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Comparative Risks of Cardiovascular Disease in Systemic Lupus Erythematosus, Diabetes and General Medicaid Patients

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Abstract

Objective: Cardiovascular disease (CVD) risk is elevated in patients with systemic lupus erythematosus (SLE) and diabetes mellitus (DM), but whether CVD risk in SLE is as high as in DM is unknown. We compared CVD risks between SLE, DM, and general population U.S. Medicaid patients.

Methods: In a cohort study, we identified age-and-sex matched (1:2:4) adults with SLE, DM or general population from Medicaid Analytic eXtract (MAX), 2007–2010. We collected baseline sociodemographic factors, comorbidities, and medications. Cox regression models calculated hazard ratios (HRs) of hospitalized non-fatal CVD events (combined myocardial infarction [MI] and stroke), and MI and stroke separately, accounting for competing risk of death and adjusting for covariates. We compared risks in age-stratified models.

Results: We identified 40,212 SLE, 80,424 DM, and 160,848 general population patients, of whom 92.5% were female, with mean age of 40.3 (±12.1) years. Non-fatal CVD incidence rate per 1,000 person-years was 8.99 for SLE, 7.07 for DM, and 2.36 for general population. Non-fatal CVD risk was higher in SLE compared to DM (HR 1.27 [95% CI 1.15–1.40]), driven by excess risk at ages 18–39 (HR 2.22 [95% CI 1.81–2.71]). SLE had higher CVD risk compared to the general population (HR 2.67 [95% CI 2.38–2.99]).

Conclusion: SLE patients had 27% higher risk of non-fatal CVD events compared to age-and sex-matched DM patients and over twice the risk of the Medicaid general population. The highest

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relative risk occurred at ages 18–39. These high risks merit aggressive evaluation for modifiable factors and research to identify prevention strategies.

Keywords

Systemic lupus erythematosus; cardiovascular disease; epidemiology; health services research

Introduction

Cardiovascular disease (CVD) risk is elevated in systemic lupus erythematosus (SLE) and is the leading cause of death (1–4). Traditional CVD risk factors, such as of smoking, hypertension, and hyperlipidemia, are prevalent among SLE patients and systemic inflammation accelerates atherosclerosis (5). Diabetes mellitus (DM) is also associated with premature atherosclerosis, conferring an approximately doubled CVD risk and increased risk of premature CVD death (6–9). CVD risk stratification algorithms and aggressive prevention strategies, widely implemented for DM, do not yet exist for SLE (10–12). DM is the prototype for aggressive CVD risk reduction efforts, but whether CVD risk is as elevated among SLE patients is unknown. As data quantifying the magnitude of CVD risk in SLE compared to more prevalent diseases using population-based data are lacking, clinicians may less vigorously seek and prevent CVD in SLE.

In this study, hypothesizing that CVD risks of SLE may be as high or higher than those of DM, we compared CVD risks of a large SLE cohort of US Medicaid recipients to age- and sex-matched DM patients and the general population. We also evaluated CVD risk by age, history of baseline CVD, and use of cardiac medications.

Patients and Methods

Study Population and Cohort Matching:

Medicaid is the U.S. health insurance program for low-income individuals, providing coverage for medical expenses and prescription drugs. We analyzed data from the Medicaid Analytic eXtract (MAX), an administrative database containing all billing claims for Medicaid patients, from the 29 most populated U.S. states between January 1, 2007 and December 31, 2010 (13). We identified adults aged ≥18–65 with prevalent SLE (using a previously developed algorithm of ≥3 International Classification of Diseases, Ninth Revision [ICD-9] codes for SLE [710.0]) or prevalent Type I or Type II DM (requiring ≥ 3 of the following codes: 249.xx, 250.xx, 357.2, 362.01–362.06, 366.41) from hospital discharge diagnoses or physician visit claims, with each claim separated by ≥30 days (14). We included only prevalent SLE patients without claims for DM and DM patients without SLE claims. We restricted analyses to patients with ≥6 months of continuous Medicaid enrollment prior to the 3rd code (index date) for collection of baseline covariates. We performed 1:2 matching (SLE: DM) based on age (within one month) and sex and ensured that our cohorts were mutually exclusive during the baseline period. We also identified an age- and sex-matched general Medicaid cohort (excluding patients with SLE or DM ICD-9 codes) with ICD-9 codes for any non-SLE, non-DM diagnoses from hospital discharge diagnoses or physician visit claims on the same index date as each SLE patient (1:4

matching), with 6 months of continuous enrollment pre-index date as the baseline period. SLE patients with DM claims during the baseline period, DM patients with SLE claims during the baseline period, and general Medicaid patients with claims for either SLE or DM during the baseline period were thus excluded. We did not exclude subjects who later developed either SLE or DM in any of the cohorts in follow-up so as not to introduce an immortal time bias. We also excluded patients >65 years old due to lack of complete claims for Medicare dual enrollees.

