Risk for Incident Arterial or Venous Vascular Events Varies Over the Course of Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** We describe the pattern of incidence of thrombovascular events after diagnosis of systemic lupus erythematosus (SLE) in a cohort of lupus patients.

Methods. Descriptive study of prospectively collected data using incidence rates of thrombovascular events and 95% confidence intervals (CI) calculated for predetermined periods of observation. Kaplan-Meier survival curves were plotted to estimate thrombovascular event-free survival.

Results. Among 426 individuals, person-years contributed were as follows: 399 persons and 4356.0 person-years for all events; 417 persons and 4691.9 person-years for arterial events; and 408 persons and 4846.6 person-years for venous events. The incidence of thrombovascular events was highest during the first year after SLE diagnosis (4.00, 95% CI 2.24–6.59) and after 20 years (ranging from 3.32, 95% CI 1.52–6.30, to 4.99, 95% CI 0.60–18.01), and was lowest between 1 and 5 years after SLE diagnosis (1.00, 95% CI 0.53–1.72). A similar pattern was observed for arterial events, while venous events showed a higher incidence rate only in the first 30 days after SLE diagnosis (12.06, 95% CI 3.29–30.87) and remained low afterwards. The probabilities of remaining event-free at 5, 10, and 15 years were as follows: 0.92, 0.85, and 0.78, respectively, for all thrombovascular events; 0.95, 0.88, and 0.82, respectively, for arterial events; and 0.98, 0.95, and 0.94, respectively, for venous events.

Conclusion. Thrombovascular events occur throughout the course of lupus, with the highest risk of arterial or venous events in the first year after diagnosis, and the pattern of occurrence varying thereafter. (First Release July 1 2006; J Rheumatol 2006;33:1780–4)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a variety of clinical and laboratory manifestations and by fluctuating disease activity. Improvement in survival (10-year survival rates between 54% and 63%[1] in the 1960s and 1970s, compared to 92%[2] more recently) have led to an increased interest in longterm morbidity of SLE.

Thrombosis and other vascular events remain a common cause of morbidity and mortality in patients with SLE[2]. Manzi, *et al* found a 52-fold higher risk for myocardial infarction (MI) and angina in women with SLE aged 35–44, compared to a similar group of women in the Framingham Offspring study[3]. Ward found a higher prevalence of hospitalizations for acute MI and cerebrovascular accident (CVA) in women with SLE aged 18–44[4]. Somers, *et al* estimated the overall rate of venous thrombosis in persons with SLE to be 5.1 per 1000 person-years[5], while the age- and sex-standardized incidence of venous thromboembolism has been estimated in the US population at between 71 and 117 cases per 100,000 person-years (reviewed in[6]).

Studies on thrombovascular events in persons with SLE have focused mainly on cumulative risk, risk in specific age groups[3,4], and/or mortality associated with thrombovascular events[1], especially arterial. Fewer studies have been performed on venous thromboembolism[5], and in some instances studies including both types have not distinguished between

them[2]. Few studies have been conducted on prospectively gathered data (Table 9 in[7]).

The etiology of and risk for thrombovascular events may vary with duration of SLE. Our objective was to describe the pattern of incidence of thrombovascular events after a diagnosis of SLE in a cohort of patients with lupus.

MATERIALS AND METHODS

We obtained data from the lupus clinic registry at the McGill University Health Centre (MUHC) in Montreal, Quebec. This registry, created in January 1978, includes persons diagnosed with SLE, based on having ≥ 4 American College of Rheumatology criteria, who consented to participate. Laboratory, clinical, and demographic data are gathered at annual visits using standardized protocols. Diagnosis and thrombovascular event dates are reported using the middle of the month if the day is unknown and the middle of the year if month is unknown. All data are recorded in Medlog. The MUHC research ethics board approved use of these data for research.

