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Racial/Ethnic Variation in Stroke Rates and Risks among Patients with Systemic Lupus Erythematosus

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Abstract

Objective: Systemic lupus erythematosus (SLE), which is associated with increased stroke risk, is more prevalent and often more severe among Blacks, Asians, and Hispanics than Whites. We examined racial/ethnic variation in stroke rates and risks, overall and by hemorrhagic versus ischemic subtype, among SLE patients.

Methods: Within Medicaid (2000-2010), we identified patients aged 18-65 with SLE (≥ 3 ICD-9 710.0 codes, ≥30 days apart) and ≥12 months of continuous enrollment. Subjects were followed from index date to first stroke event, death, disenrollment, or end of follow-up. Race/ethnicity-specific annual event rates were calculated for stroke overall and by subtypes (hemorrhagic vs. ischemic). We used Cox proportional hazard models to estimate hazard ratios (HR) of stroke by race/ethnicity, adjusting for comorbidities and the competing risk of death.

Results: Of 65,788 SLE patients, 93.1% were female. Racial/ethnic breakdown was 42% Black, 38% White, 16% Hispanic, 3% Asian, and 1% American Indian/Alaska Natives. Mean follow-up was 3.7 ±3.0 years. After multivariable adjustment, Blacks were at increased risk of overall stroke (HR 1.34 [95%CI 1.18-1.53), hemorrhagic stroke (HR 1.42 [1.00-2.01]), and ischemic stroke (HR 1.33 [1.15-1.52]) compared to Whites. Hispanics were at increased risk of overall stroke (HR 1.25

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Conflict of Interest Statement

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[1.06-1.47)] and hemorrhagic stroke (HR 1.79 [95% CI 1.22-2.61]), but not ischemic stroke, compared to Whites.

Conclusion: Among SLE patients enrolled in Medicaid, we observed elevated stroke risk (overall and by subtype) among Blacks and Hispanics compared to Whites, suggesting the importance of early recognition and screening for stroke risk factors among Blacks and Hispanics.

Keywords

Stroke; CVA; Systemic lupus erythematosus; SLE; Cardiovascular; Risk; Race; Ethnicity; Medicaid

Introduction

Systemic lupus erythematosus (SLE), a chronic systemic autoimmune disease, disproportionately affects non-White racial/ethnic groups, with more severe systemic involvement and end-organ damage (1-5). SLE is associated with increased risk of stroke, accounting for up to 30% of SLE deaths (6, 7). In past studies, stroke risks among SLE patients were more than double those of non-SLE controls (8-10). Stroke morbidity and mortality may be especially high among lupus nephritis patients, who have high rates of hypertension, hyperlipidemia, and high-dose glucocorticoid use (11-13). Additionally, younger SLE patients are reported to have increased stroke risks compared to the general population, independent of traditional cardiovascular risk factors (14, 15).

Among SLE patients enrolled in U.S. Medicaid, a poor and racially/ethnically diverse population, we have observed that Blacks had a 21% increased risk of mortality and 14% increased risk of cardiovascular disease (CVD, a composite of myocardial infarction [MI] and stroke), compared to Whites(16, 17). Conversely, Hispanics and Asians had lower mortality risk and CVD events than Whites (16, 17). Additionally, Blacks and Hispanics had a 31% and 22% elevated risk of stroke of any type compared to Whites (17). Whereas risk of stroke shows substantial sociodemographic variation in the general U.S. population, little is known about racial/ethnic variation in risk of ischemic and hemorrhagic stroke and specific risk factors among SLE patients.

We examined racial/ethnic variation of rates and relative risks of stroke events, overall and stratified by hemorrhagic versus ischemic subtypes, among SLE and LN patients in a multiracial, Medicaid cohort of >65,000 SLE patients. We hypothesized that Black and Hispanic SLE patients would have an increased risk of stroke, overall and by stroke subtype, compared to Whites, given higher stroke rates among Blacks in the general population and the known increased cardiovascular risk factors and poor quality of care and healthcare access among SLE patients(18, 19). We also hypothesized that stroke risk would be higher among younger Blacks and Hispanics (<age 50) and those with lupus nephritis, but potentially lower among Asians, compared to Whites. We investigated the role of baseline stroke risk factors, including anticoagulation use, prior stroke, and atrial fibrillation/flutter, which we hypothesized to contribute to increased stroke risk among Blacks compared to Whites.

MATERIALS AND METHODS

Study population:

We utilized the Medicaid Analytic eXtract (MAX), containing billing claims for patients in Medicaid, the U.S. health insurance for those with low-income and limited resources (20). We included adults aged 18 to 65 years from January 1, 2000 - December 31, 2010 from the 29 most populated U.S. states. (Individuals >65 years old were excluded as >90% are dually enrolled in Medicare).

