Cardiovascular Disease a Hazard Despite Improved Prognosis in Patients with Systemic Lupus Erythematosus: Results from a Swedish Population Based Study 1964–95

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ABSTRACT. ***Objective.*** Although short term prognosis has improved in patients with systemic lupus erythematosus (SLE) during the early disease course, less is known about the longterm prognosis.

Methods. A cohort of 4737 patients with a diagnostic code of SLE was identified 1964–94 in the Swedish Hospital Discharge Register and followed by linkage to the Cause of Death Register until the end of 1995. Mortality was separately analyzed in 3 different calendar periods (1964–75, 1975–84, 1985–95). The relative risk of death was estimated as standardized mortality ratio (SMR) using the Swedish population as a reference.

Results. In total 2314 patients were deceased. Mortality was 3-fold increased (SMR = 3.63, 95% CI 3.49, 3.78) and cardiovascular disease (CVD) was the major cause of death. Patients aged 20–39 years at the first discharge had a 16-fold increased risk of death from coronary heart disease (SMR = 15.99, 95% CI 10.4, 23.6). All-cause mortality had decreased since 1975 and the reason for this decrease was entirely due to a decrease in causes attributed to SLE, but not CVD. Patients aged 20–39 years at the first discharge had a pronounced decrease in mortality, with SMR 33.59 (95% CI 24.3, 45.3) before 1975 compared with SMR 14.23 (95% CI 8.70, 22.0) after 1984.

Conclusion. Cardiovascular disease was the major cause of death in patients with SLE and young patients had a pronounced increased risk of death. Even if all-cause mortality had declined during the last 2 decades due to causes attributed to SLE, the risk of cardiovascular death remained unchanged. (J Rheumatol 2004;31:713–9)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS MORTALITY EPIDEMIOLOGY
CORONARY HEART DISEASE CARDIOVASCULAR STROKE

The prognosis for patients with systemic lupus erythematosus (SLE) seems to have improved during the last decades[1-3], at least during the first years after diagnosis. However, in a longer perspective, mortality is increased compared to that expected[2,4,5]. Much is known about the causes of death in early disease and related to various organ involvement due to SLE such as nephritis and infections[4-8]. Much less is known why the prognosis is less favorable in the later stages of SLE. However, cardiovascular diseases (CVD) have been reported to be more frequent in late stage disease[5-7]. Studies from the US[4] and Canada[5] have reported a vascular event as the cause of death in 24% (34 of 144 deaths) and 36% (45 of 124 deaths) of all deaths, respectively. Data from a Swedish community-based study reported vascular diseases to be the major cause of death[2]. It is not known whether the risk of CVD is associated with disease duration, or if the risk for cardiovascular death has changed with time. With a better short-term prognosis among patients with SLE, CVD might be an increasing clinical problem.

A problem in determining the overall influence of CVD on mortality in SLE is that most previous studies have been from referral centers. Information on causes of death might thus have been biased toward those directly related to SLE, which are more readily detected in an SLE referral center. Studies with a population-based design would overcome these disadvantages, but such studies are hampered by a limited number of deaths, as in Minnesota (n = 20)[3], Iceland (n = 17)[9], and southern Sweden (n = 17)[2].

We estimated the influence of CVD on all-cause mortality in patients with SLE, and analyzed trends over time in a population large enough to permit analyses of time trends in different causes of death. Using the population-

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Supported by The Heart and Lung Foundation, Sweden.

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Submitted February 12, 2003; revision accepted October 21, 2003.

based national registers in Sweden we identified a cohort of patients with a discharge diagnosis of SLE consisting of 4737 individuals followed during 1964–95.

MATERIALS AND METHODS

The Hospital Discharge Register. Since 1964 the Swedish National Board of Health and Welfare has received annual reports from the medical institutions in the country. These data are gathered in The Hospital Discharge Register, which contains information on all individual discharges, including the date of admittance and discharge and a principal discharge diagnosis, coded according to the 7th revision of the *International Classification of Diseases* (ICD-7) through 1968, ICD-8 from 1969–86, and ICD-9 from 1987–95. Each record in The Hospital Discharge Register contains the National Registration Number (NRN), an individually assigned 10-digit number given to all Swedish residents.

Validations of the register by analyzing medical data in the records both in 1986 and in 1990 confirmed a correct ICD code at the 4 digit level in 86% of the principal discharge diagnoses[10]. As an example, for ulcerative colitis or Crohn's disease, a correct diagnostic code was assigned to 84–89% of the patients[11]. For rheumatoid arthritis (RA), previous studies using The Hospital Discharge Register reported a specificity of at least 80% in patients fulfilling the Rome and New York criteria[12], as well as the American College of Rheumatology criteria[13]. However, for the diagnosis of SLE, no validation of the diagnostic codes in the register has been reported to date.