All thrombovascular events were confirmed by physician review of medical records. Confirmation included information obtained from clinical notes, discharge diagnoses, and positive diagnostic imaging procedures. Diagnostic tests used to confirm events included: Doppler, contrast venogram, and ventilation perfusion scans for pulmonary embolus (PE) and deep vein thrombosis (DVT) in an extremity or another location; electrocardiograms, angiograms, and multiple gated acquisition scans for MI; angiograms and thallium tests for angina; and magnetic resonance imaging and computed tomography scans for cardiovascular accidents (CVA). History and neurological reports were used to confirm transient ischemic attack (TIA).

All visits up to June 30, 2004, were included in the analysis. The outcomes of interest were (1) any thrombovascular event (TE); (2) arterial thrombovascular event (ATE) (including MI, CVA, angina, TIA, and small-vessel arterial thrombovascular event); and (3) venous thrombosis (VTE) (including DVT, pulmonary embolus, and small-vessel thrombosis). For each person, the first outcome event (incident event) was used. An individual with only VTE could thus still be at risk for an incident ATE, and vice versa. In analyses with TE as the outcome, persons with both ATE and VTE were counted once and the earliest event date was used. Followup time was defined as the interval between the date of diagnosis and either the date of the first event or, if no event occurred, the dates of the last visit available. Persons with ATE preceding SLE diagnosis contributed no followup time for TE or ATE outcome but would contribute followup time for VTE. Similarly, persons with VTE preceding SLE diagnosis contributed no followup time for TE or VTE outcome but would contribute followup time for ATE. Incidence rates of TE, ATE, and VTE were calculated for the following periods of observation post-diagnosis: (1) 0–30 days, (2) > 30 days to 1 year, (3) > 1–5 years, (4) > 5–10 years, (5) > 10–20 years, (6) > 20–30 years, (7) > 30–40 years, (8) > 40–50 years. Corresponding 95% CI were calculated based on the Poisson distribution.

Kaplan-Meier survival curves were plotted for all 3 outcomes. Time zero was defined as date of SLE diagnosis, and persons without events in the category of interest were censored at the time of their last visit.

RESULTS

Of the 426 persons included in this analysis, 112 (26.3%) had at least one thrombovascular event (72 arterial only, 35 venous only, 5 both). Twenty-seven persons had their first event prior to SLE diagnosis (9 arterial, 18 venous). The number of persons who remained at risk for an incident event after SLE diagnosis, and the total person-years of followup contributed were: 399 persons and 4356.0 person-years for TE; 417 persons and 4691.9 person-years for ATE; and 408 persons and 4846.6 person-years for VTE. The median time to event was 8.6 years for any TE, 9.3 years for ATE, and 6.8 years for VTE.

Demographic characteristics are shown in Table 1 for persons with no event in the entire followup period, persons with a first event after SLE diagnosis but before the median time to any TE ("early events"), and persons with a first event after the median time to any TE ("later events"). Characteristics were similar between the 3 groups; however, persons with a later first event had a longer mean time between the date of SLE diagnosis and the date of their first visit to the MUHC clinic.

After SLE diagnosis, there were 68 individuals with an incident ATE and 22 with an incident VTE; 85 persons had their first event of either type and 5 persons had both. The most frequent types of ATE and VTE were CVA and DVT, respectively. Incidence rates (in events/100 person-yrs) and types of TE, ATE, and VTE are presented in Tables 2, 3, and 4, respectively. The incidence rate for TE was highest during the first year after SLE diagnosis (4.00, 95% CI 2.24–6.59) and after 20 years (ranging from 3.32, 95% CI 1.52–6.30, to 4.99, 95% CI 0.60–18.01), and was lowest between 1 and 5 years after SLE diagnosis (1.00, 95% CI 0.53–1.72). Within the first year after diagnosis, the incidence rate observed in the first 30 days was very high (24.80, 95% CI 10.69–48.85, vs 2.04, 95% CI 0.82–4.20, for months 2–12) and the 95% CI excludes all the later estimated incidence rates.

