. Each of the 2 RA cohorts thus had its own comparison cohort drawn from the general population. We did not exclude individuals with an RA diagnosis (approximately 0.8%[13]) from the comparison cohorts.

In this type of register-based study, complete information on vital status is a prerequisite for inclusion into the analyses. Less than 0.2% of all individuals were excluded up front because of incomplete data precluding analysis (eg, missing information on sex or age).

Data Sources Used to Detect Outcomes During Follow-up

Using the personal identification number, we linked the 2 cohorts of patients with RA and the 2 matched comparison cohorts to the following data sources, for which data were available through December 31, 2010: the National Patient Register, the Prescribed Drug Register, and the Population Register.

The National Patient Register contains, in addition to the outpatient component described above, information on inpatient care since 1964, with nationwide 100% coverage since 1987.[15] The register lists date of admission, date of discharge, and the discharge diagnosis (primary and secondary diagnoses) as set by the discharging physician and classified according to the calendar-year–specific *ICD* version. The Prescribed Drug Register contains data (Anatomical Therapeutic Chemical [ATC] codes) on all drugs dispensed from pharmacies in Sweden from July 2005 onward. The coverage of the register is complete for filled prescriptions in ambulatory care, whereas in-hospital use of drugs is not recorded on a patient level. The Population Register includes information on deaths, emigration, and immigration for the entire Swedish population.[16]

Through these linkages, we identified all hospitalizations and non–primary care outpatient visits, before or after the index date, all filled prescriptions after July 2005, and all deaths and emigrations during follow-up. The nationwide and near complete coverage of the National Patient Register ensured very low (but not formally assessable) missing data. It is unlikely that such structural missingness would differ by exposure status.

Definition of Outcome

The primary outcome was first-time hospitalization for or outpatient diagnosis of VTE (see eAppendix for *ICD* codes). As a sensitivity analysis to increase the specificity of our outcome definition, we defined incident VTE as above but also required 2 filled prescriptions of a vitamin K antagonist or heparin, including low-molecular-weight heparin, to be filled within 6 months of the event (see eAppendix for ATC codes). Secondary outcomes were DVT and pulmonary embolism separately.

Follow-up

In the prevalent RA cohort, follow-up started 60 days after index date to reduce the risk of detecting outcome related to inclusion into the cohort. As a sensitivity analyses, follow-up was started 1 year after the index date. In the incident RA cohort, follow-up started at date of RA diagnosis. For all

Table 2. Number of Events, Person-Years at Risk, and Rates of Venous Thromboembolism in Patients With Prevalent Rheumatoid Arthritis (RA) Identified Between 2005 and 2009 and Matched Individuals From the General Population, as Well as Patients With Incident RA Diagnosed Between 1997 and 2009 and Matched Individuals From the General Population[a]