Outcomes:

The primary outcome was the first non-fatal CVD event, defined as a composite measure of acute MI or stroke (Supplementary Table 4) (15–17). Secondary outcomes were non-fatal acute MI and stroke separately. Outcomes were based on primary and secondary hospital discharge diagnosis codes. Patients were followed from the day after index date to first non-fatal CVD event, death, Medicaid disenrollment, or end of follow-up on December 31, 2010, whichever was first. Deaths were reported directly to Medicaid and also obtained from the National Death Index (18). Cause of death was not available.

Covariates:

Baseline data from 6 months prior to index date included sociodemographic and CVD-related covariates, SLE- and medical comorbidities, and medications. Sociodemographic variables were age, sex, and U.S. Census-based region of residence (Northeast, Midwest, South, or West) determined by ZIP code. For area-based socioeconomic status (SES), we used a validated composite index of seven ZIP code SES indicators from 2000 U.S. Census data (18, 19). We divided area-level SES into quartiles (14). Race/ethnicity in the MAX database is self-reported based on mutually exclusive categories of White, African American, American Indian/Alaska Natives, Hispanic or Latino, and Asian (including Native Hawaiian or other Pacific Islander (20).

We evaluated baseline CVD risk factors and co-morbidities using validated ICD-9 and/or Current Procedural Terminology (CPT) and/or Diagnosis Related Group (DRG) codes for hypertension, hyperlipidemia, smoking, obesity, acute MI, old MI, stroke, angina, carotid stenosis, coronary atherosclerosis, peripheral vascular disease, valvular disease, heart failure, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) (Supplementary Table 4) (21–26). A composite “any CVD co-morbidities” was defined as any of the following during baseline: angina, coronary atherosclerosis, carotid stenosis, stroke, acute MI, old MI, heart failure, peripheral vascular disease, valvular disease, PCI or CABG.

We evaluated baseline comorbidities and medications using the Charlson comorbidity index, from which we excluded diabetes and systemic lupus erythematosus (27). In SLE patients, we used “SLE risk adjustment index”, associated with SLE in-hospital mortality to account for comorbidities (28), dividing patients at the median into high or low risk categories. We identified filled prescriptions using National Drug Codes (NDC) and summed the number of unique medications filled per subject during the baseline period. For SLE patients, we assessed prescriptions for glucocorticoids (prednisone, methylprednisolone, dexamethasone,

hydrocortisone, prednisolone, and cortisone defined as prednisone equivalents), hydroxychloroquine, and immunosuppressive drugs (mycophenolate mofetil, mycophenolic acid, cyclophosphamide, azathioprine, cyclosporine, methotrexate, leflunomide, rituximab, and tacrolimus). We categorized mean baseline glucocorticoid use (0 to 5, >5 to 15, or >15 mg/day). We also examined use (ever/never) of insulin, statins, angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), beta blockers, and anticoagulants (including heparin, warfarin, and enoxaparin).

Statistical Analysis:

Within age- and sex-matched cohorts, we calculated unadjusted non-fatal CVD incidence rates (IRs) and incidence rate ratios per 1,000 person-years, with 95% confidence intervals (95% CIs) within SLE, DM, and general population groups (using DM and general population cohorts as reference groups separately). To investigate the contribution of different sets of baseline factors, we fit two multivariable Cox sub-distribution proportional hazards models, calculating cause-specific risk while accounting for the competing risk of death (29). We estimated hazard ratios (HR) for each outcome for SLE versus DM or general population in our main models (A and B), accounting for death as a competing risk. Model A included age (continuous), sex, race/ethnicity, region of residence, year, and zip code-level SES. Model B added the Charlson score (excluding diabetes), CVD-specific risk factors (including hypertension, smoking, hyperlipidemia, and obesity), and number of medications to model A. We performed subgroup analyses by age, stratifying each cohort into three age groups (18–39, 40–49, and 50–65 years). We tested the proportional hazards assumption, using Kaplan-Meier curves as well as time-varying covariates, for the variables of interest, and observed no deviations in our models. We repeated the main analysis using Cox regression proportional hazards models (without accounting for the competing risk of death).

We also performed two sensitivity analyses. First, we excluded patients with a history of “any CVD co-morbidities” at baseline. Second, to determine whether baseline cardiac medications attenuated risk of CVD events, we added baseline cardiac medication use to model B (including ever/never use of statins, ACE inhibitor/ARBs, beta-blockers, and anticoagulants) (Model C).

All analyses were conducted using SAS version 9.4. Data were obtained from Centers for Medicare and Medicaid Services (CMS) and presented in accordance with Federal policies. The Partners Institutional Review Board approved all aspects of this study.