SLE and lupus nephritis definitions:

As in prior studies, we identified adults in MAX with ≥3 International Classification of Diseases, Ninth Revision (ICD-9, instituted in 1978 and used during the study period of 2000-2010) codes specific for SLE (710.0), from hospital discharge diagnoses or physician visit claims, ≥30 days apart (5, 21). We restricted analyses to patients with ≥12 months of continuous Medicaid enrollment prior to the third or subsequent SLE code (index date) allowing a 12-month period for covariate collection. Among SLE patients, we identified those with lupus nephritis (≥2 additional ICD-9 claims for nephritis, proteinuria, and/or renal failure on or after index date, ≧30 days apart) (22).

Definition of race/ethnicity:

Race/ethnicity was self-reported in MAX, in mutually exclusive categories of White, Black or African American, American Indian/Alaska Natives, Hispanic or Latino, and Asian (including Native Hawaiian or other Pacific Islander)(23). We excluded individuals whose race/ethnicity information was missing or non-classifiable (e.g. “other/unknown” or “more than one race” categories).

Subject characteristics and covariates:

Patient characteristics, including demographic-, SLE-, cardiovascular disease (CVD)-, and medication-related covariates, were obtained during the 12-months prior to index date. Age, sex, and region of residence, determined by ZIP code and categorized as Northeast, Midwest, South, or West were obtained at index date. We used a validated composite index of seven ZIP code socioeconomic status (SES) indicators from 2000 U.S. Census data to determine area-level SES, divided into quartiles (5, 24). We utilized the validated “SLE risk adjustment index” of comorbidities specific for SLE (25) and divided patients at the median into high or low risk categories. We categorized mean baseline daily glucocorticoid use (0 to 5mg/day, >5 to 15 mg/day, and >15 mg/day) using prednisone-equivalent doses. We evaluated anticoagulation during the baseline period to indirectly assess antiphospholipid antibody syndrome (and other indications not captured by ICD-9 codes). We linked our Medicaid SLE cohort to the U.S. Renal Data System (USRDS), the national registry of patients with end-stage renal disease (ESRD) to identify individuals with ESRD (26).

We utilized validated ICD-9 and/or Current Procedural Terminology (CPT) and/or Diagnosis Related Group (DRG) codes to assess traditional CVD risk factors and comorbidities, including hypertension, hyperlipidemia, diabetes mellitus, smoking, obesity, acute MI, old MI, angina, percutaneous coronary intervention (PCI), coronary atherosclerosis, and

coronary artery bypass graft (CABG), and atrial fibrillation and/or flutter (Supplementary Table 1) (27-33). “Any CVD” was defined as a composite variable consisting of any of the following: angina, MI, old MI, PCI, coronary atherosclerosis, stroke, CABG, peripheral vascular disease, carotid stenosis, heart failure, and valvular disease.

Outcomes:

The first stroke, ischemic or hemorrhagic, after the index date was the primary outcome. (Supplementary Table 1) (34-37). Secondary outcomes were first ischemic or hemorrhagic stroke, evaluated separately, with participants censored at the first stroke event (ischemic or hemorrhagic). Outcomes were based on primary and secondary hospital discharge diagnoses codes. Deaths were reported within MAX in National Death Index-linked data. (Cause of death was not available).

Statistical analysis:

Subjects were followed from the day after index date to first hospitalized stroke, death, Medicaid disenrollment, end of follow-up (December 31, 2010), or loss to follow-up. We calculated unadjusted incidence rates (IRs) for stroke (all strokes and by ischemic or hemorrhagic subtype) and incidence rate ratios (IRRs) overall and by race/ethnicity for SLE per 1,000 person-years, with 95% confidence intervals (95% CIs) for the first stroke after index date, using Poisson regression models. To investigate the role of covariates, we fit three sequential multivariable Cox sub-distribution proportional hazards models, calculating cause-specific risk and accounting for the competing risk of death (38). In each model (A-C), we estimated hazard ratios (HR) for each outcome by race/ethnicity among SLE and lupus nephritis patients. Model A included age (continuous) and sex. Model B further adjusted for sociodemographic variables and SLE-related risk factors, including SLE-specific risk adjustment index, glucocorticoid use and lupus nephritis. Finally, model C additionally controlled for cardiac-specific risk comorbidities, including history of hypertension, smoking, hyperlipidemia, diabetes mellitus, and obesity. We tested the proportional hazards assumption, using Kaplan-Meier curves as well as time-varying covariates by race/ethnicity, for the variables of interest, and observed no significant deviations in our models. We compared stroke risk, stratifying each race/ethnicity by age group (18-39, 40-50, and 50-65 years). We also stratified each race/ethnicity category by baseline factors including: 1) anticoagulation, 2) atrial fibrillation/flutter, and 3) stroke.

All analyses were conducted using SAS version 9.4. Data were obtained from both Centers for Medicare and Medicaid Services (CMS) and USRDS through approved Data Use Agreements and presented in accordance with Federal policies. The Partners’ Institutional Review Board approved this study.