	Prevalent RA Cohort (n = 37 856)			Matched General Population Cohort (n = 169 921)				
	Events, No.	Person-Years	Rate per 1000 Person-Years (95% CI)	Events, No.	Person-Years	Rate per 1000 Person-Years (95% CI)	Adjusted HR (95% CI)	*P* Value
Overall	838	142 909	5.9 (5.1-6.6)	1866	658 896	2.8 (2.6-3.1)	2.0 (1.9-2.2)	<.001
Sex								
Women	597	104 561	5.7 (4.8-6.6)	1290	480 243	2.7 (2.4-3.0)	2.0 (1.9-2.3)	<.001
Men	241	38 347	6.3 (4.8-7.8)	576	178 652	3.2 (2.7-3.7)	1.9 (1.7-2.2)	<.001
Rheumatoid factor[b]								
Positive	729	119 408	6.1 (5.2-7.0)	1866	658 896	2.8 (2.6-3.1)	2.1 (1.9-2.3)	<.001
Negative	109	23 501	4.6 (3.1-6.2)	1866	658 896	2.8 (2.6-3.1)	1.6 (1.4-2.0)	<.001
Age, y								
16-52	75	36 329	2.1 (1.1-3.0)	154	176 780	0.9 (0.6-1.1)	2.4 (1.8-3.1)	<.001
53-62	161	40 085	4.0 (2.8-5.3)	371	189 136	2.0 (1.6-2.4)	2.1 (1.7-2.5)	<.001
63-71	238	34 559	6.9 (5.2-8.6)	578	159 466	3.6 (3.0-4.2)	1.9 (1.6-2.2)	<.001
72-94	364	31 934	11.4 (9.3-13.5)	763	133 512	5.7 (5.0-6.5)	2.0 (1.7-2.3)	<.001
	Incident RA Cohort (n = 7904)			Matched General Population Cohort (n = 37 350)				
Overall	223	49 845	4.5 (3.0-5.9)	648	235 603	2.8 (2.2-3.3)	1.6 (1.4-1.9)	<.001
Sex								
Women	142	34 728	4.1 (2.4-5.8)	437	162 630	2.7 (2.1-3.3)	1.5 (1.3-1.8)	<.001
Men	81	15 117	5.4 (2.5-8.2)	211	72 972	2.9 (1.9-3.9)	1.8 (1.4-2.4)	<.001
Rheumatoid factor[b]								
Positive	148	33 389	4.4 (2.6-6.2)	648	235 603	2.8 (2.2-3.3)	1.7 (1.5-2.1)	<.001
Negative	75	16 456	4.6 (2.0-7.1)	648	235 603	2.8 (2.2-3.3)	1.4 (1.1-1.8)	.007
Age, y								
16-52	45	13 713	3.3 (0.9-5.7)	149	64 888	2.3 (1.4-3.2)	1.4 (1.0-2.0)	.03
53-62	61	9978	6.1 (2.3-9.9)	164	46 866	3.5 (2.2-4.8)	1.7 (1.3-2.3)	<.001
63-71	34	17 830	1.9 (0.2-3.6)	84	85 557	1.0 (0.4-1.5)	1.9 (1.3-2.9)	<.001
72-94	83	8322	10.0 (5.0-15.0)	251	38 291	6.6 (4.7-8.5)	1.6 (1.2-2.0)	<.001

Abbreviation: HR, hazard ratio.
[a] Matching factors were birth year, sex, and residential area. Hazard ratios, 95% CIs, and *P* values adjusted for age at index date.
[b] Rheumatoid factor–positive and –negative patients with RA compared separately with all comparison individuals.

participants, follow-up ended at outcome, death, first emigration, or December 31, 2010, whichever came first.

Statistical Analyses

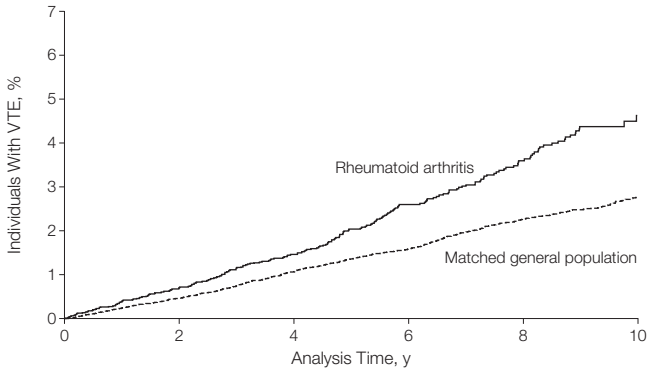
Rates were expressed as events per 1000 person-years. Confidence intervals with a 95% confidence level were estimated for incidence rates by assuming that the number of VTE events followed a Poisson distribution. To assess whether there already were differences in the risk of VTE by the time of clinical onset of RA, we compared the proportions of individuals in the incident RA cohort and its general population comparison cohort with a history of VTE up until the reported onset of RA symptoms, using conditional logistic regression conditioned on the matching factors. Participants with a history of VTE before the index date were thereafter excluded from the prospective follow-up. We did not include or exclude individuals on the basis of specific indications/contraindications or therapeutic exposures other than history of VTE before follow-up. Failure functions were estimated using Kaplan-Meier methods.