Results

Baseline Characteristics

We matched 40,212 prevalent SLE patients, 80,424 prevalent diabetes patients, and 160,848 general population patients; 92.5% were female and mean age was 40.3 (±12.1) years in each cohort. There were more African Americans (42.0% vs. 30.1% vs. 21.1%) and fewer Whites (34.9% vs. 45.7% vs. 46.3%) in the SLE vs. DM vs. general population cohorts; the largest proportion of participants in each cohort resided in the U.S. South. Mean follow-up

was 1.86 (±1.11) years for SLE, 1.86 (±1.11) years for DM, and 1.73 (±1.14) years for general population.

The following baseline CVD comorbidities were more prevalent among SLE patients (Table 1): stroke, acute MI, valvular disease, heart failure, and "any CVD" at baseline. However, DM had higher rates of traditional cardiovascular risk factors including hypertension, hyperlipidemia, and obesity compared to SLE or general population. SLE and DM patients had elevated but similar rates of angina, CABG, coronary atherosclerosis, PCI, carotid stenosis, and peripheral vascular disease compared to the general population.

Among SLE patients, 16.8% had lupus nephritis and 5.3% of diabetes patients had renal involvement (Table 1). Charlson comorbidity index was highest in SLE compared to DM or the general population. Although total number of medications received was similar in SLE versus DM patients, both were elevated compared to the general population.

There were 3,235 deaths in the general population, 2,550 in the diabetes group, and 1,798 in the SLE group. The incidence rate (IR) of death per 1,000 person years was nearly doubled in SLE (IR 23.78 [95% CI 22.71–24.90]) compared to the general population (IR 11.58 [95% CI 11.19–11.99]) and increased in SLE relative to diabetes (IR 16.86 [95% CI 16.22–17.53].

Primary Outcome: CVD

SLE patients had the highest annual non-fatal CVD event rate per 1,000 person years (IR 8.99 [95% CI 8.34–9.70] compared to DM (IR 7.07 [95% CI 6.66–7.51]) and the general population (IR 2.36 [95% CI 2.19–2.55]) (Table 2). Compared to DM, SLE patients had a significantly higher annual CVD event rate (IRR 1.27 [95% CI 1.23–1.30]), and both SLE and DM had a nearly 3-to-4-fold higher annual unadjusted CVD event rate compared to the general population.

After adjustment for sociodemographic factors (Model A), SLE patients had a significantly increased risk of non-fatal CVD events compared to DM (HR 1.22 [95% CI 1.10–1.34]), which increased further (HR 1.27 [95% CI 1.15–1.40]) after additional adjustment for the Charlson score, CVD risk factors, and total number of medications (Model B). Compared to the general population, SLE patients had a greater than doubled risk of CVD events in models adjusted for the same covariates (Model B, HR 2.67 [95% CI 2.38–2.99]) (Table 3). Additionally, repeating the main analysis using a Cox regression proportional hazards model revealed similar results (data not shown).

Secondary outcomes: MI and stroke separately

Compared to DM or general population, SLE patients had a significantly higher unadjusted annual non-fatal MI event rate than DM (IRR 1.07 [95% CI 1.04–1.10) and the general population (IRR [3.85 (3.72–3.99)] (Table 2). However, after multivariable-adjustment (Model B) SLE patients had a similar MI risk compared to DM patients (HR 1.09 [95% CI 0.93–1.28]), but still significantly higher risk compared to the general population (HR 2.87[95% CI 2.38–3.47]) (Table 3).

In all three cohorts, there were more acute strokes than MIs during follow-up (Table 2). SLE patients had a significantly increased unadjusted annual non-fatal stroke rate compared to DM (IRR 1.40 [95% CI 1.36–1.44] and the general population (IRR 3.82 [95% CI 3.71–3.94]). The elevated stroke risk persisted for SLE patients compared to DM (HR 1.37 [95% CI 1.21–1.55]) and general population patients (HR 2.56 [95% CI 2.23–2.95]) after multivariable-adjustment (Table 3).

Age Stratification:

Absolute risks of MI and stroke (IRs) by age group are shown in Table 4. While IRs increased with age in each cohort, IRs of both MI and stroke were in fact *more* elevated among SLE patients ages 18–39 than among general population patients aged 50–65. After multivariable adjustment, the relative risks remained the highest in SLE patients in the youngest age group: CVD risk was significantly higher in SLE versus DM patients aged 18–39 years (Model B, HR 2.22 [95% CI 1.81–2.71]) and similar for ages 40–49 years (HR 0.96 [95% CI 0.79–1.16]) or 50–65 years (HR 1.03 [95% CI 0.88–1.20]). This pattern remained true for both MI (HR 2.04 [95% CI 1.44–2.88]) and stroke (HR 2.25 [95% CI 1.77–2.87]). Compared to the general population, SLE patients had a significantly increased CVD risk across all three age groups, with the highest relative risk for those aged 18–39 years (HR 7.79 [95% CI 5.77–10.50]) (Table 5).