Results

Baseline characteristics of the 65,788 SLE cases from 2000-2010 are shown in Table 1: 93% were female and the largest proportion resided in the U.S. South (40%). Mean age (± standard deviation [SD]) was 40.8 (± 12.1) years, with the largest proportion age 18-39 (47%). Racial/ethnic breakdown among SLE patients was 42% Black, 38% White, 16%

Hispanic, 3% Asian, 1% American Indian/Alaska Natives. Compared to other races/ethnicities, Blacks had the highest prevalence of hypertension, heart failure, and composite CVD; Whites had the highest prevalence of atrial fibrillation/flutter, hyperlipidemia, and anticoagulation; American Indian/Alaska Natives had the highest prevalence of diabetes mellitus, obesity, and MI; and Asians had the highest prevalence of lupus nephritis, ESRD and use of glucocorticoids >5 mg/day at baseline. The SLE risk adjustment index was highest among Blacks and lowest among Hispanics.

Among SLE cases, 14,787 (23%) met our definition of lupus nephritis. They were slightly younger (mean age 37.8 ± 12.4 years), with 58% between 18-39 years old. Lupus nephritis patients had higher baseline prevalence of angina (5.27 vs. 4.23%), coronary atherosclerosis (10.46 vs 6.93%), diabetes (20.60 vs 15.03%), hyperlipidemia (17.20 vs 13.95%), hypertension (66.84 vs. 39.85%), stroke (8.53 vs 5.63%), heart failure (21.28 vs 8.60%), PCI (1.06 vs 0.65%), CABG (0.97 vs. 0.32%), MI (5.00 vs 2.54%), anticoagulation (14.22 vs 8.68%), and ESRD (19.01 vs 3.95%) compared to SLE (Supplementary Table 2). The proportion of subjects with any CVD was 41% among lupus nephritis versus 25% among all SLE.

Among all SLE patients, mean follow-up was 3.7 ± 3.0 years during which time there were 1441 first stroke events, including 1208 ischemic and 233 hemorrhagic strokes. The mean [±SD] age at onset of strokes overall among SLE patients was 47.04 [± 11.66] years, and was highest among American Indian/Alaska Natives (51.00 ± 11.08) and lowest among Asians (43.79 ± 13.19 years)(Table 2). The incidence rate (IR) per 1,000 person-years was 5.88 (95%CI 5.58-6.19) for any stroke, 0.94 (95% CI 0.83-1.07) for hemorrhagic strokes, and 4.92 (95% CI 4.65-5.21) for ischemic strokes. Compared to other race/ethnicities, Blacks had the highest overall stroke event rate (IR 6.88 [95% CI 6.39-7.41]) and the highest ischemic stroke rate (IR 5.80 [95% CI 5.35-6.29]), whereas Asians had the highest hemorrhagic stroke rate (IR 1.28 [95% CI 0.67-2.46]). Compared to Whites, both Blacks and Hispanics had significantly increased rates of all stroke (IRR 1.36 [95% CI 1.30-1.43] and IRR 1.11 [95% CI 1.04-1.18]), and Blacks, Hispanics, and Asians had significantly increased rates of hemorrhagic stroke (IRR 1.58 [95%CI 1.49-1.68], IRR 1.85 [95%CI 1.72-2.00], IRR 1.92 [1.67-2.22]) (Table 2). Blacks had an increased rate of ischemic strokes (IRR 1.33 [95% CI 1.27-1.39]), whereas Asians had a significantly lower rate of ischemic strokes (IRR 0.73 [95% CI 0.62-0.85]) compared to Whites.

After adjustment for sociodemographic factors, Blacks and Hispanics with SLE had significantly increased risk of all strokes (HR 1.50 [95%CI 1.32-1.70] and HR 1.28 [95%CI 1.09-1.50]), which persisted after additional adjustment for medications, SLE- and CVD-specific risk factors (HR 1.34 [95% CI 1.18-1.53] and HR 1.25 [1.06-1.47]) (Table 3). Blacks, Hispanics, and Asians demonstrated a significantly increased risk of hemorrhagic stroke compared to Whites after adjustment for sociodemographic factors (HR 1.73 [95% CI 1.24-2.42], HR 1.99 [95% CI 1.37-2.89], HR 2.00 [1.00-3.98]). However, after additional adjustment for medications, SLE-and CVD- specific risk factors, only Blacks and Hispanics demonstrated increased hemorrhagic stroke risk (HR 1.42 [95% CI 1.00-2.01] and HR 1.79 [95% CI 1.22-2.61]) vs. Whites. Ischemic stroke risk was also elevated among Blacks vs. Whites (HR 1.33 [95% CI 1.15-1.52]) after multivariable adjustment. In age group stratified

analyses by race, the increased all stroke risk was observed primarily among Black and Hispanic SLE patients versus Whites aged 18-39 years and 40-49 years (Table 4).