To compare the risk of incident VTE in patients with RA with that in individuals in the comparison cohorts, Cox models were used with time since index date used as time scale, stratified by birth year, residential area, and sex, and adjusted for age at index date. In the incident cohort, we further assessed the role of RA duration by using time-dependent covariates (<1, 1-4, 5-9, and 10-14 years since RA diagnosis). We also assessed stratum-specific rates and hazard ratios (HRs) for sex, rheumatoid factor status, age (quartiles), and calendar period of RA diagnosis. The proportional hazards assumption was tested by introducing an interaction term between follow-up time and RA status in the prevalent and incident RA cohorts. The proportional hazards assumption was not violated in the prevalent cohort ($P=.30$) or in the incident cohort ($P=.50$).

We assessed the association of hospitalization with VTE in 2 steps. First, we identified all individuals in the general population comparison cohort matched to the incident RA cohort who had been hospitalized, regardless of cause, after index date. The incidence of VTE following hospital discharge in this subset of the comparison cohort, counting from discharge date of this first hospitalization until end of follow-up, was compared with that of the entire comparison cohort originally matched to the incident RA cohort. Second, to assess whether hospitalization modified the relative risk of VTE in patients with RA, we identified all individuals in the incident RA cohort and its comparison cohort with at least 1 hospitalization (regardless of cause) after the index date and compared the incidences of VTE following discharge from hospital in the 2 groups using Cox regression.

All significance tests were 2-sided. All P values <.05 were considered statistically significant. SAS version 9.2 was used for all analyses.

Figure 1. Failure Functions of Venous Thromboembolism (VTE) in Patients With Incident Rheumatoid Arthritis Diagnosed With RA Between 1997 and 2009 and Matched Individuals From the General Population



Rheumatoid arthritis, No.						
At risk	7904	6886	5437	3836	2525	1451
VTE events	0	54	48	53	32	22
Matched general population, No.						
At risk	37 350	32 410	25 554	18 122	12 051	6967
VTE events	0	168	176	118	104	48

	<1 y	1-4 y	5-9 y
Incidence rate/100 patient-years (95% CI)			
Rheumatoid arthritis	3.8 (2.5-5.2)	4.1 (2.7-5.5)	5.4 (3.3-7.5)
Matched general population	2.4 (1.9-2.9)	2.8 (2.3-3.3)	2.9 (2.2-3.6)
Hazard ratio (95% CI)	1.6 (1.1-2.5)	1.4 (1.1-1.8)	1.9 (1.4-2.4)
P value	.02	.002	<.001

Number of events, person-years at risk, and rates were stratified by time since diagnosis of rheumatoid arthritis. Hazard ratios, 95% CIs, and *P* values were adjusted for age at index date.

RESULTS

In total, 39 372 patients with prevalent RA and 173 417 matched individuals in the general population comparison cohort were identified, as well as 8077 patients with incident RA and 37 973 matched individuals. After excluding individuals with a VTE event before the index date, 37 856 patients with prevalent RA and 169 921 matched individuals in the comparison cohort remained, as did 7904 patients with incident RA and 37 350 matched individuals (TABLE 1).

VTE in RA and the General Population

Prevalent RA. Of the patients with prevalent RA and the matched individuals in the general population comparison cohort, 838 patients (2.2%) and 1866 matched individuals (1.1%) had a VTE event after the index date. The rates were 5.9 (95% CI, 5.1-6.6) per 1000 person-years for patients with RA and 2.8 (95% CI, 2.6-3.1) per 1000 person-years for the individuals in the comparison cohort (ad-

justed HR, 2.0 [95% CI, 1.9-2.2]; $P<.001$) (TABLE 2). Separate analyses of DVT and pulmonary embolism, respectively, resulted in HRs similar to those for VTE (eTable 1A).

