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Timing and Predictors of Incident Cardiovascular Disease in Systemic Lupus Erythematosus: Risk Occurs Early and Highlights Racial Disparities

Shivani Garg[1], Christie M. Bartels[1], Gaobin Bao[2], Charles G. Helmick[3], Cristina Drenkard[4], and S. Sam Lim[4]

ABSTRACT. ***Objective.*** Systemic lupus erythematosus (SLE) affects Black people 2 to 3 times more frequently than non-Black people and is associated with higher morbidity and mortality. In total, 4 studies with predominantly non-Black SLE cohorts highlighted that cardiovascular disease (CVD) is no longer primarily a late complication of SLE. This study assessed the timing and predictors of incident CVD in a predominantly Black population-based SLE cohort.

Methods. Incident SLE cases from the population-based Georgia Lupus Registry were validated as having a CVD event through review of medical records and matching with the Georgia Hospital Discharge Database and the National Death Index. The surveillance period for an incident CVD event spanned a 15-year period, starting from 2 years prior to SLE diagnosis.

Results. Among 336 people with SLE, 253 (75%) were Black and 56 (17%) had an incident CVD event. The frequency of CVD events peaked in years 2 and 11 after SLE diagnosis. There was a 7-fold higher risk of incident CVD over the entire 15-year period; this risk was 19-fold higher in the first 12 years in Black people as compared to non-Black people with SLE. Black people with SLE ($P < 0.001$) and those with discoid rash (hazard ratio 3.2, 95% CI 1.4-7.1) had a higher risk of incident CVD events.

Conclusion. The frequency of incident CVD events peaked in years 2 and 11 after SLE diagnosis. Being Black or having a discoid rash were strong predictors of an incident CVD event. Surveillance for CVD and preventive interventions, directed particularly toward Black people with recent SLE diagnoses, are needed to reduce racial disparities.

Key Indexing Terms: early risk, incident cardiovascular disease, predictors, racial disparities, systemic lupus erythematosus

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[1]S. Garg, MD, MS, Assistant Professor, C.M. Bartels, MD, MS, Associate Professor, Rheumatology Division, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; [2]G. Bao, MPH, Senior Statistician, Division of Rheumatology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; [3]C.G. Helmick, MD, Professor, Division of Population Health, Centers for Disease Control and Prevention, Atlanta, Georgia; [4]C. Drenkard, MD, PhD, Associate Professor, S.S. Lim, MD, MPH, Professor, Division of Rheumatology, Department of Medicine, Emory University School of Medicine, and Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia, USA.

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Address correspondence to Dr. S. Garg, Rheumatology Division, Department of Medicine, University of Wisconsin School of Medicine and Public Health, 1685 Highland Ave, MFCB #4122, Madison, WI 53705, USA. Email: sgarg@medicine.wisc.edu.

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Systemic lupus erythematosus (SLE) is a leading cause of mortality in young women, with a 3- to 5-fold higher mortality rate and an accelerated risk of cardiovascular disease (CVD) compared with the general population.[1-3] Previously, a bimodal distribution of mortality in SLE was observed, with deaths early in the disease course related to active SLE or infection and later deaths (> 10 years) associated with CVD.[4] Also previously reported was a 16- to 52-fold higher risk of CVD in younger patients with SLE compared with healthy controls, with risk peaking around year 10.[5] More recently, 4 predominantly non-Black cohorts challenged the paradigm of CVD being mostly a late complication of SLE.[6-9] These studies also reported a higher risk of CVD around the time of SLE diagnosis.[6,7]

It is important to examine findings in communities of color given the significant racial disparities that exist, particularly in Black women. SLE afflicts Black women at a 3-fold higher rate and at a significantly younger age compared with non-Black women.[10,11] Black women have a 3-fold higher risk of developing nephritis compared with White women with SLE.[12] Black people with SLE have a 3-times higher risk of developing endstage renal

disease (ESRD) compared with White people with SLE (15.3% vs 4.5%).[10] Black women with SLE have a 3-times higher risk of early death compared with Black women from the general population.[13] Moreover, Black people in the general population have higher rates of fatal coronary heart disease and stroke than White people after controlling for age.[14,15] However, most SLE studies of CVD have been conducted in predominantly White cohorts,[5-7,16-18] limiting the generalizability of the findings.[11-13] This study assessed the timing and predictors of incident CVD events in a population-based cohort of predominantly Black people with incident SLE over a 15-year period.