A similar pattern was observed when ATE was considered alone, with the incidence rate high very soon after SLE diagnosis (11.80 events/100 person-yrs, 95% CI 3.21–30.20, in the first 30 days), varying between 0.87 and 2.23 for the next few decades, and possibly increasing after 30 years, although this trend is uncertain due to insufficient person-years of followup. The pattern for VTE, however, differed, with the incidence rate peaking in the first 30 days after SLE diagnosis (12.06, 95% CI 3.29–30.87) and remaining low afterwards.

Figure 1 shows the probability of remaining event-free over time. Each line on the graph represents a different outcome (TE, ATE, or VTE) and was plotted using the followup information for persons at risk for that outcome at the time of SLE diagnosis. As expected from the differences in incidence rates over time, the curve corresponding to ATE drops more quickly than that for VTE. The median event-free times for TE and ATE were 28.6 and 36.3 years, respectively; a median event-free time for VTE was not available since the estimated probability of remaining free of venous events never dropped below 0.8. The probabilities of remaining event-free at 5, 10, and 15 years were as follows: 0.92, 0.85, and 0.78, respectively, for TE; 0.95, 0.88, and 0.82, respectively, for ATE; and 0.98, 0.95, and 0.94, respectively, for VTE.

DISCUSSION

This study assessed the occurrence of first thrombosis over the course of SLE. The followup time was divided into short intervals to identify periods with a higher risk for developing a thrombus. Incidence rates for ATE and VTE were evaluated separately. To avoid inflation of incidence rates, only the first ATE or VTE was included in the analyses.

Table 1. Characteristics of SLE patients with no thrombovascular events, early events, and later events.

	No Thrombovascular Event, n = 314	Early First Event, n = 42	Later First Event, n = 43
Age at SLE diagnosis, mean (SD) yrs	33.6 (14.2)	36.6 (17.1)	32.9 (13.6)
Age at most recent visit (if no event) or first event			
Mean (SD)	44.7 (15.3)	39.9 (17.8)	49.8 (13.7)
Median (IQR)	42.9 (33.1–55.1)	36.0 (27.3, 52.6)	45.5 (38.9, 60.1)
Sex, n (%) female	280 (89.2)	38 (90.5)	37 (88.4)
Ethnicity, n (%) Caucasian	223 (76.1) (missing for n = 21)	33 (80.5) (missing for n = 1)	37 (86.1)
Years from SLE diagnosis to first clinic visit			
Mean (SD)	4.1 (6.0)	3.3 (4.9)	9.9 (8.1)
Median (IQR)	1.8 (0.2–6.0)	1.2 (0.2, 5.9)	10.0 (1.8, 16.2)
Years from SLE diagnosis to event or last clinic visit			
Mean (SD)	11.1 (8.0)	3.3 (2.9)	16.9 (7.0)
Median (IQR)	10.1 (4.2–16.2)	3.0 (0.2, 6.1)	15.4 (11.2, 21.3)
Type of first event			
Arterial		29 (69.0)	35 (81.4)
Venous		13 (31.0)	8 (18.6)

* Early events: Those occurring between SLE diagnosis date and median time to any thrombovascular event (8.6 yrs). Later events: Those occurring after median time. The actual numbers of persons with incident arterial and venous events differ from those shown in this table, because of the timing of events.

Table 2. Annual incidence rates of thrombovascular events and type of first event.

Time after SLE Diagnosis	N with Events	Person–Years	Incidence Rate	First Thrombovascular Event							
				DVT	PE	Other VT	MI	CVA	TIA	Angina	Other ATE
0–1 yr	15	375.3	4.00 (2.24, 6.59)	5	2	0	0	4	1	0	3
0–30 days	8	32.26	24.80 (10.69, 48.85)	3	1	0	0	2	1	0	1
> 30 days– 1yr	7	343.1	2.04 (0.82, 4.20)	2	1	0	0	2	0	0	2
> 1–5 yrs	13	1295	1.00 (0.53, 1.72)	0	0	1	1	7	1	1	2
> 5–10 yrs	21	1199	1.75 (1.08, 2.68)	5	1	0	3	7	1	2	2
> 10–20 yrs	25	1173	2.13 (1.38, 3.15)	5	0	0	4	9	3	2	2
> 20–30 yrs	9	271.1	3.32 (1.52, 6.30)	2	0	0	4	1	2	0	0
> 30–40 yrs	2	40.08	4.99 (0.60, 18.01)	0	0	0	0	1	1	0	0