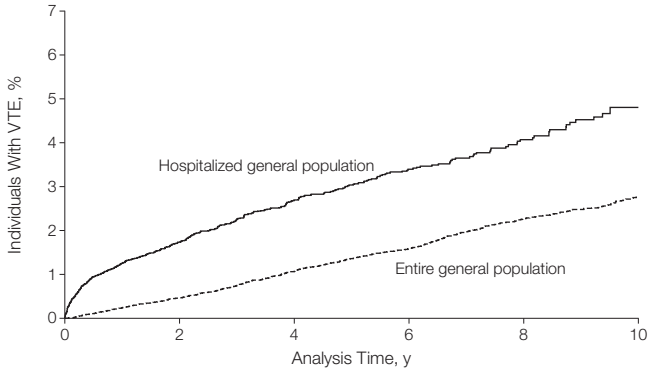
Incident RA. By the time of RA symptom onset, 150 patients with RA (1.9%) and 587 matched individuals in the general population comparison cohort (1.6%) had a history of VTE, corresponding to an adjusted odds ratio for a history of VTE in patients with incident RA of 1.2 (95% CI, 1.0-1.4; $P=.08$). Counting from RA diagnosis over a median follow-up of 5.8 years, 223 patients with RA (2.8%) and 648 individuals in the comparison cohort (1.7%) were registered with a VTE event. The rates were 4.5 (95% CI, 3.0-5.9) per 1000 person-years for patients with RA and 2.8 (95% CI, 2.2-3.3) per 1000 person-years for the individuals in the comparison cohort (adjusted HR, 1.6 [95% CI, 1.4-1.9]; $P<.001$) (Table 2).

The adjusted HRs for DVT and pulmonary embolism separately were similar to the HRs for VTE (eTable 1B). Similar results were found when adding a lag of 12 months before start of follow-up (eTable 2). Sensitivity analyses requiring the combination of *ICD* codes and prescriptions for anticoagulants to define the outcome generated somewhat lower rates but HRs consistent with the main analysis (eTable 3).

VTE in Relation to Time Since RA Diagnosis

In the incident RA cohort, analyses stratified by time since index date (RA diagnosis) demonstrated HRs vs matched individuals in the general population comparison cohort similar to the overall HR for VTE throughout follow-up. Higher rates of VTE in patients with RA compared with the general population were already observed within 1 year since RA diagnosis (3.8 [95% CI, 2.5-5.2] per 1000 person-years vs 2.4 [95% CI, 1.9-2.9] per 1000 person-years; adjusted HR, 1.6 [95% CI, 1.1-2.5]; $P=.02$) (FIGURE 1).

Figure 2. Failure Functions of Venous Thromboembolism (VTE) in Hospitalized Individuals From the General Population and the Entire General Population Cohort Originally Matched to the Incident Rheumatoid Arthritis Cohort



Hospitalized general population, No.						
At risk	16 894	11 248	7345	4395	2342	1014
VTE events	0	256	92	42	22	13
Entire general population, No.						
At risk	37 350	32 410	25 554	18 122	12 051	6967
VTE events	0	168	176	118	104	48

	<1 y	1-4 y	5-9 y
Incidence rate/100 patient-years (95% CI)			
Hospitalized general population	13.1 (11.3-14.8)	4.7 (3.5-5.8)	3.6 (2.1-5.2)
Entire general population	2.4 (1.9-2.9)	2.8 (2.3-3.3)	2.9 (2.2-3.6)
Hazard ratio (95% CI)	5.1 (3.9-6.6)	1.5 (1.3-1.9)	1.2 (0.9-1.7)
P value	<.001	<.001	.24

Number of events, person-years at risk, and rates were stratified by time since hospitalization. Hazard ratios, 95% CIs, and *P* values were adjusted for age at index date.

VTE in in Relation to Hospitalization

Of the 37 350 individuals in the general population comparison cohort originally matched to those in the incident RA cohort, 16 894 (45%) were hospitalized for any reason during follow-up. Of these, 429 (2.5%) experienced a VTE event, counting from discharge date of the first hospitalization following the index date until end of follow-up (eTable 4). Among all 37 350 individuals in the entire general population cohort, 648 (1.7%) experienced a VTE event. The corresponding rates were 6.2 (95% CI, 5.1-7.4) per 1000 person-years among previously hospitalized individuals and 2.8 (95% CI, 2.2-3.3) per 1000 person-years among all individuals in the entire general population cohort (adjusted overall HR, 2.1 [95% CI, 1.8-2.4]; $P<.001$). The risk increase was more than 5-fold (adjusted HR, 5.1 [95% CI, 3.9-6.6]; $P<.001$) during the first year following hospital discharge but decreased markedly over time and was null after 5 years (FIGURE 2).