Sensitivity Analyses

Exclusion of Baseline CVD: After excluding participants with baseline “any CVD comorbidities”, SLE patients still had the highest unadjusted annual CVD event rate (IR 5.89 [95% CI 5.32–6.53]) (Supplementary Table 1). CVD risk remained similarly increased in SLE versus DM (HR 1.23 [95% CI 1.07–1.40]) and the general population (HR 2.68 (95% CI 2.32–3.10)], as in the main analysis (Supplementary Table 2).

Role of Cardiac Medications: After further adjustment of Model B for baseline cardiac medication use, similar findings to the main analysis were demonstrated for overall CVD risk in SLE versus DM (HR 1.26 [95% CI 1.14–1.40]) and the general population (Model C, HR 2.63 [95% CI 2.35–2.95]) (Supplementary Table 3).

Discussion

Within a racially, ethnically- and geographically-diverse cohort of Medicaid patients from the 29 most populated U.S. states, SLE patients had a 27% higher overall CVD risk than age-and sex-matched DM patients and more than doubled risk compared to general population patients. Despite fewer traditional CVD risk factors, SLE patients had similar adjusted MI risk and a 37% higher adjusted stroke risk than age-and sex- matched DM patients. Overall CVD, MI, and stroke relative risks were over twice as high in young SLE patients aged 18–39 years, but similarly elevated in those aged 40–65, compared to their DM counterparts. Compared to age-and-sex matched general population patients, MI and stroke relative risks were seven-to-nine-fold higher among SLE patients aged 18–39 years and more than doubled in SLE overall. Even the absolute risks for MI and stroke were more elevated among 18–39 year-old patients with SLE compared to 50–65 year-old general

Medicaid patients. Adjustment for sociodemographic factors, Charlson co-morbidity score, and CVD risk factors, did not attenuate CVD risk, overall or by MI and stroke subtype, suggesting that modifiable factors may not fully explain the elevated risk in SLE patients. Additionally, elevated CVD risks demonstrated in SLE patients persisted after exclusion of patients with baseline CVD.

To our knowledge, no prior studies directly quantify CVD risks in SLE versus DM. In a recent vascular ultrasound study of 460 individuals without CVD history, age-and sex-matched SLE and DM patients had nearly twice as many carotid and femoral artery atherosclerotic plaques as did healthy controls (30). A multi-center Swiss study comparing 241 SLE and 193 type 1 DM patients demonstrated similar vascular event rates overall (13.3% vs. 15%) and in a single center subgroup of 100 age-and sex-matched SLE and Type I DM patients (31). Both of these studies were limited by cross-sectional study design, small sample sizes, and the Swiss study used a type 1 DM control group under intensified insulin therapy, known to have lower CVD risk than unselected diabetic patients (32).

Our results are consistent with prior estimates of SLE CVD risk in general population studies from the US, Sweden, UK, and South Korea that similarly demonstrate an overall 2-to-3 fold increase in CVD events in SLE compared to general population controls (33–37). A population-based study revealed that, among SLE patients, rates of acute MI and stroke hospitalizations increased from 1996 to 2012, despite decreasing in the general population(38). A recent study in the Nationwide Inpatient Sample also demonstrated increased odds of atherosclerotic CVD (OR 1.46 [95% CI 1.41–1.51]) in hospitalized SLE patients compared to age-sex-race- and calendar year-matched non-SLE patients, although that study employed a single ICD-9 SLE code to identify the analytic sample, possibly causing misclassification(39). Additionally, the increased MI and stroke risks among SLE patients before age 40 in our current study emphasizes the risk imparted by accelerated premature atherosclerosis observed in past studies, particularly among young women (1, 2, 40).

The biology underlying accelerated atherosclerosis in SLE is complex and multifactorial. The vascular, immune, and inflammatory processes of SLE, including Raynaud's phenomenon, antiphospholipid antibodies, systemic inflammation, circulating immune complexes, and atherogenic lipids, all contribute to CVD risk (41, 42). Emerging data support a role for genetic determinants of CVD in individuals with SLE compared to non-SLE (43). Untreated and unrecognized traditional (overweight/obesity, hypertension, hyperlipidemia), and non-traditional (disease activity, duration, and treatment [anti-malarial, corticosteroid, immunosuppressive]) risk factors in younger SLE patients may also contribute to the high CVD risk (44, 45). Additionally, SLE patients in Medicaid receive substandard preventative care and SLE treatment (46), as evidenced in the current study by the relatively low baseline use of hydroxychloroquine (37%), but high use of corticosteroids (39%). In fact, similar to other analyses suggesting that SLE patients are undertreated with lipid–lowering therapies (47), we previously noted that SLE patients in Medicaid are 66% less likely to have lipid tests and 82% less likely) to fill a statin prescription than matched DM patients (48). While SLE Medicaid patients may receive less CVD-protective therapies than DM, our analysis adjusted for use of these cardiac medications.