METHODS

The Georgia Lupus Registry (GLR) is a population-based registry of residents of Atlanta, Georgia, who meet the classification criteria for SLE, and is supported by the Centers for Disease Control and Prevention. The GLR methods are described in detail elsewhere.[11] Briefly, the Georgia Department of Public Health (GA DPH) designated Emory University as its agent; this allows investigators to use the public health surveillance exemption to the Health Insurance Portability and Accountability Act Privacy Rule to obtain protected health information, including review of medical records, without written consent and to ascertain cases on a population level.[19] The GLR protocol was reviewed and approved by the Institutional Review Boards (IRBs) at Emory University and the GA DPH (IRB number: IRB00003656).

The primary sources of case ascertainment included hospitals, rheumatologists, nephrologists, and dermatologists in and around the catchment area. Administrative databases were queried for billing codes for SLE and related conditions. Other sources included laboratories and queries of other population databases. Medical records were abstracted, and regular data quality assessments were conducted.

SLE case validation. Incident SLE cases were identified in the years 2002 to 2004; these were defined as either meeting the 1997 update of the 1982 American College of Rheumatology (ACR) revised classification criteria for SLE or meeting 3 ACR criteria with a documented SLE diagnosis by the patient's board-certified rheumatologist.[20,21]

ESRD. Validated SLE cases were matched with the US Renal Data System database for the years 2002 to 2015 to capture ESRD after SLE diagnosis.

Race and ethnicity. Race and ethnicity were defined as reported in medical and administrative records and included physician-identified or patient self-identified Black, White, Asian, and Hispanic groups. Very few sites reported race and ethnicity as separate categories, or included other racial or ethnic groups or mixed race. Less than 5% Hispanic ethnicity was recorded; thus, groups were analyzed by race only (Supplementary Data S1, available with the online version of this article).

CVD event ascertainment and validation. Incident SLE cases from the GLR from 2002 to 2004 were matched to the Georgia Hospital Discharge Database from 2000 to 2017 and the National Death Index from 2002 to 2017, capturing all hospitalizations throughout the state and deaths across the nation. Surveillance for CVD events started 2 years prior to SLE diagnosis and continued for 13 years after diagnosis. CVD-related hospitalizations and deaths were identified following published algorithms using the first 3 codes for billing at hospitalization or cause of death.[22,23] CVD events were defined as follows:

1. Ischemic heart disease, including myocardial infarction (MI), coronary artery revascularization, abnormal stress test or echocardiogram, ≥ 50% abnormal angiogram, and events documented by a cardiologist.[24,25]
2. Cerebrovascular disease, including thrombotic and ischemic stroke, and transient ischemic attack.[26]
3. Peripheral vascular disease (PVD), including abnormal ankle-brachial index, abnormal peripheral angiography, limb ischemia undergoing bypass or angioplasty, or documented by a surgeon.[27,28]

Patients with baseline CVD were excluded, and only the first event was included in the analysis.

Analysis. Descriptive results were reported as means with SDs for normally distributed data or medians with ranges for data that were not normally distributed. The 15-year surveillance period was divided into 3 subperiods, based on the distribution of CVD events: the pre-SLE period (2 years before SLE diagnosis until SLE diagnosis), the initial period (SLE diagnosis through the 10th year after diagnosis), and the late period (the 11th through the 13th year after SLE diagnosis; Figure 1).

We annualized rates of incident CVD events over the 15-year surveillance period. A particular period of incident CVD events was defined by the start of a unique peak followed by a downward trend. Trends over time were compared with each other using interrupted time series analysis (ITSA).[29] We estimated coefficients using the Newey-West model, with 1 lag in each model, and used the Cumby-Huizinga test for autocorrelation to confirm the correct model with 1 lag using Stata version 15 (StataCorp).[30]

We categorized our data by age group and sex, similar to the National Health and Nutrition Examination Survey (2009-2012), to calculate age group–specific and sex-specific rates of CVD and CVD subtypes in our SLE cohort. We then compared these rates with published rates of CVD subtypes categorized by age group and sex in the general population over a 4-year period.[31] Additionally, we compared the 7-year race-specific incidence of MI by age group and sex in our SLE cases with the 7-year published incidence of MI (2005-2012) and the annual rate of race-specific stroke in SLE vs the healthy population.[31]

We examined Kaplan-Meier survival analyses by racial groups. We focused on 2 follow-up periods with accelerated risk of CVD occurrence derived from ITSA analysis: (1) the first 12-year follow-up period (pre-SLE and initial periods, years −2 through 10 from SLE diagnosis) and (2) the full 15-year surveillance period. In these 2 periods, we examined predictors of incident CVD events using univariable and multivariable Cox proportional hazards models. Factors studied included sociodemographics, ESRD, and ACR criteria within 1 year of SLE diagnosis (Table 1).[21] ACR criteria with $P < 0.10$ in the univariable models, along with sociodemographics and ESRD, were included in the multivariable analyses. We performed Schoenfeld residual analyses to verify that the proportional hazards model assumptions were not violated for covariates.[32] We performed competing risk analysis to compare the cumulative incidence of CVD events and deaths with the cumulative incidence of non-CVD deaths in our cohort. Last, we performed a separate analysis stratified by race to compare CVD events in Black people with SLE and in non-Black people with SLE.

