

# Long-Term Cardiovascular Outcomes in Systemic Lupus Erythematosus



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## ABSTRACT

**BACKGROUND** Data on long-term cardiovascular outcomes in systemic lupus erythematosus (SLE) are sparse.

**OBJECTIVES** This study sought to examine the long-term risk and prognosis associated with cardiovascular outcomes, including heart failure (HF), in patients with SLE.

**METHODS** Using Danish administrative registries, risks of outcomes were compared between SLE patients (diagnosed 1996 to 2018, no history of cardiovascular disease) and age-, sex-, and comorbidity-matched control subjects from the background population (matched 1:4). Furthermore, mortality following HF diagnosis was compared between SLE patients developing HF and age- and sex-matched non-SLE control subjects with HF (matched 1:4).

**RESULTS** A total of 3,411 SLE patients (median age: 44.6 years [25th to 75th percentile: 31.9 to 57.0 years]; 14.1% men) were matched with 13,644 control subjects. The median follow-up was 8.5 years (25th to 75th percentile: 4.0 to 14.4 years). Absolute 10-year risks of outcomes were: HF, 3.71% (95% confidence interval [CI]: 3.02% to 4.51%) for SLE patients, 1.94% (95% CI: 1.68% to 2.24%) for control subjects; atrial fibrillation, 4.35% (95% CI: 3.61% to 5.18%) for SLE patients, 2.82% (95% CI: 2.50% to 3.16%) for control subjects; ischemic stroke, 3.75% (95% CI: 3.06% to 4.54%) for SLE patients, 1.92% (95% CI: 1.66% to 2.20%) for control subjects; myocardial infarction, 2.17% (95% CI: 1.66% to 2.80%) for SLE patients, 1.49% (95% CI: 1.26% to 1.75%) for control subjects; venous thromboembolism, 6.03% (95% CI: 5.17% to 6.98%) for SLE patients, 1.68% (95% CI: 1.44% to 1.95%) for control subjects; and the composite of implantable cardioverter-defibrillator implantation/ventricular arrhythmias/cardiac arrest, 0.89% (95% CI: 0.58% to 1.31%) for SLE patients, 0.30% (95% CI: 0.20% to 0.43%) for control subjects. SLE with subsequent HF was associated with higher mortality compared with HF without SLE (adjusted hazard ratio: 1.50; 95% CI: 1.08 to 2.08).

**CONCLUSIONS** SLE patients had a higher associated risk of HF and other cardiovascular outcomes compared with matched control subjects. Among patients developing HF, a history of SLE was associated with higher mortality. (J Am Coll Cardiol 2021;77:1717-27) © 2021 by the American College of Cardiology Foundation.

Systemic lupus erythematosus (SLE) is an autoimmune disorder with a predilection for women characterized by chronic inflammation and immune complex deposition in involved organs (1,2). Clinical manifestations are heterogeneous and include the skin, musculoskeletal system, kidneys,

and central nervous system (1). The prevalence of cardiovascular involvement in SLE is estimated to be more than 50%, but estimates vary substantially, possibly because of differences in patient selection (3). Most studies have focused on pericarditis (3), atherosclerotic events (including stroke and



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## ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HF = heart failure

HR = hazard ratio

ICD = implantable  
cardioverter-defibrillator

SLE = systemic lupus  
erythematosus

myocardial infarction) (4-7), and venous thromboembolism (8). Other cardiovascular manifestations, including heart failure (HF) (9-11), arrhythmic outcomes (12-16), and endocarditis (17,18), have also been described, but data on the long-term risk and prognosis associated with these cardiovascular outcomes are sparse and limited by short follow-up (10,12,13,18) or small, selected study populations (14,16,18). HF is generally associated with high morbidity and mortality (19), which makes it particularly important to quantify the risk of its development in SLE patients and determine the prognosis in SLE patients who develop HF. Assessing the long-term risk of HF and other cardiovascular manifestations in a large, unselected cohort of SLE patients is a necessary step before investigation of optimal treatment strategies in SLE patients with cardiovascular manifestations. Consequently, the aims of this nationwide cohort study were to examine the long-term risk of incident HF and other adverse cardiovascular outcomes in patients diagnosed with SLE compared with matched control subjects from the Danish background population and to compare mortality in patients with incident HF with and without SLE.

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## METHODS

**DATA SOURCES.** Denmark has a universal, tax-funded health care system. All Danish residents are assigned a unique personal identification number that is used in contacts with the health care system and enables individual-level linkage between nationwide registries. For this study, we used: 1) The Danish National Patient Registry, which contains information on hospital contacts including discharge diagnoses according to the International Classification of Diseases-8th revision and -10th revision and surgical procedures according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures (20); 2) The Danish National Prescription Registry, which contains information on claimed drug prescriptions in Danish pharmacies (21); and 3) The Danish Civil Registration System, which contains information on birth date, sex, and vital status, including date of death and emigration (22).