Our study has both strengths and limitations. We included administrative claims from >40,000 SLE, >80,000 DM, and >160,000 age- and sex-matched general population patients in a large, diverse, non-academic cohort treated in usual care settings. Although we used previously developed algorithms to identify SLE and DM patients, use of an administrative case definition for SLE and DM may introduce misclassification and overestimate the prevalence of SLE (14, 49). We included a 6-month baseline period that may incompletely capture baseline variables, although results were similar when we tested expansion to a 12-month baseline period. We included lifestyle factors such as cigarette smoking and obesity, although these are not well captured in administrative data. Other important factors related to CVD risk, such as physical exercise, diet, and alcohol consumption and clinical/laboratory results, including antiphospholipid antibodies and disease activity indices in SLE patients are unfortunately not available in administrative claims data. As fatal events cannot be easily categorized as CVD-related or -unrelated in administrative data, we restricted our analysis to non-fatal events. We were thus unable to estimate the association of SLE or DM with fatal CVD in our population, but did adjust for the competing risk of all-cause death in our analyses. Additionally, as this was a prevalent SLE population and stroke and CVD events occurring in the first few years after SLE diagnosis may not have been captured (36, 37), these results may actually underestimate CVD risks for patients with incident SLE. Although our SLE and DM cohorts were mutually exclusive, future studies may assess whether the co-occurrence of these diagnoses further increase CVD risk. Despite the mutual exclusion of the cohorts, we did note some insulin use in the SLE and general population cohorts, which may have been prescribed during glucocorticoid therapy. Additionally, although our main analysis reports the relative risks comparing SLE to DM, we note that the risk differences, particularly in the older age groups (40–49 years or 50–65 years), were small. Finally, our results may not be generalizable to patients with higher socioeconomic status or those with private medical insurance who have lower prevalence of traditional CVD risk factors and events. However, as all subjects in this study were enrolled in Medicaid, the *relative* comparisons to age- and sex-matched patients likely would be similar in other sociodemographic groups.

In conclusion, in this large Medicaid cohort, despite lower prevalence of traditional CVD risk factors, SLE patients had higher non-fatal stroke but similar MI risks than DM; MI and stroke risks were over doubled in SLE patients aged 18–39 years compared to their DM counterparts. In DM, excess CVD mortality is also particularly prominent in younger patients and substantial efforts are directed at CVD risk stratification and prevention; guidelines are available for statin initiation, antihypertensive treatment, and other lifestyle and pharmacologic interventions (6, 10, 11, 50). However, no such guidelines or CVD risk stratification tools exist for primary or secondary prevention in SLE patients. Our data suggest that early and aggressive screening and better means of personalized CVD risk stratification and modification for SLE patients are needed. Furthermore, future studies identifying the underlying mechanism of the observed excess CVD risk in SLE compared to DM are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovation:

- Cardiovascular disease (CVD) risk is elevated in systemic lupus erythematosus (SLE), especially among young patients, and remains the leading cause of death.
- While the prototype for aggressive treatment to reduce CVD risk is Diabetes Mellitus (DM), another chronic disease associated with premature atherosclerosis, whether the CVD risk in SLE is as severe as in DM is unknown.
- Our study showed that despite lower prevalence of traditional CVD risk factors, SLE patients had higher non-fatal stroke but similar MI risks than DM; MI and stroke risks were over twice the risk in SLE patients aged 18–39 years compared to their DM counterparts.
- Our data suggest that early and aggressive screening and better means of personalized CVD risk stratification and modification for SLE patients are needed.

Table 1.

Baseline Characteristics of Age- and Sex- matched Systemic Lupus Erythematosus (SLE), Diabetes Mellitus (DM), and General Population Patients (Non-SLE/Non-DM) enrolled in Medicaid (2007–2010)

