

# Atherosclerotic Vascular Events in Systemic Lupus Erythematosus: An Evolving Story

Murray B. Urowitz , Jiandong Su, and Dafna D. Gladman 

**ABSTRACT. Objective.** Atherosclerotic vascular events (AVE) are a major cause of mortality and morbidity in systemic lupus erythematosus (SLE). We aimed to determine the effect of early recognition and therapy for both classic risk factors for AVE and for SLE, on the burden of AVE in SLE in recent decades.

**Methods.** Inception patients who entered the University of Toronto Lupus Clinic between 1975 and 1987 followed to 1992 (Cohort 1), and between 1999 and 2011 followed to 2016 (Cohort 2) were studied. AVE attributed to atherosclerosis and occurring during the 17 years were identified. SLE disease activity and therapy as well as hypertension, hypercholesterolemia, hyperglycemia, and smoking were assessed. Analysis included descriptive statistics on baseline characteristics, traditional risk factors over the followup, outcome rates by each 100 person-years (PY), Kaplan-Meier cumulative AVE curves, as well as competing risk Cox models adjusted by inverse probability weights.

**Results.** Of the 234 patients in Cohort 1, 26 patients (11%) had an AVE compared with 10 of 262 patients (3.8%) in Cohort 2. The rate per 100 PY of followup was 1.8 in Cohort 1 and 0.44 in Cohort 2 ( $p < 0.0001$ ). Better control of all risk factors and disease activity was achieved in Cohort 2. There was a reduction of 60% in the risk for AVE in Cohort 2.

**Conclusion.** The incidence of AVE in SLE in the modern era has declined in large part owing to more effective management of classic coronary artery risk factors and of SLE. (J Rheumatol First Release May 15 2019; doi:10.3899/jrheum.180986)

## Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS

RISK FACTORS

ARTERIOSCLEROSIS

The description of the bimodal mortality pattern of systemic lupus erythematosus (SLE) highlighted the importance of premature atherosclerotic vascular events (AVE) as an important cause of late mortality in SLE<sup>1</sup>. Cardiovascular (CV) disease remains a major cause of death in SLE<sup>2</sup>. Further, subsequent studies described the increased prevalence of AVE as a significant comorbidity in SLE<sup>3,4,5,6</sup>. Risk factors for accelerated atherosclerosis in SLE include both traditional risk factors [e.g., hypertension (HTN), hyperlipidemia, smoking, and diabetes] as well as SLE-related factors (e.g., disease activity, damage)<sup>3,7,8,9,10</sup>. Current recommendations for monitoring for CV risk in SLE indicate that high-quality evidence would recommend regular monitoring

for HTN, dyslipidemia, diabetes, and smoking<sup>11</sup>. Subclinical atherosclerosis has also been documented in a significant proportion of patients with SLE<sup>12–18</sup>, further emphasizing the importance of this comorbidity.

We aimed to determine the prevalence of AVE in the current millennium compared to the prevalence in the 1970–80s, and the effect of early recognition and newer therapy for both classic risk factors for AVE and for the treatment of SLE, on the burden of AVE in SLE in recent decades.

## MATERIALS AND METHODS

**Setting.** The Toronto Lupus Cohort was established in 1970 and has followed patients prospectively according to a standard protocol at 2- to 6-month intervals<sup>19</sup>. Disease activity is measured by the SLE Disease Activity Index 2000 (SLEDAI-2K)<sup>20</sup>. Disease activity over time is measured by the adjusted mean SLEDAI-2K (AMS)<sup>21</sup>. The research program is approved by the Research Ethics Board of University Health Network (REB# 11-0397-AE), and all patients have consented.

**Patient selection.** Patients who entered the Lupus Clinic within 12 months of diagnosis without a prior AVE were included. The first cohort (Cohort 1) included patients who entered between 1975 and 1987, and was followed until the end of 1992. The second cohort who entered between 1999 and 2011 was followed until the end of 2016.