As private inpatient care in Sweden is almost nonexistent, patients are obliged to use the public hospitals in their own county. Thus the data in The Hospital Discharge Register refers to the whole population in each county. The register covers virtually all discharges in the population, as the nonreporting rate was estimated to be 2% or less[14]. The Hospital Discharge Register has gradually expanded and encompassed 20% of all Swedish counties in 1964, 35% in 1970, 73% in 1974, 85% by the end of 1983[15], and 100% of the population from 1987.

The Causes of Death Register. The Swedish National Board of Health and Welfare administers the Causes of Death Register, which comprises all deaths from 1952 and onwards among persons registered as Swedish residents. The register covers almost 100% of the death certificates[16]. In addition to the NRN, the register records the underlying and contributing causes of death, the date of death, and the home county and sex of the deceased.

Validation studies of the cause of death certification for coronary heart disease from the 1970s and the late 1980s have reported a specificity of 92–96%[17,18].

The study cohort. The basis for the study was the 5833 patients who were discharged for the first time with a diagnostic code for SLE (ICD-7 456.20, ICD-8 734.10, ICD-9 710A) between 1964 and 1994. We excluded 244 (4.2%) patients due to incorrect sex notation or erroneous NRN. By linkage through the Swedish Cancer Register, 375 (6.4%) patients were excluded due to a malignancy diagnosed prior to the first discharge. As well, 354 (6.1%) patients were excluded because of age younger than 20 years. Finally, as 122 (2.1%) patients died at the first discharge and were thus not available for followup, 4737 patients remained for followup.

Followup. The cohort was followed through computerized linkage by the NRN in the Hospital Discharge Register and the Cause of Death Register. The NRN allowed us to select the first recorded discharge in SLE for each patient and to follow each individual throughout the study. The person-years at risk were calculated from the date of the first discharge and until death or the end of the observation period, December 31, 1995. All underlying causes of death were studied.

The cohort was stratified for sex, age at first discharge (20–39, 40–59, 60 years or above), the number of years of followup, periods of the first discharge (1964–74, 1975–84, 1985–94), the frequency of discharges (1–3, ≥ 4), and the type of discharging unit (rheumatology unit or not).

Statistical methods. The standardized mortality ratio (SMR), the ratio of observed to expected number of deaths, was used as an indicator of risk. Nationwide statistics from the Cause of Death Register include annual sex- and age-specific mortality rates for different ICD codes. The number of expected deaths was calculated by multiplying the numbers of person-years at risk according to each 5-year age group, sex, and calendar year, by the corresponding age, sex, and year-specific mortality rates in the general population. The 95% confidence interval (CI) of the SMR was then calculated on the assumption that deaths in different categories followed a Poisson distribution[19].

Mortality was also analyzed by Cox regression stratified by age at the first discharge of SLE by 5 year subgroup and county. Stratification by county was done because of the increasing number of counties included in the Hospital Discharge Register during the observation period. The calendar year of the first discharge of SLE was the primary explanatory variable, which also included sex and an indicator variable for a discharge due to CVD diagnosis prior to the first discharge of SLE as covariables. The calendar year was used as a continuous variable in the analyses, but the model fit was also checked by categorization into 3 periods (1964–74, 1975–84, 1985–94). Differences of calendar time effects with respect to other variables were investigated by introducing interaction terms between calendar time and age at the first discharge, sex, and previous CVD into the model. The strong interaction between age at first discharge and calendar time led us to investigate the results stratified in 3 age groups (20–39, 40–59, 60+). Further, a deviation from proportional hazards for the calendar time effect was investigated by an interaction between calendar time and attained time on the study.

RESULTS

The cohort of all SLE cases including 4737 patients constituted 44,026 person-years (Table 1).

A previous population-based study of SLE in Sweden reported a prevalence of 42/100,000 and an incidence of 4/100,000[20]. According to our calculations, after adjusting for the incomplete coverage of the counties before 1987, at least 80% of all patients with SLE in the population were included in this cohort.

In all, 2314 (49%) patients in the cohort died during followup (Table 2). All-cause mortality was increased more than 3-fold compared with the general population. CVD, causes of death attributed to SLE, and malignancies were the major underlying causes of death (Table 3).