In the incident RA cohort, 4364 patients (55%) were hospitalized after RA diagnosis. Among these, 154 (3.5%) experienced a VTE event, counting from this hospital discharge until end of follow-up. This corresponded to a rate of 7.8 (95% CI, 5.2-10.5) per 1000 person-years among patients with RA following hospital discharge. When compared with the rate for the 16 894 hospitalized individuals from the general population cohort (6.2 [95% CI, 5.1-7.4] per 1000 person-years), the overall adjusted HR for VTE was 1.3 (95% CI, 1.1-1.6; $P=.01$), ie, somewhat lower than the overall HR in the incident RA cohort. When stratifying by time since hospital discharge, the risk of VTE was not higher during the first year after hospital discharge among patients with RA than among individuals in the general population cohorts but then increased and was doubled 5 to 9 years following hospital discharge (FIGURE 3). Subgroup analyses based on hospitalization specifically for orthopedic surgery resulted in similar HRs (eTable 5).

Risks for VTE in RA in Specific Patient Segments

The rates of VTE increased with age but were largely similar in women and men as well as in patients with rheumatoid factor–positive and –negative RA (Table 2). The HRs of VTE were, however, broadly similar across these patient segments. We could not detect any association of VTE with calendar period of RA diagnosis between 1997 and 2009 (eTable 6).

COMMENT

The results of this study suggest that patients with RA are at increased risk of VTE (both DVT and pulmonary embolism) and that the risk of VTE increases shortly after RA diagnosis and remains similarly elevated during the first decade. By contrast, we noted no higher rates of VTE within the first year following hospital discharge among patients with RA than in the general population, and although we noted higher rates in the oldest age group, HRs were broadly similar across age, sex, rheumatoid factor status, and calendar period of RA diagnosis.

Strengths and Weaknesses

By using nationwide population-based nonprimary care visit data with almost complete coverage (approximately 95%)[17,18] to identify the prevalent RA cohort, this cohort comprises virtually all patients with RA in Sweden seen by a rheumatologist/internist during the study period (2005-2009). Similarly, using the Swedish Rheumatology Quality Register allowed for the identification of a large clinical incident RA cohort with less than 12 months of symptom history at the time of RA diagnosis as well as estimation of risks in relation to RA onset and duration.

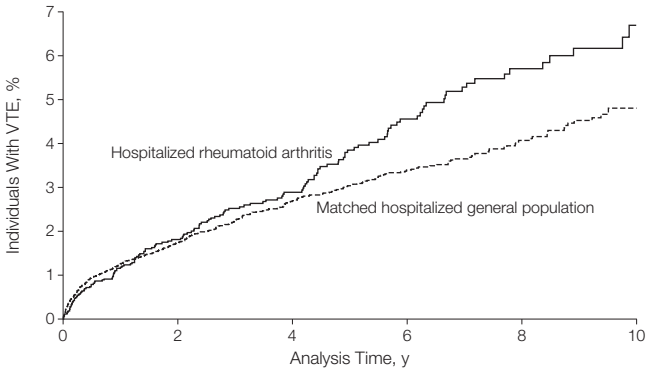
Further strengths include the large number of events during follow-up and the duration of follow-up. Also, the identification of the outcome was independent of RA status and identical for the RA and general population cohorts.

Patients with RA are at increased risks for Baker cysts and some other manifestations that might be misinterpreted as DVT. Although workup for DVT during the study period included imaging (that would differentiate Baker cysts from DVT events), we cannot formally exclude such misclassification bias. However, the HRs for DVT in patients with RA remained similar in sensitivity analyses that required not only a DVT diagnosis but also repeated dispensing of antithrombotic medications. Also, misclassification of DVT events is unlikely to explain the doubled risk observed for pulmonary embolism, which further requires its own workup.