**AVE outcomes.** AVE that occurred within the first 17 years from enrollment were included. AVE are collected prospectively in the data collection form according to the following definitions: (1) myocardial infarction [defined as one of the following: definite electrocardiographic (ECG) abnormalities, typical symptoms with probable ECG abnormalities and abnormal enzymes

From the University of Toronto Lupus Clinic, Centre for Prognosis Studies in The Rheumatic Disease, Toronto Western Hospital, Toronto, Ontario, Canada.

M.B. Urowitz, MD, FRCPC, Professor of Medicine, University of Toronto, and Senior Scientist, Krembil Research Institute, and Director, Centre for Prognosis Studies in The Rheumatic Disease and University of Toronto Lupus Clinic, Toronto Western Hospital; J. Su, MB, BSc, Biostatistician, Centre for Prognosis Studies in The Rheumatic Diseases, University of Toronto Lupus Clinic; D.D. Gladman, MD, FRCPC, Professor of Medicine, University of Toronto, Senior Scientist, Krembil Research Institute, Deputy Director, Centre for Prognosis Studies in The Rheumatic Disease and University of Toronto Lupus Clinic, Toronto Western Hospital.

Address correspondence to Dr. M.B. Urowitz, Centre for Prognosis Studies in The Rheumatic Diseases, Toronto Western Hospital, 399 Bathurst St. 1E-410B, Toronto, Ontario M5T 2S8, Canada.

E-mail: m.urowitz@utoronto.ca

Accepted for publication January 14, 2019.

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(> 2× upper limit of normal), typical symptoms and abnormal enzymes]; (2) angina [defined as severe pain or discomfort over the upper or lower sternum or anterior left chest and left arm, of short duration, relieved by rest or vasodilators, and confirmed by a cardiologist]; (3) transient ischemic attack (defined as a brief episode of neurological dysfunction without residua); (4) stroke (defined as an abrupt onset of neurological dysfunction resulting in neurological damage); (5) congestive heart failure due to ischemic heart disease requiring treatment (in these cases, either the evidence of atherosclerosis was present prior to entering our clinic and the first AVE in our clinic was congestive heart failure, or the patients presented with congestive heart failure and the atherosclerosis was identified in the course of investigation, all in the absence of active SLE); and (6) bradyarrhythmia due to ischemic heart disease requiring pacemaker insertion. Angioplasty and coronary artery bypass surgery were not included because they occurred only after a previous diagnosis of an AVE. AVE are recorded as being due to atherosclerosis and not related to active SLE based on SLE being inactive at the time of the event and/or typical atherosclerotic changes on angiogram or evidence of atherosclerosis elsewhere. Only the first AVE was included with its corresponding date defined as the outcome date. For patients without AVE, their censoring dates were the last clinic visit or cutoff dates when they reached 17 years of followup since the first visit.

**Disease factor outcomes.** Disease activity was measured by the AMS at 5 years; use of corticosteroids ever, or average to first AVE or last clinic visit; and antimalarials and immunosuppressive therapy ever to the time of first AVE or last assessment.

**Classic risk factor outcomes.** The percent of time over the 17 years that patients had normal blood pressure ( $\leq 140/90$  mmHg), normal total cholesterol ( $\leq 5.2$  mmol/l), normal blood sugar ( $\leq 7$  mmol/l), and the percent of time patients smoked was calculated.

**Statistical analysis.** Baseline information was described by mean  $\pm$  SD/median (interquartile ranges) or counts (frequencies) for continuous and binary variables, respectively, and tested using unpaired t test, 2-sided Mann-Whitney test, Wilcoxon test, or chi-square test as appropriate. The unadjusted prevalence of AVE in the 2 cohorts was calculated by counts of patients with AVE divided by cohort sizes. The rate of AVE per 100 person-years (PY) within the 17 years of followup was calculated. Kaplan-Meier survival curve was plotted without adjusting for any covariates.

Risk factors over the 17 years were calculated individually as outlined above.