**STUDY POPULATION.** We identified all Danish residents with a first-time SLE diagnosis between January 1, 1996 and June 30, 2018. Patients were excluded if they had a history (primary or secondary inpatient or outpatient diagnosis) of HF, atrial fibrillation/flutter, ischemic stroke, ischemic heart

disease, venous thromboembolism (deep venous thrombosis or pulmonary embolism), ventricular arrhythmias (ventricular tachycardia/flutter/fibrillation), cardiac arrest, atrioventricular block (advanced 2nd or 3rd degree), sinoatrial dysfunction, or endocarditis, or if they had an implantable cardioverter-defibrillator (ICD) or pacemaker implantation before SLE diagnosis (Supplemental Table 1 for diagnosis and procedure codes). For SLE patients, index was defined as the date of diagnosis. Control subjects from the background population were assigned the same index date as an SLE patient and subject to the same exclusion criteria. Each patient was matched with 4 control subjects from the background population by age (up to 1-year difference), sex, year of index date, and comorbidities before inclusion (peripheral artery disease, diabetes, hypertension, chronic obstructive pulmonary disease, chronic kidney disease) using risk-set matching.

## COMORBIDITY AND CONCOMITANT PHARMACOTHERAPY.

Comorbidity was obtained using primary and secondary inpatient and outpatient diagnoses any time before index (Supplemental Table 1 for diagnosis codes) with the following exceptions: diabetes and hypertension were identified using claimed drug prescriptions as described previously (23,24). Concomitant pharmacotherapy was defined using claimed prescriptions within 6 months before index. Medical treatment after SLE diagnosis was defined by claimed prescriptions within 6 months after diagnosis, and medical treatment after HF diagnosis was defined by claimed prescriptions within 4 months after diagnosis (Supplemental Table 2 for Anatomical Therapeutic Chemical Classification System codes).

**OUTCOMES.** Outcomes were defined as primary or secondary inpatient or outpatient diagnoses, unless otherwise stated (Supplemental Table 1 for diagnosis and procedure codes). No postmortem diagnoses were included. The primary outcome was incident HF. Secondary incident outcomes were atrial fibrillation/flutter; ischemic stroke (only inpatient diagnoses); myocardial infarction (only inpatient diagnoses); venous thromboembolism; composite of ICD implantation, ventricular arrhythmias (ventricular tachycardia/flutter/fibrillation), and cardiac arrest; composite of pacemaker implantation, advanced second- or third-degree atrioventricular block, and sinoatrial dysfunction; endocarditis (inpatient stay of at least 14 days or <14 days if the patient died during hospitalization [25]); and all-cause mortality. Diagnosis codes for outcomes have been validated with high positive predictive values in the Danish National Patient Registry (25-30). Patients were followed from

index until the outcome of interest, death, emigration, or end of the study (December 31, 2018), whichever came first.

**SECONDARY ANALYSIS.** In a secondary analysis, we used risk-set matching to match SLE patients who developed HF 1:4 by age (up to 1-year difference), sex, year of index date (HF diagnosis), and type of diagnosis (inpatient or outpatient diagnosis) with non-SLE control subjects with HF. The primary outcome of this analysis was all-cause mortality.

**STATISTICS.** Baseline characteristics were reported as frequencies and percentages for categorical variables and median (25th to 75th percentile) for continuous variables. Differences in baseline characteristics between groups were examined using the Wilcoxon test for continuous variables and the chi-square or Fisher exact test for categorical variables. Absolute risks of outcomes except all-cause mortality were estimated using the Aalen-Johansen estimator, taking the competing risk of death into account; differences between groups were assessed using Gray test. Absolute risks of all-cause mortality were estimated using the Kaplan-Meier estimator; differences between groups were assessed using the log-rank test. Incidence rates per 1,000 person-years with 95% confidence intervals (CI) were calculated for all outcomes. Cause-specific Cox regression models conditional on the matching were used to examine rates of outcomes in SLE patients and matched control subjects. Because of differences in baseline characteristics, hazard ratios (HRs) with 95% CIs were adjusted for a history of malignancy and liver disease. The proportional hazards assumption was not met for several outcomes (HF, atrial fibrillation/flutter, ischemic stroke, venous thromboembolism, all-cause mortality); therefore, incidence rates and HRs for these outcomes were determined for 2 periods in landmark analyses (0 to 365 days and 366 days to full follow-up). There was no interaction between SLE status and sex or calendar year on the rate of outcomes. However, there was a significant interaction with age (both as a continuous variable and a categorical variable above/below the median age). Therefore, Cox regression analyses were also determined for age groups according to the median age (<44.6 and ≥44.6 years). In the secondary analysis comparing all-cause mortality between SLE and non-SLE patients with HF, the proportional hazards assumption was fulfilled, and HRs were adjusted for a history of ischemic stroke, ischemic heart disease, atrial fibrillation, hypertension, diabetes, peripheral artery disease, venous thromboembolism, malignancy, chronic kidney disease (no chronic kidney