It may be that rheumatologists are less likely to include patients in a clinical register intended for long-time follow-up if the predicted survival of the patient is very short. This could lead to an underestimation of the true rates in the incident RA cohort, at least in the short term. Conversely, it may be that the 2 rheumatology outpatient visits used to identify the patients with RA were somehow related to factors associated with the outcome and that our 60-day lag period used for washout was too short. However, using a 1-year lag period did not materially alter the HRs. We lacked information on certain potential risk factors for VTE, eg, immobilization, and thus the ability to assess their association with VTE in RA. Our aim was, however, to assess rates and relative risks for VTE in RA rather than to attribute risks to specific risk factors. Although a limitation, their absence is unlikely to affect the validity of our results.

Considering that the incidence of VTE to some extent depends on the diagnostic intensity, inflated incidences in the RA cohorts attributable to surveillance bias cannot be excluded. We did not exclude individuals with RA from the comparison cohorts. This could in theory lead to an underestimation of the true HRs. Given the low prevalence of RA in Swe-

Figure 3. Failure Functions of Venous Thromboembolism (VTE) in Hospitalized Patients With Incident Rheumatoid Arthritis Diagnosed With RA Between 1997 and 2009 and Hospitalized Matched Individuals From the General Population



Hospitalized rheumatoid arthritis, No.						
At risk	4364	3122	2146	1341	746	324
VTE events	0	70	30	30	13	5
Matched hospitalized general population, No.						
At risk	16 894	11 248	7345	4395	2342	1014
VTE events	0	256	92	42	22	13
	<1 y		1-4 y		5-9 y	
Incidence rate/100 patient-years (95% CI)						
Hospitalized rheumatoid arthritis	11.8 (8.6-15.1)		6.8 (4.1-9.5)		6.3 (2.5-10.0)	
Matched hospitalized general population	13.1 (11.3-14.8)		4.7 (3.5-5.8)		3.6 (2.1-5.2)	
Hazard ratio (95% CI)	1.0 (0.7-1.4)		1.4 (1.0-1.8)		2.0 (1.2-3.4)	
P value	.90		.03		.009	

Number of events, person-years at risk, and rates were stratified by time since hospitalization. Hazard ratios, 95% CIs, and *P* values were adjusted for age at index date.

den (0.6%-0.8%),[13] it is unlikely that this potential misclassification of exposure would have changed the interpretation of our findings.

Previous Research

Few studies have reported on risks of VTE in RA.[4-8] Several of these have reported relative risks greater than 1, but the designs (mainly cross-sectional or hospital-based) have not permitted estimations of the underlying clinical risks or rates overall in population-based cohorts or of the risks or rates in relation to different patient characteristics, such as rheumatoid factor status or RA duration.[5,7] In a recent population-based cohort study, a tripled risk of VTE in a cohort of patients with RA compared with risk in a comparison cohort of individuals without RA was presented[4] but because the number of events during follow-up was small (19 in patients with RA, 11 in those without), the study was underpowered to study the association between VTE and subgroups of RA. Another recent study based on hospitalization data to define RA and to detect the outcome (pulmonary embolism) suggested a 6-fold increased risk of pulmonary embolism in RA (compared with the general population not required to be hospitalized) which decreased over time.[8]

These results are similar to ours regarding hospitalization in the general population (HR at <1 year in the absence of RA, 5.1 [95% CI, 3.9-6.6]; $P<.001$; HR at 5-9 years, 1.2 [95% CI, 0.9-1.7]; $P=.24$) but in sharp contrast to our observation of no additional increase in the risk of VTE during the first year following hospital discharge comparing patients with RA following hospital discharge to the general population following hospital discharge. This observation emphasizes the need to separate effects of disease (in this case, RA) from effects of, or associated with, hospitalization on the risk of VTE. From a thromboprophylaxis perspective, this is of importance, because our data lead to opposite clinical and scientific inferences: in general, patients with RA should be considered at a moderately elevated risk of VTE; this risk is present almost irrespective of disease duration, does not decline with time, and is not disproportionally higher in patients with RA than in those without following hospital discharge.

In conclusion, RA is associated with an increase in the risk of VTE. This risk did not vary with RA duration up to 10 years from RA diagnosis. Hospitalization is a strong risk factor for VTE in the general population and in patients with RA, but the short-term (<1 year after hospital discharge) rates for VTE are similar in both groups. VTE rates varied with age, less so with sex, calendar period of RA diagnosis, and rheumatoid factor status, but the relative risks of VTE were largely similar across these patient subgroups.