	SLE N=40,212	DM N=80,424	General Population N=160,848
Sociodemographic Variables			
Female (N,%)	37,174 (92.45)	74,348 (92.45)	148,696 (92.45)
Age (mean, SD)	40.34 (12.14)	40.35 (12.14)	40.34 (12.14)
Age group 18–39 (N,%)	19,726 (49.06)	39,402 (48.99)	78,806 (48.99)
Age group 40–49 years (N,%)	10,509 (26.13)	21,055 (26.18)	42,193 (26.23)
Age group 50–65 years (N,%)	9,977 (24.81)	19,967 (24.83)	39,849 (24.77)
Race/Ethnicity (N,%)			
African American	16,878 (41.97)	24,184 (30.07)	33,997 (21.14)
Hispanic	6,535 (16.25)	13,801 (17.16)	40,682 (25.29)
Asian	1,177 (2.93)	2,257 (2.81)	5,326 (3.31)
White	14,039 (34.91)	36,755 (45.70)	74,435 (46.28)
Native American	393 (0.98)	1,129 (1.40)	1,590 (0.99)
Other	1,190 (2.96)	2,298 (2.86)	4,818 (3.00)
Residential Region (N, %)			
Midwest	7,887 (19.61)	17,435 (21.68)	31,037 (19.30)
Northeast	8,560 (21.29)	16,043 (19.95)	30,769 (19.13)
South	15,703 (39.05)	31,530 (39.20)	53,081 (33.00)
West	8,062 (20.05)	15,416 (19.17)	45,961 (28.57)
Area Median Household Income (Mean, SD) **	45.72 (17.26)	44.46 (15.87)	47.94 (17.46)
CVD Comorbidities (N,%) *			
Angina	806 (2.00)	1,775 (2.21)	1,139 (0.71)
CABG	89 (0.22)	132 (0.16)	117 (0.07)
Coronary Atherosclerosis	1,825 (4.54)	3,884 (4.83)	2,603 (1.62)
Stroke	1,526 (3.79)	2,058 (2.56)	1,830 (1.14)
Acute MI	370 (0.92)	563 (0.70)	410 (0.25)
Old MI	344 (0.86)	484 (0.60)	342 (0.21)
PCI	180 (0.45)	355 (0.44)	235 (0.15)
Valvular Disease	2,641 (6.57)	2,174 (2.70)	2,085 (1.30)
Carotid Stenosis	231 (0.57)	506 (0.63)	470 (0.29)
Peripheral Vascular Disease	361 (0.90)	768 (0.95)	455 (0.28)
Heart failure	2,310 (5.74)	3,767 (4.68)	2,153 (1.34)
Any CVD Comorbidity at baseline (N, %) €	7,153 (17.79)	10,570 (13.14)	8,075 (5.02)
Cardiac Risk Factors (N, %)			
Hypertension	13,429 (33.40)	31,046 (38.60)	19,458 (12.10)

	SLE N=40,212	DM N=80,424	General Population N=160,848
Hyperlipidemia	3,844 (9.56)	18,178 (22.60)	9,334 (5.80)
Obesity	1,550 (3.85)	9,003 (11.19)	3,600 (2.24)
Smoking	2,588 (6.44)	4,508 (5.61)	6,159 (3.83)
SLE and Medical Comorbidities			
Lupus Nephritis (N, %)	6,741 (16.76)	N/A	N/A
Diabetic Nephropathy (N,%)	N/A	4,294 (5.34)	N/A
SLE Risk Adjustment Index[¥] (Mean, SD)	1.02 (1.99)	N/A	N/A
Charlson Comorbidity Index (Mean, SD)	0.89 (1.32)	0.56 (1.23)	0.36 (1.22)
Medications			
Glucocorticoid use (N, %)	15,526 (38.61)	5,727 (7.12)	6,571 (4.09)
Hydroxychloroquine use (N, %)	14,806 (36.82)	208 (0.26)	257 (0.16)
Immunosuppressant use (N, %)	7,929 (19.72)	769 (0.96)	645 (0.40)
Insulin use (N, %)	189 (0.47)	22,253 (27.67)	927 (0.58)
Statin use (N, %)	3,166 (7.87)	19,453 (24.19)	6,642 (4.13)
ACE/ARB use (N, %)	7,500 (18.65)	25,358 (31.53)	9,017 (5.61)
Beta blocker use (N, %)	4,286 (10.66)	8,881 (11.04)	6,327 (3.93)
Anticoagulation use (N, %)	2,306 (5.73)	1,251 (1.56)	1,234 (0.77)
Total Medications (Mean, SD)	9.88 (9.34)	10.27 (9.40)	3.44 (5.38)

Cohorts are mutually exclusive and matched on age and sex.

CVD: cardiovascular disease, CABG: *coronary artery bypass graft,* CVA: cerebrovascular accident, MI: myocardial infarction, PCI: percutaneous coronary intervention, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker.

[*] Comorbidities collected during baseline

[**] Zip-code level median household income based on the 2010 US Census (Missing data in 316). Cell sizes under 11 suppressed per Center for Medicare and Medicaid Services (CMS) policy.

[6,] Any CVD" defined as presence of any of the following during baseline: 'old MI', acute MI, stroke, heart failure, coronary atherosclerosis, PCI or CABG.

[¥] SLE specific index ranges from 0–46.

[∞] Glucocorticoid medications included the following: prednisone, methylprednisolone, dexamethasone, hydrocortisone, prednisolone, and cortisone defined as prednisone equivalents.

[α] Immunosuppressant medications included the following: mycophenolate mofetil, mycophenolic acid, cyclophosphamide, azathioprine, cyclosporine, methotrexate, leflunomide, rituximab, and tacrolimus.

Table 2.