We analyzed 2 racial groups: Black people and non-Black people. Non-Black people were mostly White, along with a few Asian and Hispanic people. We performed a sensitivity analysis by excluding patients who did not report ethnicity. We then performed another sensitivity analysis stratifying Black and White racial groups and excluding the relatively few individuals from other groups. Additionally, we calculated E-values to quantify how extreme the bias from the unmeasured confounders would need to be to remove the effect of race on CVD incidence.[33] We used R statistical software (version 3.4.1; The R Foundation) for the analysis.

RESULTS

Cohort characteristics. Among 336 people with SLE, 87% were female and the group had a mean age at SLE diagnosis of 40 (SD 17) years. Of the 336 people, 75% identified as Black, 22% identified as White, and 3% identified as Asian (Table 1 and Supplementary Table S1, available with the online version of this article). ACR SLE classification criteria within 1 year of diagnosis are shown in Table 1.

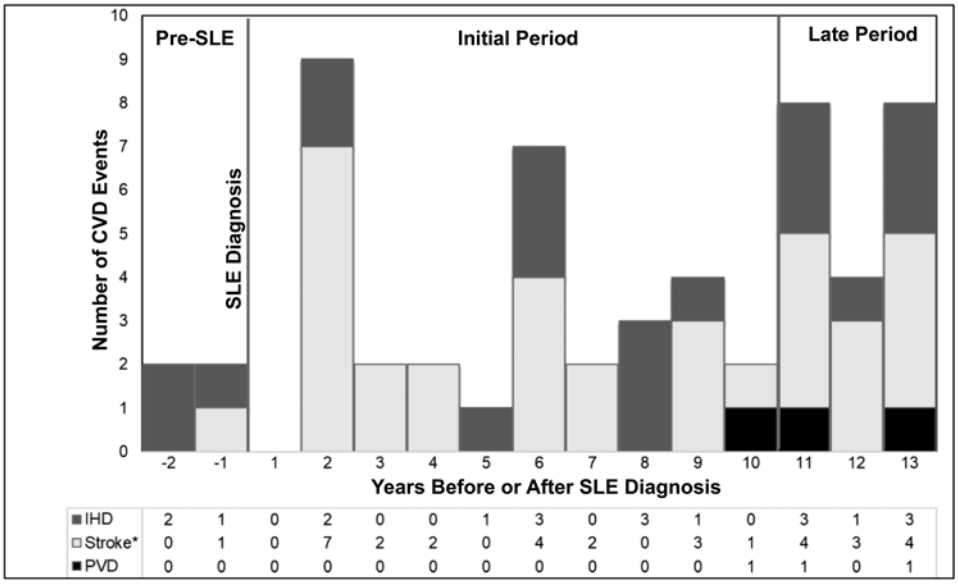


Figure 1. Incident CVD events among 336 people with SLE over 15 years—from 2 years before through 13 years after SLE diagnosis—by CVD subtype (IHD, stroke, PVD). Bar heights reflect annual incident CVD. * Stroke includes cerebrovascular accident and transient ischemic attack. CVD: cardiovascular disease; IHD: ischemic heart disease; PVD: peripheral vascular disease; SLE: systemic lupus erythematosus.

Table 1. Demographics and manifestations of people with incident SLE from the Georgia Lupus Registry, 2002-2004.

	Value, n = 336
Demographics	
Racial group	
White	72 (22)
Black	253 (75)
Asian[a]	11 (3)
Age at SLE diagnosis, yrs	
Mean (SD)	40 (17)
Age group, yrs	
< 19	28 (8)
19 to 34	104 (31)
35 to 49	113 (34)
50 to 64	63 (19)
≥ 65	28 (8)
Sex	
Female	292 (87)
Male	44 (13)
ACR criteria within 1 year of diagnosis	
Malar rash	64 (20)
Discoid rash	48 (14)
Photosensitivity	61 (19)
Oral ulcers	75 (22)
Arthritis	220 (66)
Serositis	118 (35)
Renal disorder	103 (31)
Neurological disorder	31 (9)
Hematological disorder	282 (84)
Immunological disorder	231 (69)
Antinuclear antibody	321 (96)
Other	
ESRD (by 2015)	36 (11)

Data are in n (%) unless otherwise indicated. [a] Includes 1 patient with unknown race. ACR: American College of Rheumatology; ESRD: endstage renal disease; SLE: systemic lupus erythematosus.