To reveal the cohort effect after adjusting for confounding variables, inverse probability weights (IPW) were calculated from propensity scores derived from the logistic regression using all important baseline variables and risk factors, as well as summary variables over the followup, irrespective of their level of statistical significance. The confounding factors included age, sex, ethnicity, AMS in the first 5 years, Systemic Lupus International Collaborating Clinics/ACR Damage Index excluding CV events, use of steroids, average steroid dose, use of antimalarial and immunosuppressives, percent of years with normal blood pressure, normal cholesterol, normal glucose, and percent of years smoking.

Finally, the IPW was entered as adjustment continuous covariate along with the cohort variable in a Cox proportional hazard model to establish the relationship between cohort effect and survival free of AVE. All-cause mortality was accounted as a competing risk<sup>22</sup>. The IPW-adjusted HR with 95% CI and p values were reported and IPW-adjusted survival curves were plotted<sup>22</sup>. All analyses were carried out in SAS 9.4 (SAS Institute Inc.);  $p < 0.05$  was adapted as the significance of statistical difference.

## RESULTS

Of the 826 patients in the inception cohort, 234 entered between 1975 and 1987 (Cohort 1) and were followed through the end of 1992. Two hundred sixty-two patients entered between 1999 and 2011 (Cohort 2) and were followed

through the end of 2016 (Table 1). The 2 inception cohorts were similar in age, sex, and disease activity. However, Cohort 1 had significantly more white patients, while Cohort 2 had more black, Chinese, and Filipino patients. More patients in Cohort 2 were receiving corticosteroids (although the mean dose was similar), antimalarials, and immunosuppressive medications.

During the 17 years of followup, interventions regarding CV risk factors varied.

Table 2 shows that patients in Cohort 1 received significantly fewer therapeutic interventions for CV risk factors and fewer aggressive therapeutic interventions for SLE than those in Cohort 2.

Twenty-six patients in Cohort 1 sustained an AVE (11%) compared to only 10 patients in Cohort 2 (3.8%;  $p < 0.001$ ; Table 3, Figure 1). Because patient followup was different between the 2 cohorts, we calculated events per 100 PY of followup. That rate was 1.8 in Cohort 1 and 0.44 in Cohort 2 ( $p < 0.0001$ ).

Table 3 shows that while there was no difference in the time to event or age at first event, there were significant differences in the classic risk factors and in disease activity over the first 5 years of the disease course. Patients in Cohort 2 sustained normal blood pressure for a greater percentage of the time than those in Cohort 1. They also spent a greater percentage of time with normal blood sugar and cholesterol levels. Patients in Cohort 2 smoked significantly less than

Table 1. Patient characteristics at enrollment.

Variables	Cohort 1, 1975–1987	Cohort 2, 1999–2011	p
No. patients	234	262	NA
Age at enrollment, yrs	35.4 $\pm$ 15.2	36.1 $\pm$ 13.8	0.62
Sex, female	205 (87.6)	232 (88.5)	0.75
Ethnicity			< 0.001
Black	19 (8.1)	52 (19.8)	
White	199 (85.0)	135 (51.5)	
Chinese	11 (4.7)	31 (11.8)	
Filipino	2 (0.9)	16 (6.1)	
Others	3 (1.3)	28 (10.7)	
Disease duration at enrollment, mos	2.9 $\pm$ 3.5	2.6 $\pm$ 3.0	0.31
SLEDAI-2K at enrollment	10.0 $\pm$ 9.0	9.8 $\pm$ 7.8	0.81
Nephritis	75 (32.1)	71 (27.1)	0.23
Vasculitis	33 (14.1)	23 (8.8)	0.06
Corticosteroids	114 (48.7)	163 (62.2)	0.003
Corticosteroid dose, mg/day	33.4 $\pm$ 28.7	30.6 $\pm$ 20.3	0.34
Antimalarials	44 (18.8)	117 (44.7)	< 0.001
Immunosuppressives	12 (5.1)	61 (23.3)	< 0.001
Hypertension	41 (17.5)	70 (26.7)	0.01
Hypercholesterolemia	70 (29.9)	108 (41.2)	0.009
Diabetes	2 (0.9)	9 (3.4)	0.05
Smoking	56 (24.1)	37 (14.4)	0.006

Values are n (%) or mean  $\pm$  SD unless otherwise specified. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; NA: not applicable.