Among lupus nephritis patients, there were 365 hospitalized stroke events (285 ischemic, 80 hemorrhagic) during 3.08 (± 2.80) years of follow-up. Mean age at all stroke onset was slightly younger in lupus nephritis (43.56 ± 12.50 years) than SLE, with Asians with lupus nephritis again presenting at the youngest age (36.81 ± 11.25 years). Annual rates per 1,000 years were higher in lupus nephritis for all stroke (IR 8.01 [95%CI 7.23-8.88]), hemorrhagic stroke (IR 1.73 [95% CI 1.39-2.15]), and ischemic stroke (IR 6.23 [95%CI 5.55-7.00]) compared to all SLE. Among Blacks and Hispanics with lupus nephritis, increased overall stroke risk persisted after multivariable adjustment (HR 1.44 [95% CI 1.07-1.94] and HR 1.47 [95% CI 1.04-2.07]) compared to Whites (Supplementary Table 3). Among lupus nephritis patients, increased all stroke risk was observed among Blacks and Hispanics aged 40-49 years (HR 2.83 [95% CI 1.53-5.22] and HR 2.47 [95% CI 1.24-4.92]), but not for age groups 18-39 or 50-65 years. Ischemic stroke risk was increased among 40-49 years old Blacks and Hispanics with nephritis (HR 2.51 [95% CI 1.26-4.99] and HR 2.55 [95% CI 1.14-5.72]). Blacks and Hispanics with lupus nephritis in age groups 18-39 years or 50-65 years had similar all and hemorrhagic stroke risks compared to Whites (data not shown).

We also stratified the main analyses (among Blacks and Hispanics compared to Whites only, due to small numbers in other race/ethnicity categories) by baseline factors including history of anticoagulation use, prior stroke, and atrial fibrillation/flutter (Table 5). Blacks and Hispanics compared to Whites had increased overall stroke whether or not they were receiving baseline anticoagulation. However, Blacks and Hispanics without a prior history of stroke had significantly elevated risks of overall stroke compared to Whites without a history of baseline stroke. Stroke risk was not significantly elevated among Blacks or Hispanics with a history of baseline stroke compared to Whites. Lastly, while Blacks and Hispanics without baseline history of atrial fibrillation/flutter had increased stroke risks only Hispanics with baseline atrial fibrillation/flutter had an increased stroke risk compared to Whites.

We also evaluated stroke risk by geographic region given that the majority of Black SLE Medicaid patients reside in the U.S. South (51.4%), which has also been long recognized as the U.S. “stroke belt” given its higher general population stroke and stroke mortality rates (39). However, no significant differences were demonstrated for stroke risks overall, or by subtype, among SLE Medicaid patients by geographic region after multivariable adjustment for demographic (including race/ethnicity), SLE-specific, and CVD-specific factors (Model C-data not shown).

Discussion

Within this cohort of >65,000 racially, ethnically- and geographically-diverse SLE patients from the 29 most populated U.S. states, Blacks with SLE had a 34% increase and Hispanics with SLE had a 25% increase in the risk of overall stroke compared to White patients. Although ischemic strokes constituted the majority of stroke events in our cohort, the risk was elevated for both hemorrhagic and ischemic strokes among Blacks (42% and 33%), whereas Hispanics had a 79% higher hemorrhagic stroke risk than Whites but similar

ischemic stroke risk. Additionally, the observed elevated stroke risks for Blacks and Hispanics with SLE was particularly elevated among those aged <50 years. Furthermore, subgroups of Blacks and Hispanics with lupus nephritis had further elevated risks of overall stroke (44% and 47%), with a greater than two-fold increased risk demonstrated among those aged 40-49 years. Adjustment for sociodemographic factors, SLE- and CVD-comorbidity attenuated stroke risk estimates somewhat, suggesting these may explain some, but not all, of the excess risk.

Blacks and Hispanics in the U.S. general population have higher risks of strokes than do Whites (40, 41). Blacks in the U.S. also have higher prevalence of cardiovascular risk factors, and nearly doubled ischemic and hemorrhagic stroke incidence as well as higher stroke mortality, compared to Whites (42-46). In a past study of U.S. hospitalizations, Blacks were younger on admission for cardiovascular disease events than Whites (47). Hispanics compared to Whites in the U.S. general population also have been shown to be at increased risks of intracranial hemorrhages and ischemic strokes (41, 45). In the current Medicaid cohort, Black SLE patients had higher rates of hypertension, heart failure, lupus nephritis, ESRD, any CVD, and a higher SLE risk adjustment index than Whites. Hispanics, on the other hand, had fewer traditional CVD risk factors and had lower SLE risk index than Whites. However, our findings persisted after adjustment for these baseline differences. Asians with SLE had a greater than doubled risk of hemorrhagic stroke compared to Whites after adjustment for sociodemographic factors, although this elevated risk did not persist after multivariable adjustment. This result appears consistent with general population studies demonstrating greater rates of hemorrhagic strokes among Asians with SLE and reduced rates of ischemic strokes compared to Whites (48, 49).

While it is not possible to determine the biologic basis of variation in stroke risk observed, possible explanations include residual effects of hypertension, untreated or unidentified traditional risk factors in younger age groups (overweight/obesity, diabetes, hyperlipidemia), racial differences in severity of SLE, and other factors that are not fully captured by covariates included in the adjusted models. We also cannot determine the extent to which the differences we observe are due to biologic differences (that we cannot measure) versus disparities in access to care that go beyond obtaining Medicaid coverage. While the underlying mechanisms of ischemic versus hemorrhagic strokes are different, thrombophilia, atherosclerosis and inflammation all occur in SLE patients.