Timing of incident CVD events. Figure 1 shows incident CVD event frequencies spanning 15 years of surveillance by CVD event type. A total of 56 patients with SLE (17%) had incident CVD: 33 had cerebrovascular disease, 20 had ischemic heart disease (IHD), and 3 had PVD. The highest frequency of incident CVD occurred in the second year after SLE diagnosis, with 7 out of 9 events being cerebrovascular disease. A total of 36 CVD events, including 5 CVD-related deaths, occurred in the first 12 years (ie, years –2 through 10). Mean ages at SLE diagnosis and at incident CVD event were 45 (SD 17) years and 49 (SD 17) years, respectively. All but 1 event occurred in Black persons with SLE. CVD events occurred in 31 women and 5 men. A total of 20 CVD events, including 1 CVD-related death, occurred in the final 3 years of surveillance (ie, years 11 through 13), with mean ages at SLE diagnosis and at incident CVD of 39 (SD 16) years and 51 (SD 16) years, respectively. In total, 17 CVD events occurred in Black persons, whereas 3 events occurred in White persons with SLE. Of the 20 CVD events, 18 occurred in women and 2 in men.

Using a 4-year follow-up, we noted that the rate of stroke was higher in women (2%) and men (3.9%) with SLE who were under 40 years of age compared with published rates of stroke in the healthy population (women: 0.7%; men: 0.02%; Supplementary Table S2, available with the online version of this article). However, we did not note higher rates of IHD in our cohort, as most IHD events occurred later in our cohort.[31] We found a 2-times higher incidence of MI (4.3 vs 2.3 per 1000 person-years) and a 7-times higher annual stroke rate in Black women with SLE who were under 55 years of age compared with healthy Black peers (23 vs 2.9 per 1000 persons; Supplementary Table S3, available with the online version of this article).

Determination of CVD event periods. Using ITSA (Supplementary

Figure S1, available with the online version of this article), 3 event periods emerged visually. Despite a visual break point in year 2, this did not reach statistical significance ($P = 0.06$). Thus, the event periods were assigned as the first 12 years of surveillance (ie, years –2 through 10) and the final 3 years of surveillance (ie, years 11 through 13).

Kaplan-Meier survival analysis by racial group. Kaplan-Meier survival analyses examined differences in the timing of incident CVD stratified by race across the 15-year surveillance period. This analysis showed significantly accelerated incident CVD in Black people compared with non-Black people with SLE ($P < 0.001$; Figure 2). Our sensitivity analysis stratifying Black vs White racial groups was similar ($P < 0.001$, data not shown). Finally, using competing risk analysis, we noted no statistical difference between the cumulative incidence of CVD events, including CVD-related deaths, and the cumulative incidence of non-CVD–related deaths in our cohort ($P = 0.97$; Supplementary Figure S2, available with the online version of this article).

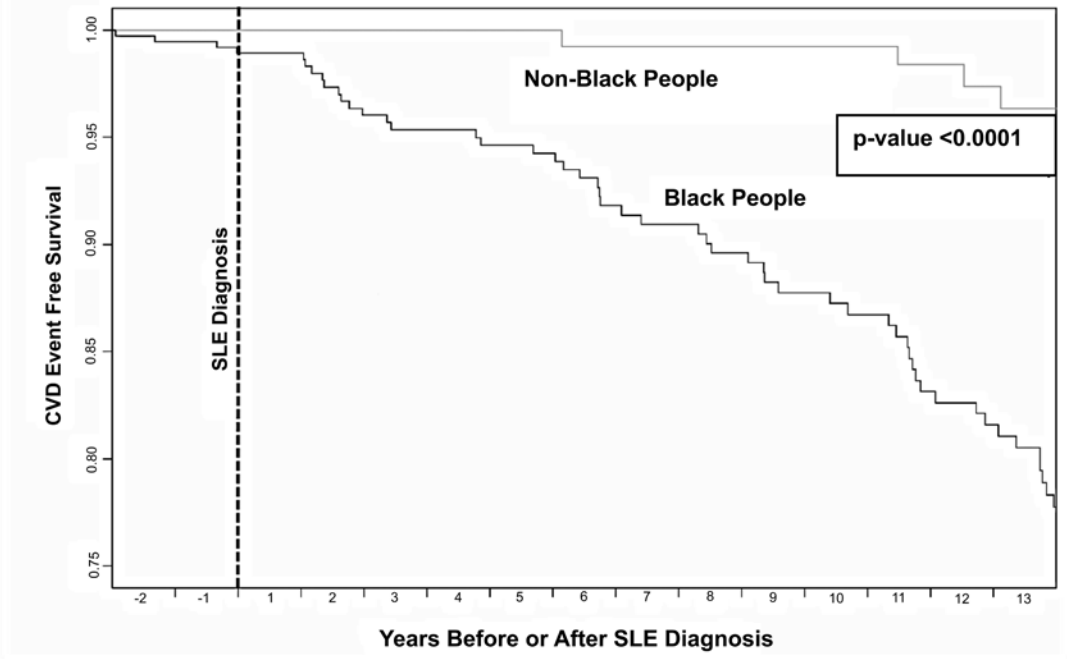
Multivariable Cox model predictors of incident CVD in SLE. In the first 12-year surveillance period (ie, years –2 through 10), incident CVD event rates in Black people with SLE were 19-fold higher compared with non-Black people with SLE (adjusted hazard ratio [HR] 19.0, 95% CI 3.0-142.0; Table 2). Being 65 years of age or older at SLE diagnosis, having renal disorder, and having discoid rash were other predictors of CVD events. To estimate bias from unmeasured confounders, we found an E-value of 35, meaning that confounders need to be associated with a 35-fold increase in CVD incidence for the causal effect of Black race on CVD to be truly null.