Table 2. Interventions during the first 17 years of followup.

Intervention	Cohort 1, 1975–1987	Cohort 2, 1999–2011	p
No. patients	234	262	
Antihypertensives	29 (12.4)	124 (47.3)	0.0001
Lipid-lowering agents	4 (1.7)*	63 (24)	< 0.0001
Diabetes	11 (4.7)	18 (6.9)	0.30
Smoking	80 (34.2)	54 (20.6)	0.0007
Ever treated with steroids	161 (68.8)	214 (81.7)	0.001
Average steroid dose, mg/day	17.6 ± 14.6	12.3 ± 8.5	0.001
Ever treated with antimalarials	114 (48.7)	241 (92.0)	0.001
Ever treated with immunosuppressives	67 (28.6)	178 (67.9)	0.001

Values are n (%) or mean ± SD unless otherwise specified. \* Earliest recorded use: May 1986.

Table 3. Outcomes.

Variables	Cohort 1, 1975–1987	Cohort 2, 1999–2011	p
No. patients	234	262	NA
Followup time, yrs	6.6 ± 4.8	8.3 ± 4.7	< 0.001
PY of followup	1480.0	2288.0	
Outcomes			
No. AVE, n (%)	26 (11.1)	10 (3.8)	0.001
MI	7	3	
Angina	8	2	
CHF	8	1	
Bradyarrhythmia requiring pacemaker	0	1	
Stroke	3	1	
TIA	0	3	
Yrs from enrollment to AVE	4.2 ± 5.0	5.9 ± 4.2	NS
Median age at first AVE, yrs	48.2	56.9	NS
Incidence of AVE per 100 PY	1.8	0.44	< 0.001
Classic risk factors, %			
Percent yrs with normal BP	72.0	86.7	0.0001
Percent yrs with normal cholesterol	39.6	72.3	0.0001
Percent yrs with normal glucose	84.8	93.2	0.0001
Percent of yrs smoked	24.7	11.3	0.0001
Disease-related factors			
AMS within 5 yrs of enrollment	5.7 ± 5.2	4.5 ± 3.4	0.003
Alive at end of 17 yrs of followup, n (%)	183 (78.2)	247 (94.3)	< 0.001

Values are mean ± SD unless otherwise specified. PY: person-years; AVE: atherosclerotic vascular events; MI: myocardial infarction; CHF: congestive heart failure; TIA: transient ischemic attack; BP: blood pressure; AMS: adjusted mean SLEDAI-2K; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; NA: not applicable; NS: not significant.

those in Cohort 1. Disease activity burden (as measured by the AMS) in the first 5 years of disease was lower in Cohort 2 than in Cohort 1. At the end of the 17-year followup, 78% of the patients in Cohort 1 were alive compared with 94% of the patients in Cohort 2.

Because of the collinearity between risk factors and the cohort effect, we did not do a multivariable analysis but rather

used the IPW score derived from the propensity score to balance the noncomparability between the 2 cohorts. The cohort effect was determined through a competing risk Cox model weighted by IPW. The 2 cohorts were different with regard to the probability of being free from AVE over the 17 years of followup (Figure 2). The HR from the IP-weighted model is 0.40 (95% CI 0.23–0.70) comparing Cohort 2 to Cohort 1 at any time, a reduction of risk of AVE of 60% (p = 0.0013).

## DISCUSSION

The bimodal mortality pattern in patients with SLE highlighted the importance of AVE in SLE as a cause of death<sup>1,23</sup>. Subsequently, we highlighted the contribution of AVE to the morbidity of patients with SLE<sup>3</sup>. Others have demonstrated the effect of AVE in young women with SLE as well as the economic burden on society<sup>24,25</sup>.

Subclinical disease long before AVE clinical manifestations has been demonstrated in patients with SLE using a variety of modalities including carotid ultrasound, cardiac perfusion studies, flow-mediated dilatation, cardiac computed tomography, and coronary angiography<sup>10,13,16,17,26</sup>.