Our stratified analyses provide further insights into the racial/ethnic variation in stroke risks among SLE patients. Stroke risks (overall and by subtype) were particularly increased among Black and Hispanic SLE patients < age 50, which may be partially explained by the accelerated and premature atherosclerosis observed in younger patients with SLE(15).This finding is also consistent with increasing hospitalization rates for stroke in the general population among younger age groups between 2003-2012 (50). Stratification by baseline stroke risk factors among Hispanics and Blacks with SLE compared to Whites demonstrated increased overall stroke risks among Blacks and Hispanics regardless of anticoagulation use and among those without history of stroke, suggesting that baseline anticoagulation use or stroke history did not confer a differentially increased stroke risk in these racial/ethnic groups. However, despite the lower prevalence of atrial fibrillation/flutter among Hispanics

compared to other race/ethnicities in our cohort, stroke risk was substantially increased among SLE Hispanics, but not Blacks, with atrial fibrillation/flutter at baseline. This suggests that atrial fibrillation/flutter may be a particularly important stroke risk factor among Hispanics with SLE, in contrast to the general population finding that atrial fibrillation confers increased stroke risk among Blacks versus Whites (51) and non-Hispanic Whites compared to Hispanics(52).

This study has a number of strengths. We included administrative claims from >65,000 SLE patients in a large, diverse, non-academic cohort, with data on sociodemographic factors, medications, SLE-and CVD-specific comorbidities. As diagnostic claims may underestimate stroke rates (53), we used primary and secondary billing codes, allowing for the possibility that SLE may have been the primary diagnosis (17). We fit several models sequentially adjusting for potential confounders that might contribute to stroke risks among SLE patients, while accounting for the competing risk of death. We evaluated risk of stroke subtypes stratified by age among each race/ethnicity, and studied the role of baseline stroke risk factors within each race/ethnicity. Additionally, we applied the previously validated SLE risk adjustment index, a proxy for SLE severity and comorbidity, as a covariate in multivariable adjusted models(25). Ischemic strokes comprised 84% of all strokes (and hemorrhagic strokes comprised 16%) in our Medicaid SLE cohort, which is a similar distribution to that in the general U.S. population in a recent study (87% ischemic and 13% hemorrhagic strokes) (54).

Limitations in utilizing this Medicaid SLE cohort to study outcomes by race/ethnicity have been previously outlined, including use of an administrative SLE case definition, which may limit sample size or introduce misclassification of cases (16, 17). Lifestyle factors related to stroke risk, such as body mass index, physical exercise, diet, alcohol consumption and clinical/laboratory data such as cholesterol, systolic blood pressure, hemoglobin A1c levels, antiphospholipid antibodies—are not adequately captured in administrative claims data. Finally, as Medicaid provides medical insurance coverage for low-income U.S. individuals, our results may not be generalizable to higher socioeconomic groups; however, given that Medicaid in 2010 covered more than one-quarter of the U.S. SLE population, they do pertain to a large proportion of SLE patients in the population(17). Additionally, we were likely underpowered to study interactions between race/ethnicity and other factors such as age group for stroke subtypes among lupus nephritis patients.

In this large Medicaid SLE cohort, compared to White SLE patients, risk of stroke was increased among Blacks and Hispanics, with Blacks at increased risk for both ischemic and hemorrhagic strokes, and Hispanics at risk for hemorrhagic strokes. Stroke risks were particularly increased among Black and Hispanic SLE patients < age 50 years, and among Black and Hispanic lupus nephritis patients aged 40-49 years. It is possible that early recognition and aggressive risk factor management may be critical for young SLE patients. Future research confirming the current findings and investigating factors such as genetics, biomarkers, lifestyle factors such as diet and physical activity, medications, other thrombotic risk factors is needed. Improved identification of SLE patients at-risk for ischemic versus hemorrhagic stroke subtypes may provide insight into prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline Characteristics among 65,788 Patients with Systemic Lupus Erythematosus (SLE) enrolled in Medicaid in the 29 most populated U.S. States, 2000-2010 by Race/Ethnicity