In the 15-year surveillance period, multivariable analysis (Table 3) showed that Black people with SLE had a 7-fold higher risk of incident CVD events over 15 years (adjusted HR [aHR] 7.3, 95% CI 2.4-22.0). Other multivariable predictors were being ≥ 65 years of age at SLE diagnosis (aHR 9.0, 95% CI 2.4-33.0), having renal disorder or ESRD (aHR 2.1, 95% CI 1.1-4.1), and having discoid rash (aHR 3.2, 95% CI 1.4-7.1). An E-value of 12 was found for this period.

Next, in a smaller Cox model stratified by race, having discoid rash (adjusted HR 3.1, 95% CI 1.4-6.9; Table 4; only Black patients: aHR 2.3, 95% CI 1.2-4.4, data not shown), having renal disorder or ESRD (aHR 2.1, 95% CI 1.1-4.0), and being ≥ 65 years of age at SLE diagnosis remained strong predictors of incident CVD (Table 4).

DISCUSSION

To our knowledge, this is the first study that examined the risk, timing, and predictors of incident CVD events in a predominantly Black population-based incident SLE cohort. Incident CVD events occurred in 17% of our cohort over 15 years, with the highest frequency of CVD events in years 2 and 11 after SLE diagnosis. We found that people who identified as Black had the highest risk of incident CVD events, and we found that discoid rash was a new predictor of incident CVD in SLE. We found



Number at risk

Time	Start	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13
Black	253	251	250	234	218	208	202	199	190	183	179	168	164	156	152	142
Non-Black	83	83	83	83	83	83	83	83	82	82	82	82	76	70	69	68

Figure 2. Incident CVD event-free survival by Kaplan-Meier survival analysis stratified by racial group. CVD: cardiovascular disease; SLE: systemic lupus erythematosus.

Table 2. Cox proportional hazards model predictors of incident cardiovascular disease events over the 12-year surveillance period: 2 years before through 10 years after SLE diagnosis.

	Unadjusted HR (95% CI)	*P*	Adjusted[a] HR (95% CI)	*P*
Demographics				
Racial group				
Non-Black	Ref	Ref	Ref	Ref
Black	**14.0 (2.0-102.0)**	**0.01**	**19.0 (3.0-142.0)**	**0.005**
Age at SLE diagnosis, yrs				
< 19	Ref	Ref	Ref	Ref
19 to 34	0.4 (0.1-1.4)	0.40	0.5 (0.1-1.7)	0.30
35 to 49	1.0 (0.3-2.9)	0.80	1.4 (0.5-4.5)	0.50
50 to 64	0.9 (0.3-3.0)	0.80	1.4 (0.4-5.0)	0.60
≥ 65	1.5 (0.4-6.0)	0.80	**6.7 (1.6-29.0)**	**0.01**
Sex				
Male	Ref	Ref	Ref	Ref
Female	0.9 (0.4-2.4)	0.90	1.1 (0.4-2.9)	0.80
ACR criteria within 1 year of diagnosis or ESRD[b] (yes vs no)				
Malar rash	0.5 (0.2-1.5)	0.10	—	—
Discoid rash	**2.3 (1.1-4.7)**	**0.03**	**3.5 (1.6-8.0)**	**0.002**
Photosensitivity	0.6 (0.2-1.6)	0.30	—	—
Oral ulcers	1.2 (0.5-2.5)	0.70	—	—
Arthritis	0.8 (0.4-1.5)	0.40	—	—
Serositis	1.3 (0.7-2.6)	0.50	—	—
Renal disorder or ESRD	**2.2 (1.1-4.0)**	**0.02**	**2.6 (1.3-5.0)**	**0.01**
Neurological disorder	1.4 (0.5-4.0)	0.50	—	—
Hematological disorder	1.3 (0.5-2.6)	0.60	—	—
Immunological disorder	1.6 (0.7-3.5)	0.30	—	—
Antinuclear antibody	1.6 (0.2-12.0)	0.60	—	—
ACR criteria total (> 4 vs ≤ 4)	1.2 (0.9-1.4)	0.20	—	—