Young age at the first discharge was the most prominent determinant for an additional increased risk (Table 2). During the first 10 years of followup, 59% (78/133) of the excess deaths were due to causes attributed to SLE and 14% (18/133) to CVD. However, after more than 10 years this pattern had reversed, revealing 37% (29/78) of the excess deaths due to CVD and 32% (25/78) of causes attributed to SLE.

Cardiovascular mortality was 3-fold increased in SLE patients and 73% of deaths were attributed to coronary heart disease or stroke (Table 3). The risk of coronary death was 3-fold increased and remained increased even 20 years after the first discharge (Table 4). An especially high risk for coronary death was observed in patients discharged at a young age (Table 5): those aged 20–39 had a 16-fold increased risk.

Mortality decreased significantly among SLE patients discharged from 1975 and onwards compared to those

Table 1. Characteristics of SLE patients in the cohort in different calendar periods.

	All, n (%)	1964–74, n (%)	1975–84, n (%)	1985–94, n (%)
All	4737 (100)	1107 (23)	1874 (40)	1756 (37)
Male	1002 (22)	228 (21)	423 (23)	351 (20)
Female	3735 (78)	879 (79)	1451 (77)	1405 (80)
Age at first discharge, yrs				
20–39	1272 (27)	304 (27)	472 (25)	496 (28)
40–59	1656 (35)	476 (43)	643 (34)	537 (31)
60 or older	1809 (38)	327 (30)	759 (41)	723 (41)

Table 2. All-cause mortality in SLE 1964–95.

	Observed	Expected	SMR	95% CI
All	2314	636.801	3.63	3.49, 3.78
Men	611	190.448	3.21	2.96, 3.47
Women	1703	446.353	3.82	3.64, 4.00
Age at first discharge, yrs				
20–39	232	20.882	11.11	9.73, 12.6
40–59	717	146.447	4.90	4.54, 5.27
60 or more	1365	469.472	2.91	2.76, 3.07
Frequency of discharges				
1–3	1620	500.102	3.24	3.08, 3.40
4 or more	694	136.699	5.08	4.71, 5.47
Type of discharging unit				
Rheumatology	316	93.737	3.37	3.01, 3.76
Other than rheumatology	1998	543.064	3.68	3.52, 3.84

SMR: standardized mortality ratio.

discharged before this time (Table 6). The decrease in mortality was most pronounced in patients aged 20–39 at the first discharge, who had a decline of 69% (Table 7). Mortality in patients aged 40–59 had decreased by 42% since 1975, whereas no decrease was found in the older age group. When we separately analyzed the calendar effect on specific causes of death (i.e., SLE, malignancies, CVD, infection), patients aged 20–39 had a decline of 85% since 1975 due to causes attributed to SLE (Table 8). When we excluded those causes from the analysis for each age-group separately, no decline in all-cause mortality was apparent. The decrease in all-cause mortality was therefore entirely due to a decrease in causes attributed to SLE. Consequently, no changes in CVD mortality due to calendar period were observed (Table 9).

DISCUSSION

Two major findings arose in this nationwide population-based study on SLE mortality. First, patients with SLE had an increased risk of cardiovascular death, which remained increased even 20 years after the first discharge. Second, the decrease in mortality during the last 2 decades was entirely due to a decline in causes attributed to SLE. Despite this decline in mortality, no change in cardiovascular mortality was evident during the followup period of more than 30 years.

Our findings confirm an increased all-cause mortality in patients with SLE, with a risk estimate close to that of 2 other population-based studies from Iceland (SMR = 3.4)[9] and Minnesota, USA (SMR = 2.7)[3]. We also determined an increased risk of CVD that persisted even up to 20 years after the first discharge, a finding that to our knowledge has not been reported before. The finding of a decrease in mortality since 1975 was consistent with the results from 2 previous studies[1,3] reporting a decline since 1977[1] and 1980[3]. We found that this decrease was entirely explained by a decline in the underlying causes of death attributed to SLE. A decline in mortality since 1980 caused by SLE manifestations has been reported[21]. Moreover, studies from both the US[22] and England[23] have revealed an increased survival in patients with lupus nephritis treated from 1976 compared to those treated before that time.

One limitation in our study was that the cohort was confined to only hospitalized patients, which might result in a selection of SLE patients with more severe disease. However, according to our calculations, around 80% of all SLE patients in the population were included in the cohort. This is in accord with results from Iceland that showed that 75% of the SLE population had sometimes been hospitalized[9].

A second limitation was the lack of validation of the discharge diagnosis of SLE. However, the strong associations we determined cannot be explained by a low specificity of the discharge diagnosis, as random

Table 3. Mortality in SLE patients by different causes of death 1964–95.