Annual Rates of Cardiovascular Disease (combined Myocardial Infarction or Stroke), and Myocardial Infarction and Stroke separately in Systemic Lupus Erythematosus (SLE), Diabetes Mellitus (DM), and General Population (Non-SLE/Non-DM) Medicaid patients (2007–2010)

	Number of Patients	Mean Age at Event, years (SD)	Number of Events	Person-years, mean (SD)	IR* (95% CI)	IRR**[a] (*Reference: DM*) (95%CI)	IRR**[b] (*Reference: General population*) (95%CI)
Cardiovascular Disease							
General Population	160,848	52.56 (8.78)	657	1.73 (1.14)	2.36 (2.19–2.55)	**0.34 (0.33–0.34)**	1.0 (ref.)
DM	80,424	49.38 (9.92)	1060	1.86 (1.11)	7.07 (6.66–7.51)	1.0 (ref.)	**2.98 (2.90–3.06)**
SLE	40,212	45.04 (12.49)	672	1.86 (1.11)	8.99 (8.34–9.70)	**1.27 (1.23–1.30)**	**3.78 (3.67–3.89)**
Myocardial Infarction							
General Population	160,848	53.40 (8.24)	233	1.73 (1.14)	0.83 (0.73–0.94)	**0.28 (0.27–0.29)**	1.0 (ref.)
DM	80,424	49.87 (9.40)	454	1.87 (1.11)	3.01 (2.75–3.30)	1.0 (ref.)	**3.60 (3.49–3.71)**
SLE	40,212	46.80 (12.16)	243	1.87 (1.11)	3.23 (2.85–3.66)	**1.07 (1.04–1.10)**	**3.85 (3.72–3.99)**
Stroke							
General Population	160,848	52.15 (8.99)	433	1.73 (1.14)	1.55 (1.41–1.70)	**0.37 (0.36–0.38)**	1.0 (ref.)
DM	80,424	49.16 (10.30)	642	1.87 (1.11)	4.27 (3.95–4.61)	1.0 (ref.)	**2.74 (2.66–2.82)**
SLE	40,212	44.14 (12.59)	448	1.87 (1.11)	5.97 (5.44–6.55)	**1.40 (1.36–1.44)**	**3.82 (3.71–3.94)**

SLE= Systemic Lupus Erythematosus, DM=Diabetes Mellitus, SD= Standard Deviation

*IR = incidence rate, annual CVD event rate per 1,000 person years

**IRR= incidence rate ratio

[a]Diabetes Mellitus used as the reference group;

[b]General Population used as the reference group.

Table 3.

Multivariable Sub-distribution Hazard Ratios for Cardiovascular Disease (combined Myocardial Infarction or Stroke), and Myocardial Infarction and Stroke separately in Systemic Lupus Erythematosus (SLE), Diabetes Mellitus (DM), and General Population (Non-SLE/Non-DM) Medicaid patients (2007–2010)

	Model A[a] (HRsd [95%CI])	Model B[a] (HRsd [95%CI])	Model A[b] (HRsd [95%CI])	Model B[b] (HRsd [95%CI])
	(Reference: Diabetes Mellitus)		(Reference: General Population)	
Cardiovascular Disease				
General Population	**0.34 (0.30–0.37)**	**0.47 (0.43–0.53)**	1.0 (Ref)	1.0 (Ref)
DM	1.0 (Ref)	1.0 (Ref)	**2.98 (2.71–3.29)**	**2.11 (1.89–2.35)**
SLE	**1.22 (1.10–1.34)**	**1.27 (1.15–1.40)**	**3.63 (3.25–4.04)**	**2.67 (2.38–2.99)**
Myocardial Infarction				
General Population	**0.27 (0.23–0.32)**	**0.38 (0.32–0.45)**	1.0 (Ref)	1.0 (Ref)
DM	1.0 (Ref)	1.0 (Ref)	**3.65 (3.11–4.28)**	**2.63 (2.21–3.14)**
SLE	1.06 (0.91–1.24)	1.09 (0.93–1.28)	**3.86 (3.22–4.63)**	**2.87 (2.38–3.47)**
Stroke				
General Population	**0.37 (0.33–0.42)**	**0.53 (0.47–0.61)**	1.0 (Ref)	1.0 (Ref)
DM	1.0 (Ref)	1.0 (Ref)	**2.70 (2.39–3.05)**	**1.87 (1.64–2.14)**
SLE	**1.31 (1.16–1.48)**	**1.37 (1.21–1.55)**	**3.53 (3.09–4.04)**	**2.56 (2.23–2.95)**

HR= hazard ratio, sd=subdistribution, SLE= Systemic Lupus Erythematosus; DM=Diabetes Mellitus

Model A: Includes Age (continuous), sex, race/ethnicity (White, African American, Hispanic, Asian, Native American, other), region of residence, year and zip code-level socioeconomic status (reference 28)

Model B: Includes Model A + Charlson score (excluding diabetes and SLE), number of medications, cardiac comorbidities at index date (hypertension, hyperlipidemia, smoking, and obesity)

[a]Diabetes Mellitus was used as the reference group;

[b]General Population was used as the reference group**. Bold= p<0.05**

Table 4.