[a] HRs adjusted for age, sex, racial groups, and ACR criteria within 1 year of SLE diagnosis with $P < 0.10$ in univariable analysis. [b] ACR criteria results from a multivariable Cox proportional hazards model that included ESRD. Results reported for criteria with $P < 0.10$ in univariable analysis. All ACR criteria were within 1 year of SLE diagnosis. ESRD was through years 2002 to 2015. All HRs for variables with significant *P* values (< 0.05) are shown in bold. ACR: American College of Rheumatology; ESRD: endstage renal disease; HR: hazard ratio; SLE: systemic lupus erythematosus.

a 19-fold higher incident CVD risk in Black people with SLE in the first 12 years of surveillance. Additionally, we found that the incidence of MI and the annual stroke rate in Black women with SLE who were < 55 years of age were 2 to 7 times higher than in their peers.[31] Our study highlights racial disparities with a high rate of incident CVD events around the time of SLE diagnosis, particularly in Black patients, and points to discoid rash as a potential novel risk factor.

We examined CVD-related morbidity and mortality in SLE and current gaps in CVD prevention. With advances in early diagnosis and treatment, the overall prognosis of SLE disease has dramatically improved, yet CVD remains a major cause of morbidity and mortality in SLE.[34] Relative to their peers, CVD is more common in premenopausal women with SLE, with a 50-fold higher CVD risk in women aged 35 to 45 years,[5] and up to a 16-fold higher risk of CVD-related mortality in patients < 45 years of age.[5,34] A Medicaid study reported marked racial and ethnic variations in CVD events, with a 31% higher stroke occurrence in Black people with SLE compared to White people.[35] Yet, there is limited information on other population- and disease-based predictors or on event timing to guide CVD prevention efforts in SLE.[34,36] Our study identifies patients with SLE who are at the highest CVD risk in order to support further studies to implement and test CVD prevention efforts.

We examined the timing of accelerated CVD risk in SLE. Historically, accelerated CVD risk was considered to be a late complication in SLE.[4,5,37-39] Multiple studies reported a median SLE duration of 7 to 10 years prior to incident CVD events.[4,5,37-39] However, previous studies reported SLE as an independent CVD risk factor and noted a key role of inflammatory cytokines and subclinical inflammation in accelerating atherosclerosis around the time of SLE diagnosis.[34,40] Bartels et al[7] reported that the risk of CVD was 2-fold higher even 2 years before SLE diagnosis in a cohort of predominantly non-Black patients with SLE. Similar studies in predominantly non-Black cohorts reported that the risk of CVD starts early, up to 2 years before SLE diagnosis, reaching a 2- to 6-fold higher risk.[6-9]

Our study highlights that incident CVD events peaked twice, during years 2 and 11 after SLE diagnosis. The early CVD peak in our study could depict accelerated and premature atherosclerosis caused by systemic inflammation from SLE or antiphospholipid antibody–mediated hypercoagulability leading to direct and indirect vascular intima damage.[6-9] Our findings in a predominantly Black population-based SLE cohort add to prior reports in predominantly non-Black populations, and they challenge

Table 3. Cox proportional hazards model predictors of incident cardiovascular disease events over the 15-year surveillance period: 2 years before through 13 years after SLE diagnosis.