Causes of Death (ICD7; ICD8; ICD9)	%*	Observed	Expected	SMR	95% CI
All causes	100	2314	636.801	3.63	3.49, 3.78
Cardiovascular including stroke (330–334, 400–455; 390–458; 390–459)	42	972	327.421	2.97	2.78, 3.16
Coronary heart disease (420, 0, 420, 2, 420, 9; 410–414; 410–414)		561	185.394	3.03	2.78, 3.29
Stroke (330–334; 430–438; 430–438)		146	70.742	2.06	1.74, 2.43
SLE	21	486	0.324	1500	1370, 1639
Malignancy (140–239)	12	269	162.713	1.65	1.46, 1.86
Respiratory (240–245, 470–527; 460–519; 460–519)	6	134	42.306	3.17	2.65, 3.75
Pneumonia (490–493; 480–486; 480–486)		88	24.638	3.57	2.86, 4.40
Obstructive pulmonary disease (500–502, 241; 490–493; 490–493, 496)		26	12.919	2.01	1.31, 2.95
Gastrointestinal (530–587; 520–577; 520–579)	5	115	20.633	5.57	4.60, 6.69
Peptic ulcer disease (540–542; 531–534, 707; 531–534)		17	4.013	4.24	2.47, 6.78
Chronic liver disease (581, 583; 571; 571)		38	4.935	7.70	5.45, 10.6
Trauma and intoxication (800–999; 800–995; 800–995)	3	66	27.36	2.41	1.87, 3.07
Urogenital (590–637; 580–629; 580–629)	2	47	8.374	5.61	4.12, 7.46
Nephritis/nephrosis (590–593; 580–584; 580–589)		24	2.481	9.67	6.20, 14.40
Pyelitis (600; 590; 590)		11	2.39	4.60	2.30, 8.24
Infection (001–138; 000–136; 001–139)	1	22	4.458	4.93	3.09, 7.47
Neurology (340–398; 320–389; 320–389)	1	15	7.603	1.97	1.10, 3.25
Psychiatric (300–326; 290–315; 290–315)		11	11.104	0.99	0.49, 177
Hematological (malignancies, etc.) (290–299; 280–289; 280–289)		9	1.552	5.80	2.65, 11.0
Endocrine (250–289; 240–246, 250–279; 240–246, 250–279)		1	0.433	2.31	0.06, 12.9

* Percentage of all-cause mortality. Observed: number of observed deaths. Expected: number of expected deaths. SMR: Standardized mortality ratio.

misclassification increases the similarity between the cohort and the general population, creating an underestimation of the risk estimates.

A third drawback was the lack of validation of the underlying cause of death attributed to SLE on the death certificates. We found that 31% of the excess mortality was attributed to SLE and urogenital diseases, a figure close to the 37% of SLE-related deaths reported by Jacobsen, *et al*[6]. We recorded only 2 cases of nephritis as underlying cause of death in patients aged 20–39 years at the first discharge. It is therefore reasonable to assume that most of the deaths due to nephritis in our study were probably categorized as a cause attributed to SLE.

The decline in mortality over time might be caused by several different factors, such as earlier diagnosis or recognition of a milder disease. There was, however, no association between age at first discharge and calendar period in the survival analysis. Identification of milder cases would lead to an increased incidence of SLE with time, but incidence studies have been contradictory[2,3,9]. Our results indicate a decreasing severity of SLE, but whether this is a result of a natural change in the disease itself or therapy or both remains to be established. Studies have indicated a decrease in renal manifestations during the last decades[2,3,9]. As for therapy, data on the treatment of patients with lupus have been contradictory[1-3]. In addition to corticosteroids and cytotoxic drugs, new treatment options for lupus during this period include loop-diuretics and antibiotics as well as the implementation of antihypertensive therapy[24,25]. Moreover, rheumatology care in Sweden underwent an expansive

Table 4. Mortality in SLE patients due to all-cause mortality and coronary deaths by the duration of followup.

No. of Years After First Discharge	Observed	Expected	SMR	95% CI
		All Causes of Deaths		
0–1	387	58.033	6.67	6.02, 7.37
1–4	752	193.515	3.89	3.61, 4.17
5–9	532	177.301	3.00	2.75, 3.27
10–14	358	117.702	3.04	2.73, 3.37
15–20	195	62.334	3.13	2.79, 3.60
20+	90	27.916	3.22	2.59, 3.96
		Deaths due to Coronary Heart Disease		
0–1	63	17.700	3.56	2.74, 4.55
1–4	169	58.350	2.90	2.48, 3.37
5–9	146	52.466	2.78	2.35, 3.27
10–14	107	33.455	3.20	2.62, 3.86
15–20	60	16.423	3.65	2.79, 4.70
20+	16	7.000	2.29	1.31, 3.71

SMR: Standardized mortality ratio.