	White	Black	Hispanic	Asian	American Indian/Alaska Native
Total number of patients (N,%)	25,204 (38.31)	27,470 (41.76)	10,562 (16.05)	1,827 (2.78)	725 (1.10)
Female (N, %)	23,401 (92.85)	25,643 (93.35)	9,846 (93.22)	1,663 (91.02)	668 (92.14)
Age, years (Mean, SD)	42.73 (11.98)	39.70 (11.79)	39.24 (12.30)	39.12 (12.72)	41.94 (11.83)
Age Categories (N, %)					
18-39 years	10,317(40.93)	13,969(50.85)	5,543 (52.48)	953 (52.16)	314(43.31)
40-50 years	7,123 (28.26)	7,473 (27.20)	2,664 (25.22)	458 (25.07)	213(29.38)
50-65 years	7,764 (30.80)	6,028 (21.94)	2,355 (22.30)	416 (22.77)	198(27.31)
Residential Region (N, %)					
Midwest	6,238 (24.75)	6,060 (22.06)	701 (6.64)	142 (7.77)	89 (12.28)
Northeast	5,151 (20.44)	4,704 (17.12)	2,848 (26.96)	440 (24.08)	74 (10.21)
South	8,874 (35.21)	14,126 (51.42)	2,555 (24.19)	197 (10.78)	271 (37.38)
West	4,941 (19.60)	2,580 (9.39)	4,458 (42.21)	1,048 (57.36)	291 (40.14)
Comorbidities (N, %) *					
Angina	1,203 (4.77)	1,122 (4.08)	398 (3.77)	47 (2.57)	15 (2.07)
CABG	88 (0.35)	85 (0.31)	31 (0.29)	--	--
Stroke	1,525 (6.05)	1,668 (6.07)	414 (3.92)	63 (3.45)	37 (5.10)
Coronary Atherosclerosis	2,056 (8.16)	1,824 (6.64)	561 (5.31)	80 (4.38)	40 (5.52)
MI	716 (2.84)	742 (2.70)	157 (1.49)	34 (1.86)	25 (3.45)
PCI	211 (0.84)	160 (0.58)	49 (0.46)	--	--
Atrial Fibrillation or Flutter	566(2.25)	464(1.69)	165(1.56)	38(2.08)	---
End Stage Renal Disease	460(1.83)	1607(5.85)	392(3.71)	116(6.35)	22(3.03)
Diabetes Mellitus	3,748 (14.87)	4,229 (15.39)	1,566 (14.83)	203 (11.11)	141 (19.45)
Heart Failure	1,849 (7.34)	2,988 (10.88)	644 (6.10)	133 (7.28)	44 (6.07)
Hypertension	8,658 (34.35)	13,309 (48.45)	3,444 (32.61)	569 (31.14)	236 (32.55)
Hyperlipidemia	4,241 (16.83)	3,102 (11.29)	1,498 (14.18)	252 (13.79)	84 (11.59)
Obesity	1,618 (6.42)	1,742 (6.34)	556 (5.26)	25 (1.37)	53 (7.31)
Smoking	2,983 (11.84)	1,898 (6.91)	334 (3.16)	37 (2.03)	84 (11.59)
Any Cardiovascular Disease **	6,299 (24.99)	7,451 (27.12)	2,155 (20.40)	374 (20.47)	142 (19.59)
Lupus Nephritis (N, %) ***	3,409 (13.53)	7,807 (28.42)	2,532 (23.97)	625 (34.21)	144 (19.86)
SLE Risk Adjustment index ¥ **(Mean, SD)**	1.55 (2.59)	1.81 (2.67)	1.44 (2.36)	1.46 (2.38)	1.69 (2.63)
Glucocorticoid Use (N, %)					
0 to 5 mg/day	21,686 (86.04)	21,553 (78.46)	8,289 (78.48)	1,308 (71.59)	623 (85.93)
>5 to 15 mg/day	2,793 (11.08)	4,517 (16.44)	1,762 (16.68)	411 (22.50)	85 (11.72)
>15 mg/day	725 (2.88)	1,400 (5.10)	511 (4.84)	108 (5.91)	17 (2.34)

	White	Black	Hispanic	Asian	American Indian/Alaska Native
Anticoagulation Use (N, %)	2,400 (9.52)	2,254 (8.21)	858 (8.12)	143 (7.83)	53 (7.31)

Baseline: 12 months prior to index date; CABG: *coronary artery bypass graft,* MI: myocardial infarction, PCI: percutaneous coronary intervention.

*Comorbidities collected at any time up to and including index date.

**Any Cardiovascular Disease defined as presence of any of the following ICD-9 codes for angina, MI, old MI, PCI, atherosclerosis, stroke, CABG, peripheral vascular disease, carotid stenosis, heart failure, or valvular disease.

***An additional 270 individuals developed lupus nephritis after the baseline period.

Cell sizes < 11 individuals suppressed in accordance with Federal reporting requirements.

¥SLE specific index ranges from 0-46 [Reference 20]

Table 2.

Annual Rates of Stroke among 65,788 SLE patients enrolled in Medicaid within the 29 most populated U.S. states, 2000-2010 by Race/Ethnicity