	Unadjusted HR (95% CI)	*P*	Adjusted[a] HR (95% CI)	*P*
Demographics				
Racial group				
Non-Black	Ref	Ref	Ref	Ref
Black	**5.4 (2.0-15.0)**	**0.001**	**7.3 (2.4-22.0)**	**< 0.001**
Age at SLE diagnosis, yrs				
< 19	Ref	Ref	Ref	—
19 to 34	0.6 (0.2-1.7)	0.30	0.7 (0.2-1.8)	0.40
35 to 49	1.5 (0.6-3.7)	0.40	1.8 (0.7-5.1)	0.30
50 to 64	0.7 (0.2-2.3)	0.60	1.2 (0.4-3.8)	0.80
≥ 65	2.0 (0.6-6.7)	0.20	**9.0 (2.4-33.0)**	**0.001**
Sex				
Male	Ref	Ref	Ref	Ref
Female	1.1 (0.5-2.3)	0.90	1.4 (0.6-3.2)	0.40
ACR criteria within 1 year of diagnosis or ESRD[b] (yes vs no)				
Malar rash	1.0 (0.5-1.9)	0.90	—	—
Discoid rash	**2.1 (1.1-3.8)**	**0.02**	**3.2 (1.4-7.1)**	**0.005**
Photosensitivity	0.9 (0.5-1.8)	0.80	—	—
Oral ulcers	1.1 (0.6-2.0)	0.80	—	—
Arthritis	1.1 (0.6-2.0)	0.70	—	—
Serositis	**1.7 (1.01-2.9)**	**0.047**	1.2 (0.6-2.4)	0.52
Renal disorder or ESRD	**1.9 (1.1-3.3)**	**0.01**	**2.1 (1.1-4.1)**	**0.03**
Neurological disorder	1.2 (0.5-3.0)	0.70	—	—
Hematological disorder	1.3 (0.6-2.8)	0.46	—	—
Immunological disorder	**2.2 (1.1-4.3)**	**0.03**	2.1 (0.9-4.5)	0.07
Antinuclear antibody	1.3 (0.3-5.1)	0.80	—	—
ACR criteria total (> 4 vs ≤ 4)	**1.3 (1.1-1.5)**	**0.002**	1.0 (0.8-1.3)	0.92

[a] HR adjusted for age, sex, racial groups, and ACR criteria within 1 year of SLE diagnosis with $P < 0.10$ in univariable analysis. [b] ACR criteria results from a multivariable Cox proportional hazards model that included ESRD. Results reported for criteria with $P < 0.10$ in univariable analysis. All ACR criteria were within 1 year of SLE diagnosis. ESRD was through years 2002 to 2015. All hazard ratios for variables with significant *P* values (< 0.05) are shown in bold. ACR: American College of Rheumatology; ESRD: endstage renal disease; HR: hazard ratio; SLE: systemic lupus erythematosus.

Table 4. Cox model predictors of incident cardiovascular disease events in Black vs non-Black people with SLE over 15 years.

	Adjusted[a] HR (95% CI)	*P*
Age at SLE diagnosis, yrs		
< 19	Ref	—
19 to 34	0.6 (0.2-1.8)	0.38
35 to 49	1.8 (0.7-5.1)	0.25
50 to 64	1.2 (0.4-3.8)	0.81
≥ 65	**8.8 (2.4-32.1)**	**0.001**
Sex		
Male	Ref	—
Female	1.4 (0.6-3.1)	0.41
ACR criteria within 1 year of diagnosis or ESRD		
Discoid rash: yes	**3.1 (1.4-6.9)**	**0.005**
ACR criteria total: > 4 vs ≤ 4	0.98 (0.8-1.3)	0.90
Serositis: yes	1.0 (0.7-2.3)	0.82
Renal disorder or ESRD[b]: yes	**2.1 (1.1-4.0)**	**0.03**
Immunological disorder: yes	2.1 (0.93-4.5)	0.07

[a] HRs adjusted for age, sex, and ACR criteria within 1 year of SLE diagnosis with $P < 0.10$ in univariable analysis and stratified by racial groups. ACR criteria with $P < 0.10$ in univariable analysis included in multivariable Cox proportional hazards model stratified by racial groups. [b] ESRD was through years 2002 to 2015. All HRs for variables with significant *P* values (< 0.05) in the multivariable analysis are shown in bold. ACR: American College of Rheumatology; ESRD: endstage renal disease; HR: hazard ratio; SLE: systemic lupus erythematosus.

the paradigm that CVD is predominantly a late complication of SLE.[6-9] Therefore, these findings support clinical and public health efforts to implement CVD prevention early as well as late in the course of SLE disease, particularly in Black people with SLE.

We examined racial disparities in CVD in SLE. CVD, including heart disease and stroke, is a leading cause of death in the US. CVD is also the largest cause of reduced life expectancy in Black adults, making it an important focus in SLE, which disproportionately afflicts Black people.[10,11] Prior multiethnic SLE cohorts have reported high CVD event rates in Black people. For example, the Hopkins SLE cohort reported a 2.7-fold higher observed CVD event rate vs expected CVD event rate using the Framingham risk calculation in Black people with SLE (relative risk 2.8, 95% CI 2.0-3.5).[18] Likewise, the LUMINA (Lupus in Minorities: Nature vs Nurture) multiethnic SLE cohort reported a higher CVD event rate in Black people (42%) compared to other racial or ethnic groups (37% in White people; 20% in those with Hispanic ethnicity), which approached but did not reach statistical significance (P = 0.07).[41] Moreover, a Medicaid study highlighted that Black race predicted a 31% higher stroke risk compared with White people with SLE.[35] Our study supports these findings and is among the first to report striking racial disparities in incident CVD in SLE: a 19-fold higher incident CVD risk in Black people during the first 12 years of surveillance. The comparator rate in our cohort was 5%, similar to the rates previously reported in other predominantly White SLE cohorts (ie, 1.6%,[6] 3.6%,[42] and 9%[5,7]). We were unable to control for traditional risk factors in our cohort, which could have confounded some of our findings. However, based on our E-values, unmeasured confounders, including traditional risk factors, would have to be associated with a 35-fold increase in incident CVD in Black people with SLE in order to explain our observed HRs.[33] Previous studies have reported that traditional risk factors conferred only a 2- to 5-fold increase in risk of CVD events in people with SLE.[43] Moreover, previous studies in patients with or without SLE have shown that Black race alone predicts 31% to 60% higher CVD occurrences, even after controlling for traditional CVD risk factors, further supporting our findings.[35,44]