Table 5. Mortality in SLE patients due to coronary heart disease by age, sex, and frequency of discharges.

	Observed	Expected	SMR	95% CI
All	561	185.394	3.03	2.78, 3.29
Men	166	67.677	2.45	2.09, 2.86
Women	395	117.717	3.36	3.03, 3.70
20–39 yrs	25	1.563	15.99	10.4, 23.6
40–59 yrs	166	34.775	4.77	4.07, 5.56
60+ yrs	370	149.056	2.48	2.24, 2.75
1–3 discharges	424	147.148	2.88	2.61, 3.17
≥ 4 discharges	137	38.246	3.58	3.01, 4.23

Table 6. All-cause mortality in different calendar periods by age at the first discharge during the first 5 years of followup.

Age at First Discharge, yrs	Calendar Period	Observed	Expected	SMR	95% CI
20–39	1964–74	43	1.28	33.59	24.3, 45.3
	1975–84	27	1.83	14.75	9.72, 21.5
	1985–94	20	1.41	14.23	8.70, 22.0
40–59	1964–74	100	10.67	9.37	7.63, 11.4
	1975–84	100	15.23	6.57	5.34, 7.99
	1985–94	64	7.68	8.34	6.42, 10.6
≥ 60	1964–74	149	37.88	3.93	3.33, 4.62
	1975–84	329	94.67	3.48	3.11, 3.87
	1985–94	307	80.91	3.79	3.38, 4.24

Table 7. All-cause mortality and calendar period of the first discharge: hazard ratios (95% CI).

Calendar Period	All Ages	20–39 yrs	40–59 yrs	≥ 60
1964–74	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1975–84	0.73 (0.64, 0.82)	0.41 (0.28, 0.58)	0.77 (0.63, 0.94)	0.79 (0.67, 0.94)
1985–94	0.68 (0.59, 0.79)	0.31 (0.19, 0.52)	0.58 (0.43, 0.78)	0.82 (0.68, 1.00)

ref: reference data.

Table 8. Causes of death attributed to SLE and calendar period of the first discharge: hazard ratios (95% CI).

Calendar Period	All Ages	20–39 yrs	40–59 yrs	≥ 60
1964–74	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1975–84	0.55 (0.43, 0.70)	0.30 (0.18, 0.52)	0.63 (0.42, 0.93)	0.71 (0.49, 1.05)
1985–94	0.35 (0.26, 0.48)	0.15 (0.07, 0.34)	0.26 (0.14, 0.48)	0.58 (0.37, 0.91)

ref: reference data.

Table 9. Causes of death attributed to CVD and calendar period of the first discharge: hazard ratios (95% CI).

Calendar Period	All Ages	20–39 yrs	40–59 yrs	≥ 60
1964–74	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1975–84	0.88 (0.72, 1.06)	0.61 (0.27, 1.39)	0.91 (0.66, 1.26)	0.88 (0.68, 1.15)
1985–94	0.92 (0.72, 1.18)	0.37 (0.09, 1.50)	0.81 (0.48, 1.37)	0.98 (0.72, 1.32)

ref: reference data.

period and there were 3 times as many rheumatology units in 1984 as there were in 1974[26].

Cardiovascular diseases were the major cause of death in our study. The risk of death due to coronary heart disease was particularly increased for young patients with SLE and close to that of young patients with insulin-dependent diabetes mellitus (SMR = 16.77)[27]. Recent studies[28,29] of women with SLE indicate that atherosclerosis is important in the development of CVD and is associated with a number of various predictors such as inflammatory markers and traditional risk factors as well as SLE-related factors, i.e., the cumulative dose of corticosteroids.

Since we found cardiovascular mortality unchanged over time, despite a pronounced decrease in causes of death attributed to SLE, factors other than disease severity are probably important. Moreover, the additional risk in the youngest patients implies a multifactorial pathogenesis in lupus, which might involve genetic as well as traditional risk factors.

Our results confirm CVD to be the major cause of death in patients with SLE. Young patients had a risk of coronary death close to that of patients with insulin-dependent diabetes. The excess mortality has declined during recent decades due to causes attributed to SLE, but not for CVD. Since some of the risk factors for CVD are known today and are potentially reversible, preventive strategies have to be developed to improve the prognosis of patients with SLE.

ACKNOWLEDGMENT

We thank Prof. R. A. Harris for linguistic advice.

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