Author Contributions: Dr Holmquist had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Holmqvist, Neovius, Askling.
Acquisition of data: Holmqvist, Neovius, Eriksson, Askling.
Analysis and interpretation of data: Holmqvist, Neovius, Eriksson, Mantel, Wållberg-Jonsson, Jacobsson, Askling.
Drafting of the manuscript: Holmqvist, Askling.
Critical revision of the manuscript for important intellectual content: Holmqvist, Neovius, Eriksson, Mantel, Wållberg-Jonsson, Jacobsson, Askling.
Statistical analysis: Holmqvist, Neovius, Eriksson, Askling.
Obtained funding: Askling.
Administrative, technical, or material support: Holmqvist, Askling.
Study supervision: Holmqvist, Neovius, Askling.
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Online-Only Material: The eAppendix and eTables 1-6 are available at http://www.jama.com.

REFERENCES

1. Xu J, Lupu F, Esmon CT. Inflammation, innate immunity and blood coagulation. *Hamostaseologie*. 2010; 30(1):5-6, 8-9.
2. McEntegart A, Capell HA, Creran D, Rumley A, Woodward M, Lowe GD. Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis. *Rheumatology (Oxford)*. 2001; 40(6):640-644.
3. Wållberg-Jonsson S, Dahlén GH, Nilsson TK, Rånby M, Rantapää-Dahlqvist S. Tissue plasminogen activator, plasminogen activator inhibitor-1 and von Willebrand factor in rheumatoid arthritis. *Clin Rheumatol*. 1993;12(3):318-324.
4. Bacani AK, Gabriel SE, Crowson CS, Heit JA, Matteson EL. Noncardiac vascular disease in rheumatoid arthritis: increase in venous thromboembolic events? *Arthritis Rheum*. 2012;64(1):53-61.
5. Matta F, Singala R, Yaekoub AY, Najjar R, Stein PD. Risk of venous thromboembolism with rheumatoid arthritis. *Thromb Haemost*. 2009;101(1):134-138.
6. Ramagopalan SV, Wotton CJ, Handel AE, Yeates D, Goldacre MJ. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study. *BMC Med*. 2011;9:1.
7. Seriolo B, Accardo S, Garnero A, Fasciolo D, Cutolo M. Anticardiolipin antibodies, free protein S levels and thrombosis: a survey in a selected population of rheumatoid arthritis patients. *Rheumatology (Oxford)*. 1999;38(7):675-678.
8. Zöller B, Li X, Sundquist J, Sundquist K. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. *Lancet*. 2012;379(9812):244-249.
9. Mameli A, Barcellona D, Marongiu F. Rheumatoid arthritis and thrombosis. *Clin Exp Rheumatol*. 2009;27(5):846-855.
10. Sanjeevi CB. Autoimmune diseases and risk of pulmonary embolism. *Lancet*. 2012;379(9812):200-201.
11. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24(11):659-667.
12. World Health Organization (WHO). International Classification of Diseases (IDC). WHO website. http://www.who.int/classifications/icd/en/. Accessed January 16, 2012.
13. Neovius M, Simard JF, Askling J; ARTIS study group. Nationwide prevalence of rheumatoid arthritis and penetration of disease-modifying drugs in Sweden. *Ann Rheum Dis*. 2011;70(4):624-629.
14. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*. 1988;31(3):315-324.
15. Swedish National Board of Health and Wellfare (Social Styrelsen). The National Patient Register. Social Styrelsen website. http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish. Accessed January 16, 2012.
16. Statistics Sweden website. http://www.scb.se/Pages/List____257499.aspx. Accessed January 16, 2012.
17. Swedish National Board of Health and Welfare (Social Styrelsen) website. http://www.socialstyrelsen.se/english. Accessed February 10, 2012.
18. Bremell T. Läkarbemanning för reumatologi. *SRF: Reuma-Bulletinen—Journal of the Swedish College of Rheumatology*. 2009;732(2):19.