Additionally, we found that the incidence of MI and the annual rate of stroke in Black women with SLE under 55 years of age were 2 to 7 times higher than in healthy peers.[31] Thus, based on these findings and the magnitude of our 19-fold CVD risk estimate in Black people with SLE, we believe that traditional risk factors alone would insufficiently explain the heightened CVD risk, particularly in young Black people with SLE in our cohort. Moreover, observed disparities remain unchanged from previous studies, thus calling for investigations of timely preventive strategies, particularly in young Black women.

We examined predictors of CVD in SLE. There has been limited research on the role of discoid rash as a predictor of CVD. What is known is that Black people have a 5-fold higher incidence of discoid lupus than non-Black people with SLE.[45] Historically, people with discoid rash were considered to have a better SLE prognosis, with a lower prevalence of nephritis.[46] One study of 155 patients with subacute and chronic cutaneous lupus erythematous (CCLE) reported a higher risk of stroke compared with a matched cohort with noncutaneous SLE, even after controlling for smoking.[47] A Danish cohort reported a 1.3-fold higher risk of CVD in patients with CCLE with or without SLE, suggesting that chronic cutaneous inflammation may be a driver of low-grade systemic inflammation resulting in atherosclerosis.[48] Our study reported a strong association between the presence of discoid rash within the first year of diagnosis and CVD, independent of race, supporting previous findings that discoid rash may serve as a predictor of incident CVD in SLE.

Next, consistent with previous studies, we found that renal disorder or ESRD were strong predictors of CVD, supporting the idea that severe renal inflammation could lead to direct and indirect damage to the vasculature contributing to accelerated atherosclerosis. Being over 65 years of age at the time of SLE diagnosis was another strong predictor of incident CVD in our study. Our study and others noted that despite milder symptoms in late-onset SLE, such groups face higher early CVD risk and mortality compared to their peers.[7] This could be the result of delays in diagnosing SLE because of the late onset of symptoms or the result of age-accelerated CVD.[7]

Strengths of this study include the use of a large, population-based incident registry made up of predominantly Black people with validated SLE cases and incident CVD events over 15 years of surveillance. We also acknowledge limitations. First, a few CVD events could have been missed as a result of migration or unavailability of records. Second, White people with SLE were underrepresented in our cohort; however, CVD rates in our cohort were similar to previously published CVD rates in other predominantly White SLE cohorts. Other racial groups were included in the non-Black racial group because of the small sample size. However, our sensitivity analysis that was stratified by White vs Black racial groups revealed similar findings. Third, we did not individually match our cohort with the general population. Fourth, data for traditional CVD risk factors and antiphospholipid syndrome (APS) were unavailable. Hydroxychloroquine and glucocorticoid use were not uniformly documented. We acknowledge that unmeasured APS, hydroxychloroquine, and other traditional risk factors may be confounders. Thus, we provided E-values that showed that confounders need to be associated with a 35-fold increase in CVD incidence for the effect of Black race on CVD to be truly null. Further, a recent study highlighted that Black patients with SLE were 66% less likely to have clinically significant APS antibody profiles compared to White patients.[49] Finally, smoking status, a risk factor for both discoid rash and CVD, was not uniformly available, and the association between discoid rash and CVD could have been confounded by smoking exposure.

To summarize, this study contributes new information that the burden of CVD was 19-fold higher in Black people with SLE. CVD risk starts early during the second year after SLE diagnosis. Finally, we found that discoid rash was a new potential predictor of future CVD events in SLE, warranting further validation and mechanistic research. Future CVD prevention may

focus on at-risk populations (ie, young, Black, and ≥ 65 years of age) and disease characteristics, such as renal disease and discoid rash, with more aggressive screening and management of CVD risk factors to reduce disparities in SLE outcomes.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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