All incidence rates and 95% confidence intervals are reported as events per 100 person-years. N with events: No. of persons with event in time interval; CI: confidence interval; DVT: deep vein thrombosis; PE: pulmonary embolus; VT: venous thrombosis; MI: myocardial infarction; CVA: cardiovascular event; TIA: transient ischemic attack; ATE: arterial thrombovascular event.

Table 3. Incidence rates and types of arterial thrombovascular events.

Time After SLE Diagnosis	N with Event	Person-Years	Incidence Rate (95% CI)	MI	CVA	TIA	Angina	Other Arterial
0–1 year	8	398.27	2.01 (0.87, 3.96)	0	4	2	0	1
0–30 days	4	33.91	11.80 (3.21, 30.20)	0	2	1	0	1
> 30 days–1 year	4	364.35	1.10 (0.30, 2.81)	0	2	1	0	0
> 1–5 years	12	1372.41	0.87 (0.45, 1.53)	1	7	1	1	2
> 5–10 years	17	1265.72	1.34 (0.78, 2.15)	5	7	1	2	2
> 10–20 years	22	1277.60	1.72 (1.08, 2.61)	4	9	3	3	3
> 20–30 years	7	314.38	2.23 (0.89, 4.59)	4	1	2	0	0
> 30–40 years	2	57.81	3.46 (0.42, 12.49)	0	1	1	0	0
> 40–50 years	0	5.69	0.00 (0.00, 64.85)	0	0	0	0	0

All incidence rates and 95% confidence intervals are reported as events per 100 person-years. For definitions see Table 2.

Table 4. Incidence rates and types of venous thrombosis.

Time After SLE Diagnosis	N with Event	Person-Years	Incidence Rate (95% CI)	DVT	PE	Other Venous
0–1 yrs	7	389.87	1.80 (0.72, 3.70)	5	2	0
0–30 days	4	33.17	12.06 (3.29, 30.87)	3	1	0
> 30 days–1 yr	3	356.70	0.84 (0.17, 2.46)	2	1	0
> 1–5	1	1369.29	0.07 (0.00, 0.41)	0	0	1
> 5–10	7	1292.76	0.54 (0.22, 1.12)	6	1	0
> 10–20	5	1343.14	0.37 (0.12, 0.87)	5	0	0
> 20–30	2	373.95	0.53 (0.06, 1.93)	2	0	0
> 30–40	0	71.27	0.00 (0.00, 5.18)	0	0	0
> 40–50	0	6.32	0.00 (0.00, 58.40)	0	0	0

All incidence rates and 95% confidence intervals are reported as events per 100 person-years. For definitions see Table 2.