Annual Rates of Myocardial Infarction or Stroke in Systemic Lupus Erythematosus (SLE), Diabetes Mellitus (DM), and General Population (Non-SLE/ Non-DM) Medicaid patients by age group (2007–2010)

	Myocardial Infarction				Stroke	
	Number of Patients	Number of Events	Person-years, mean (SD)	IR* (95% CI)	Number of Events	IR* (95%CI))
Age group 18–39 years						
General Population	78,806	17	1.67 (1.14)	0.13 (0.08–0.21)	49	0.37 (0.28–0.49)
DM	39,402	73	1.84 (1.12)	1.00 (0.80–1.26)	73	1.86 (1.57–2.20)
SLE	19, 726	85	1.85 (1.12)	2.32 (1.88–2.87)	181	4.97 (4.30–5.75)
Age group 40–49 years						
General Population	42, 193	68	1.77 (1.13)	0.91 (0.72–1.15)	49	1.71 (1.44–2.03)
DM	21,055	162	1.89 (1.11)	4.07 (3.49–4.75)	73	5.08 (4.43–5.83)
SLE	10,509	57	1.89 (1.10)	2.87 (2.21–3.72)	181	5.41 (4.48–6.54)
Age group 50–65 years						
General Population	39,849	148	1.82 (1.14)	2.04 (1.74–2.40)	256	3.54 (3.13–4.00)
DM	19,967	219	1.91 (1.09)	5.74 (5.03–6.55)	305	8.02 (7.17–8.97)
SLE	9,977	101	1.89 (1.10)	5.35 (4.40–6.50)	160	8.49 (7.27–9.91)

SLE= Systemic Lupus Erythematosus, DM=Diabetes Mellitus, SD= Standard Deviation

*IR = incidence rate, annual CVD event rate per 1,000 person years

Table 5:

Multivariable Sub-distribution Hazard Ratios for Cardiovascular Disease (combined Myocardial Infarction or Stroke), and Myocardial Infarction and Stroke separately in Systemic Lupus Erythematosus, Diabetes Mellitus, and General Population (Non-SLE/Non-DM) Medicaid patients, stratified by Age group (2007–2010)

	Age 18–39 years (HRsd [95%CI])	Age 40–49 years (HRsd [95%CI])	Age 50–65 years (HRsd [95%CI])	Age 18–39 years (HRsd [95%CI])	Age 40–49 years (HRsd [95%CI])	Age 50–65 years (HRsd[95%CI])
	(Reference: Diabetes Mellitus)			(Reference: General Population)		
	Cardiovascular Disease					
General Population	**0.29 (0.21–0.39)**	**0.44 (0.36–0.54)**	**0.55 (0.47–0.63)**	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
DM	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	**3.51 (2.58–4.79)**	**2.26 (1.85–2.75)**	**1.83 (1.59–2.11)**
SLE	**2.22 (1.81–2.71)**	0.96 (0.79–1.16)	1.03 (0.88–1.20)	**7.79 (5.77–10.50)**	**2.16 (1.74–2.69)**	**1.88 (1.59–2.22)**
	Myocardial Infarction					
General Population	**0.22 (0.12–0.40)**	**0.32 (0.24–0.45)**	**0.45 (0.36–0.57)**	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
DM	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	**4.51 (2.52–8.07)**	**3.08 (2.25–4.23)**	**2.23 (1.77–2.81)**
SLE	**2.04 (1.44–2.88)**	0.76 (0.56–1.04)	0.96 (0.75–1.22)	**9.19 (5.28–16.01)**	**2.34 (1.63–3.37)**	**2.13 (1.62–2.79)**
	Stroke					
General Population	**0.30 (0.21–0.44)**	**0.55 (0.43–0.71)**	**0.60 (0.50–0.72)**	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
DM	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	**3.29 (2.28–4.75)**	**1.82 (1.41–2.33)**	**1.66 (1.39–1.98)**
SLE	**2.25 (1.77–2.87)**	1.10 (0.87–1.41)	1.07 (0.88–1.30)	**7.41 (5.21–10.56)**	**2.01 (1.53–2.63)**	**1.77 (1.44–2.18)**

HR= hazard ratio, sd=subdistribution, SLE= Systemic Lupus Erythematosus; DM=Diabetes Mellitus

*Model adjusted for Age (continuous), sex, race/ethnicity (White, African American, Hispanic, Asian, Native American, other), region of residence, year and zip code-level socioeconomic status (reference 28), Charlson score (excluding diabetes and SLE), number of medications, cardiac comorbidities at index date (hypertension, hyperlipidemia, smoking, and obesity)

Bold= $p<0.05$

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