In this study we examined 2 inception cohorts within our SLE population, one entered in the 1970s and early 1980s, after the recognition of the importance of AVE in SLE, and a more recent cohort entered in the current millennium, when therapeutic approaches would have been significantly different. Our study demonstrated that Cohort 1 had significantly more AVE than Cohort 2 over a 17-year period. Our findings are in keeping with the declining incidence of myocardial infarction noted in the general population<sup>27,28</sup>. In a study of British men, there was a decline of 3.8% per year in the incidence of coronary heart disease. In a mixed population study from Norway, there was an annual decrease of 4.3% in hospitalized acute myocardial infarctions. This has also been observed in the Framingham population study<sup>29</sup>.

The therapeutic approaches used in the 2 eras of our cohorts were significantly different, with less treatment of hypertension, hyperlipidemia, diabetes, and smoking cessation in terms of the traditional risk factors, in Cohort 1. In addition, patients in Cohort 2 were more often treated for their SLE with antimalarials and immunosuppressive medications. To assess the effect of the therapeutic intervention, we calculated the percent of time patients achieved normal risk factor levels and showed that patients in Cohort 2 had a longer period over the 17 years with normal blood pressure, cholesterol, and glucose, and smoked less than those in Cohort 1. In addition, the disease burden in the first 5 years of SLE was lower in Cohort 2 than in Cohort 1. As a consequence, survival was greater among the patients who entered in the later cohort.

To take into account these improvements in disease and risk factor management in patients in Cohort 2, we adjusted

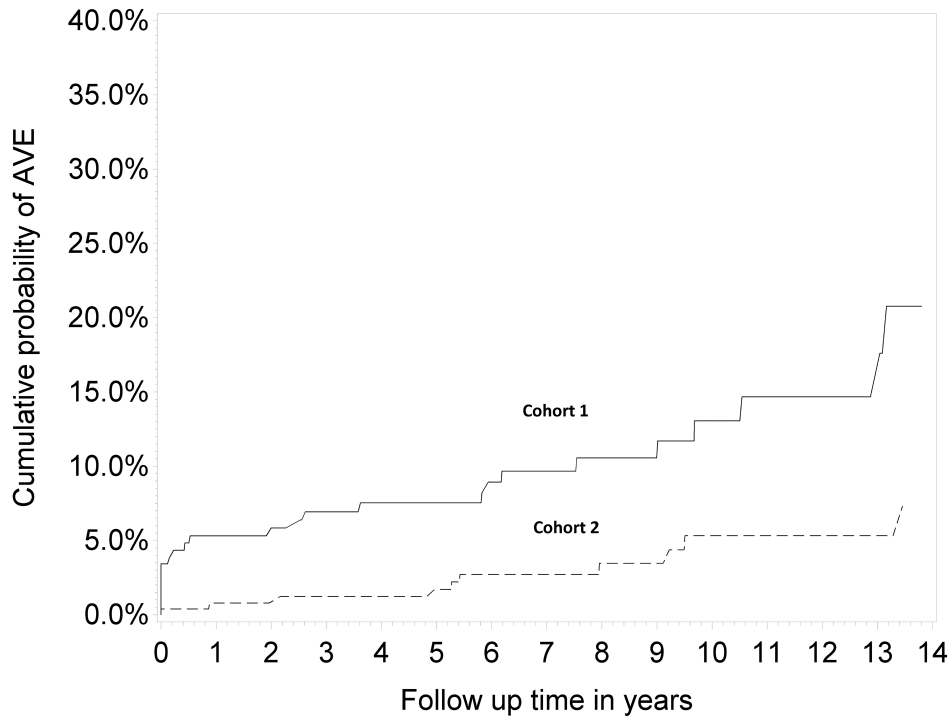


Figure 1. Kaplan-Meier cumulative probability of developing AVE in 2 cohorts ( $p = 0.0003$  from log-rank test). AVE: atherosclerotic vascular events.