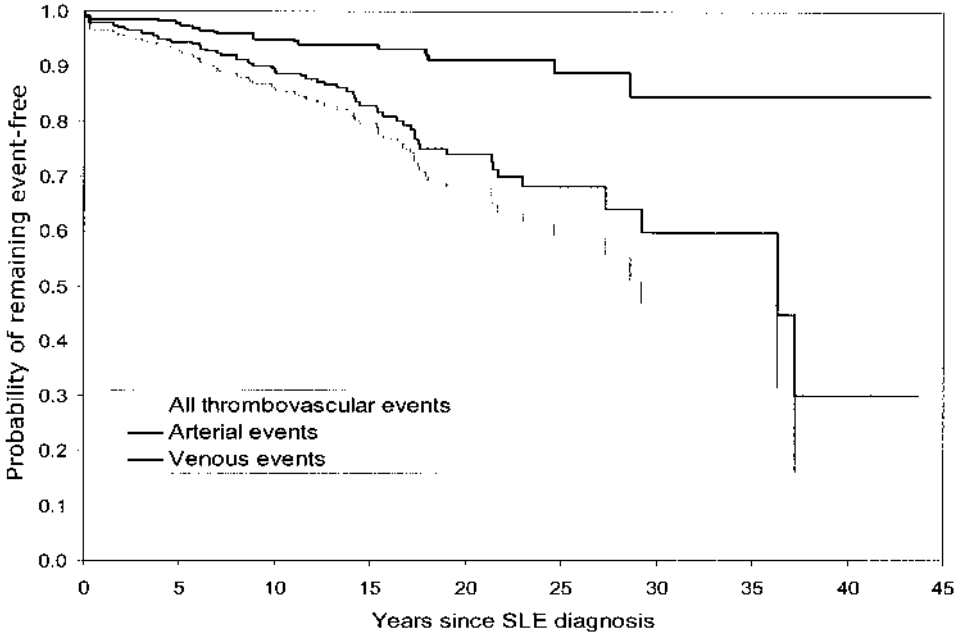

Figure 1. Probability of remaining event-free over time for different outcomes, using followup information for persons at risk for the outcome at the time of SLE diagnosis.

We observed higher incidence rates of both ATE and VTE in our lupus cohort around the time of SLE onset, with rates peaking within 30 days of diagnosis. However, while incidence rates decreased for both types of thrombosis one year post-diagnosis, the incidence of ATE appeared to gradually increase over time, whereas incidence of VTE remained low throughout. This suggests that the underlying disease process and risk factors vary for ATE and VTE and may change over time.

Various factors may have contributed to the early peak in ATE and VTE incidence. The inflammatory process leading to SLE may result in vascular reactivity, damage, or thrombosis. However, since our study is purely descriptive, we would like to remain cautious and await replication of these patterns in larger and ideally prospective studies before hypothesizing what factors may contribute to this early peak.

Very few studies have evaluated incidence rates of TE in SLE. Similar to our findings, Brouwer, *et al*[8] observed that the frequency of both ATE and VTE was higher soon after SLE diagnosis, compared to later in the course of the disease. However, we found a higher overall incidence of ATE than VTE, whereas Brouwer, *et al* observed similar rates for each. This may have been due to the inclusion of angina in our definition of ATE or to other differences in the 2 study populations. Somers, *et al* estimated, using survival analysis, that 9% of SLE patients would develop a DVT or PE within 20 years of their diagnosis[5]. Arterial thrombosis was not evaluated. In a 10-year followup of 1000 European SLE patients, Cervera, *et al* observed a higher incidence of thrombosis in the first 5 years of followup compared to the last 5 years[2]. However, not all of their patients had new diagnoses of thrombosis, the thrombotic events were not classified, and recurrent events may have been counted.

The observed incidence rates may have been affected by selection bias. Persons who had thrombosis soon after SLE diagnosis could have been underrepresented in the cohort because of early death. This would lead to an underestimate of thrombosis incidence rates in early SLE. Conversely, observation bias may have inflated the peridiagnostic incidence rates for both ATE and VTE. For example, persons who were diagnosed with SLE at the time they presented with thrombosis would lead to an overestimation of incidence rates in early SLE. In addition, the classification of events during this period as pre- or post-diagnosis may be a detection artifact rather than an actual difference in the nature of the events. In a recent study, we used an inception cohort design that would eliminate these selection biases and found remarkably similar incidence rates[9]. Therefore, these possible selection biases do not appear to play an important role here. Another limitation of this study was the imprecision of the estimated incidence rates, reflected in the wide 95% CI. Longer followup of the persons in the MUHC registry will be required to determine if the trends in ATE and VTE incidence that we observed are genuine or caused by random variation.

In summary, the incidence of thrombosis appears to be greatest during the first year of diagnosis of SLE. These results advocate early management of inflammation and traditional risk factors associated with thrombosis in persons with newly diagnosed SLE.

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