	Number of Patients	Age at Event, Mean (SD)	Number of Events	Person-years of followup, mean (SD)	IR* (95% CI)	IRR** (95%CI)
All Stroke						
All patients	65,788	47.04 (11.66)	1441	3.72 (3.04)	5.88 (5.58-6.19)	-
White	25,204	49.38 (11.19)	464	3.66 (3.02)	5.03 (4.59-5.51)	1.0 (ref)
Black	27,470	46.08 (11.44)	702	3.72 (3.03)	6.88 (6.39-7.41)	**1.36 (1.30-1.43)**
Hispanic	10,562	45.40 (12.34)	229	3.87 (3.12)	5.60 (4.92-6.37)	**1.11 (1.04-1.18)**
Asian	1,827	43.79 (13.19)	31	3.82 (3.08)	4.45 (3.13-6.33)	0.89 (0.77-1.02)
American Indian/Alaska Native	725	51.00 (11.08)	15	3.68 (3.03)	5.62 (3.39-9.32)	1.12 (0.91-1.37)
Hemorrhagic Stroke						
All patients	65,788	45.47 (12.07)	233	3.78 (3.06)	0.94 (0.83-1.07)	-
White	25,204	49.29 (11.39)	62	3.71 (3.04)	0.66 (0.51-0.85)	1.0 (ref)
Black	27,470	44.99 (11.60)	109	3.78 (3.06)	1.05 (0.87-1.27)	**1.58 (1.49-1.68**
Hispanic	10,562	42.54 (12.19)	51	3.92 (3.14)	1.23 (0.93-1.62)	**1.85 (1.72-2.00)**
Asian	1,827	40.14 (16.07)	---	---	1.28 (0.67-2.46)	**1.92 (1.67-2.22)**
American Indian/Alaska Native	725	52.28 (11.78)	---	---	0.74 (0.19-2.96)	1.12 (0.84-1.48)
Ischemic Stroke						
All patients	65,788	47.34 (11.56)	1208	3.73 (3.05)	4.92 (4.65-5.21)	-
White	25,204	49.39 (11.17)	402	3.67 (3.02)	4.35 (3.94-4.80)	1.0 (ref)
Black	27,470	46.28 (11.41)	593	3.73 (3.03)	5.80 (5.35-6.29)	**1.33 (1.27-1.39)**
Hispanic	10,562	46.22 (12.29)	178	3.88 (3.12)	4.34 (3.75-5.03)	1.00 (0.93-1.07)
Asian	1,827	45.29 (11.93)	22	3.83 (3.09)	3.15 (2.07-4.78)	**0.73 (0.62-0.85)**
American Indian/Alaska Native	725	50.81 (11.46)	13	3.68 (3.03)	4.87 (2.83-8.39)	1.12 (0.91-1.38)

* IR = incidence rate, annual CVD event rate per 1,000 person years,
IRR= incidence rate ratio, SD= Standard deviation; Cell sizes of < 11 individuals suppressed in accordance with Federal reporting requirements

Table 3.

Multivariable-Adjusted Sub-distribution Hazard Ratios* for Stroke among 65,788 SLE patients enrolled in Medicaid within the 29 most populated U.S. states, 2000-2010 by Race/Ethnicity

	Model A (HRsd [95%CI])	Model B (HRsd [95%CI])	Model C (HRsd [95%CI])
All Stroke			
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Black	**1.50 (1.32-1.70)**	**1.40 (1.23-1.59)**	**1.34 (1.18-1.53)**
Hispanic	**1.28 (1.09-1.50)**	**1.25 (1.06-1.47)**	**1.25 (1.06-1.47)**
Asian	0.99 (0.69-1.43)	0.95 (0.66-1.37)	0.95 (0.66-1.37)
American Indian/Alaska Native	1.18 (0.71-1.97)	1.11 (0.67-1.87)	1.14 (0.68-1.92)
Hemorrhagic Stroke			
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Black	**1.73 (1.24-2.42)**	**1.51 (1.07-2.13)**	**1.42 (1.00-2.01)**
Hispanic	**1.99 (1.37-2.89)**	**1.83 (1.26-2.67)**	**1.79 (1.22-2.61)**
Asian	**2.00 (1.00-3.98)**	1.71 (0.86-3.42)	1.64 (0.82-3.27)
American Indian/Alaska Native	1.15 (0.28-4.75)	1.06 (0.25-4.42)	1.05 (0.25-4.38)
Ischemic Stroke			
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Black	**1.46 (1.27-1.67)**	**1.38 (1.20-1.58)**	**1.33 (1.15-1.52)**
Hispanic	1.16 (0.97-1.39)	1.14 (0.95-1.37)	1.15 (0.95-1.38)
Asian	0.83 (0.54-1.27)	0.81 (0.52-1.25)	0.81 (0.53-1.26)
American Indian/Alaska Native	1.18 (0.68-2.06)	1.13 (0.65-1.96)	1.16 (0.67-2.03)

*Competing risk analysis taking competing risk of death into account

HRsd=subdistribution hazard ratios; CI=confidence intervals

Model A: Age (continuous), sex, region of residence, year and area-level SES

Model B: Model A + SLE-specific index, glucocorticoid use, (0 to 5 mg/day [ref], >5 to 15 mg/day,

>15 mg/day), anticoagulation use (defined as use of warfarin and/or heparin,and/or enoxaparin ever vs. never), Lupus Nephritis

Model C: Model B + comorbidities at study index date including history of hypertension, hyperlipidemia, diabetes mellitus, smoking and obesity, atrial fibrillation and/or atrial flutter

Bold= p<0.05

Table 4.