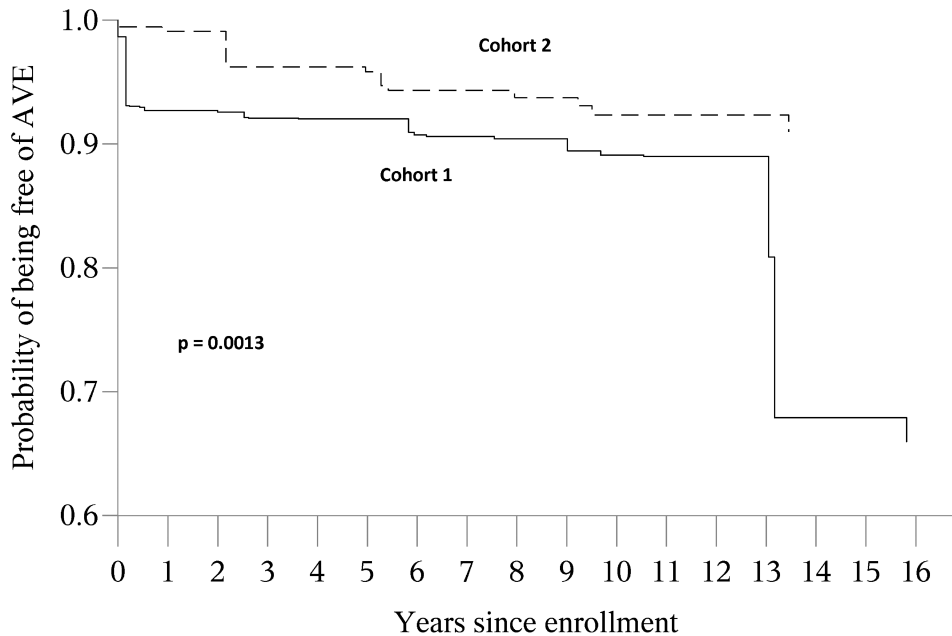


Figure 2. The HR from IP-weighted model is 0.40 (95% CI 0.23–0.70) comparing later to early cohort ( $p = 0.0013$ ). AVE: atherosclerotic vascular events; IPW: inverse probability weights.

for these risk factors and outcomes and found that the HR for AVE was significantly reduced by 60% in Cohort 2 compared to Cohort 1. Thus, the cohort effect is not entirely explained

by the successful management of the risk factors and disease control. Similarly, in the British and Norwegian studies, the treatment of risk factors accounted for only 46% of the

decline in British men and 66% of the decline in the Norwegian population<sup>27,28</sup>.

A major strength of our study is that the data have been collected prospectively according to a standard protocol and definitions that were set up initially. Information is entered when it is confirmed. Thus, although this is a retrospective analysis, all data were collected systematically in real time. In our study the risk factors assessed included only some of the classic cardiac risk factors, as well as disease-related factors, and these did not entirely explain the cohort effect. We were unable to evaluate other important factors such as body mass index, degree of physical activity, novel SLE therapies, family history of AVE in first-degree relatives, nor antiphospholipid levels, all of which were either not recorded or not yet available in the first cohort and which could contribute to the cohort effect noted.

These results provide an insight as to how physicians may improve outcomes due to AVE in patients with SLE. Studies of subclinical coronary artery disease in patients with SLE have revealed that 23–35% of patients with no history of coronary artery disease have abnormal screening tests such as dual isotope myocardial perfusion imaging and flow-mediated dilatation<sup>2,12,30</sup>. These findings would not have been discerned by the classic Framingham risk score<sup>31,32</sup>, but will now afford the physician the knowledge to intensify therapy as indicated. Indeed, a previous systematic review has stressed the importance of monitoring risk factors and disease activity on a regular basis to reduce the incidence of AVE in patients with SLE<sup>33</sup>.

The incidence of AVE in SLE in the modern era has declined, in large part owing to more effective management of classic coronary artery disease risk factors and better management of SLE. Further improvement may be anticipated with more aggressive screening and therapy of subclinical disease.

## ACKNOWLEDGMENT

The University of Toronto Lupus Clinic has been supported by The Arthritis Society, Canadian Institutes of Health Research, University Health Network, the Rocca family, and the Bozzo family.

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