Multivariable-Adjusted Sub-distribution Hazard Ratios* for Stroke Risk among 65,788 SLE patients enrolled in Medicaid within the 29 most populated U.S. states, 2000-2010, by Race/Ethnicity and Age Group

	Age 18-39 years (HRsd [95%CI])	Age 40-49 years (HRsd [95%CI])	Age 50-65 years (HRsd [95%CI])
All Stroke			
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Black	**1.43 (1.12-1.81)**	**1.49 (1.19-1.87)**	1.15 (0.93-1.42)
Hispanic	**1.36 (1.02-1.83)**	**1.51 (1.13-2.03)**	0.97 (0.73-1.30)
Asian	1.39 (0.82-2.35)	0.65 (0.29-1.47)	0.81 (0.41-1.58)
American Indian/ Alaska Native	0.51 (0.13-2.05)	1.33 (0.57-3.08)	1.47 (0.69-3.13)
Hemorrhagic Stroke			
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Black	1.60 (0.88-2.92)	1.61 (0.84-3.09)	1.12 (0.62-2.03)
Hispanic	**1.95 (1.07-3.53)**	**2.22 (1.07-4.63)**	1.32 (0.63-2.74)
Asian	2.07 (0.79-5.41)	1.51 (0.35-6.42)	1.34 (0.32-5.68)
American Indian/ Alaska Native	---	1.54 (0.18-13.34)	1.45 (0.20-10.65)
Ischemic Stroke			
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Black	**1.40 (1.08-1.81)**	**1.47 (1.15-1.87)**	1.15 (0.92-1.44)
Hispanic	1.24 (0.89-1.74)	**1.39 (1.01-1.92)**	0.92 (0.67-1.26)
Asian	1.21 (0.64-2.30)	0.51 (0.19-1.38)	0.73 (0.34-1.57)
American Indian/Alaska Native	0.61 (0.15-2.48)	1.29 (0.52-3.20)	1.48 (0.65-3.35)

*Competing risk analysis taking competing risk of death into account

HRsd=subdistribution hazard ratios; CI=confidence intervals

Model C results presented here: Adjusted for age (continuous), sex, region of residence, year and area-level SES, SLE-specific index, glucocorticoid use (in categories: 0 to 5 mg/day [ref], >5 to 15 mg/day, >15 mg/day), anticoagulation use (defined as use of warfarin and/or heparin, and/or enoxaparin ever vs. never),lupus nephritis, comorbidities at study index date including history of hypertension, hyperlipidemia, diabetes mellitus, smoking and obesity, atrial fibrillation and/or atrial flutter **Bold= p<0.05**

Table 5.

Multivariable-Adjusted Sub-distribution Hazard Ratios* for Stroke Risk among 65,788 SLE patients enrolled in Medicaid within the 29 most populated U.S. states, 2000-2010 by Race/Ethnicity and baseline factors

	No Baseline Anticoagulation Use HRsd (95%CI)	Baseline Anticoagulation Use HRsd (95%CI)	No Baseline Atrial Fibrillation/ Flutter HRsd (95%CI)	Baseline Atrial Fibrillation/ Flutter Present HRsd (95%CI)	No Baseline History of Stroke HRsd (95%CI)	Baseline History of Stroke HRsd (95%CI)
Overall Stroke						
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Black	**1.31(1.14-1.51)**	**1.49(1.10-2.02)**	**1.34(1.18-1.53)**	1.27(0.65-2.48)	**1.37(1.18-1.59)**	1.27(0.99-1.63)
Hispanic	**1.19(1.00-1.43)**	**1.50(1.01-2.24)**	**1.19(1.00-1.41)**	**3.30(1.66-6.57)**	**1.35(1.13-1.63)**	0.95(0.65-1.40)
Hemorrhagic Stroke						
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Black	1.25(0.85-1.82)	**2.56(1.07-6.08)**	**1.45(1.01-2.06)**	0.66(0.09-4.90)	1.42(0.97-2.10)	1.43(0.64-3.19)
Hispanic	**1.56(1.03-2.35)**	**3.43(1.28-9.18)**	**1.71(1.16-2.53)**	4.41(0.66-29.37)	**1.80(1.19-2.73)**	1.75(0.66-4.63)
Ischemic Stroke						
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Black	**1.32(1.13-1.54)**	1.36(0.98-1.89)	**1.32(1.15-1.53)**	1.34(0.66-2.73)	**1.36(1.16-1.60)**	1.25(0.96-1.62)
Hispanic	1.12(0.91-1.37)	1.28(0.82-2.01)	1.09(0.90-1.32)	**2.98(1.36-6.52)**	**1.26(1.02-1.55)**	0.87(0.57-1.32)

*Competing risk analysis taking competing risk of death into account.

HRsd=subdistribution hazard ratios; CI=confidence intervals

Model C results presented here: adjusted for age (continuous), sex, region of residence, year and area-level SES, SLE-specific index, glucocorticoid use (in categories: 0 to 5 mg/day [ref], >5 to 15 mg/day, >15 mg/day), anticoagulation use (defined as use of warfarin and/or heparin, and/or enoxaparin ever vs. never), lupus nephritis (Note: lupus nephritis only adjusted for in the SLE cohort), comorbidities at study index date including history of hypertension, hyperlipidemia, diabetes mellitus, smoking and obesity, atrial fibrillation and/or atrial flutter

*Reference group is same race/ethnicity without presence of the risk factor **Bold= p<0.05**