**TABLE 1 Baseline Characteristics of Study Population**

	Background Population (n = 13,644)	SLE Population (n = 3,411)	p Value
<b>Demographics</b>			
Age, yrs	44.6 (31.9–57.0)	44.6 (31.9–57.0)	N/A
Male	1,928 (14.1)	482 (14.1)	N/A
<b>Comorbidities</b>			
Hypertension	1,928 (14.1)	482 (14.1)	N/A
Peripheral artery disease	140 (1.0)	35 (1.0)	N/A
Diabetes	240 (1.8)	60 (1.8)	N/A
Chronic kidney disease	696 (5.1)	174 (5.1)	N/A
Chronic obstructive pulmonary disease	396 (2.9)	99 (2.9)	N/A
Malignancy	474 (3.5)	169 (5.0)	<0.0001
Liver disease	107 (0.8)	95 (2.8)	<0.0001
<b>Medical treatment</b>			
Lipid-lowering medication	601 (4.4)	127 (3.7)	0.08
Acetylsalicylic acid	370 (2.7)	166 (4.9)	<0.0001
ADP receptor inhibitors	22 (0.2)	20 (0.6)	<0.0001
Beta-blockers	584 (4.3)	146 (4.3)	1.00
Calcium-channel blockers	667 (4.9)	244 (7.2)	<0.0001
RAS inhibitors	1,139 (8.4)	289 (8.5)	0.81
Loop diuretics	310 (2.3)	167 (4.9)	<0.0001

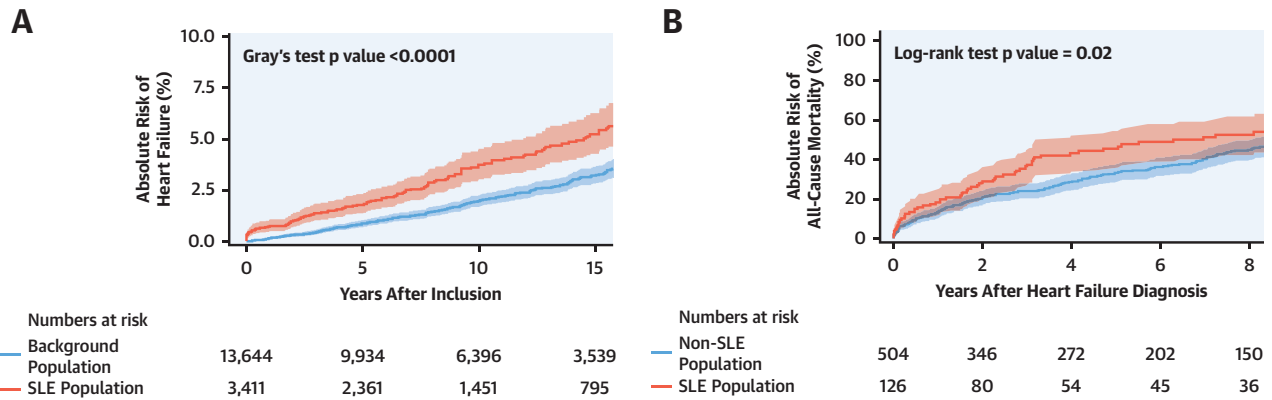
Values are median (25th to 75th percentile) or n (%).  
 ADP = adenosine diphosphate; N/A = not applicable; RAS = renin-angiotensin system; SLE = systemic lupus erythematosus.

disease; non-end-stage kidney disease; end-stage kidney disease), chronic obstructive pulmonary disease, and liver disease.

The level of statistical significance was set at 5%. Data management and statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

**SENSITIVITY ANALYSES.** To test the robustness of our findings, we restricted the definition of HF to primary HF diagnoses and inpatient HF diagnoses. Additionally, we examined the rate of HF in SLE patients and matched control subjects in a cause-specific Cox regression for HF adjusting for incident myocardial infarction as a time-dependent covariate and incident myocardial infarction, atrial fibrillation, and ICD implantation/ventricular arrhythmia/cardiac arrest as a time-dependent covariate. We also performed an analysis that excluded all patients who were diagnosed with HF or died within the first 14 days after index (11 SLE patients and 8 control subjects). In this analysis, index was set 14 days after the original index date. Finally, to improve the validity of the SLE diagnosis, we used the following previously validated definition of SLE (positive predictive value: 86% to 89%) to identify cases: SLE diagnosis followed by 1 year of outpatient follow-up or consecutive inpatient admissions with SLE diagnoses with <3-month intervals during the first year

**CENTRAL ILLUSTRATION Absolute Risk of Heart Failure in Patients With Systemic Lupus Erythematosus and Matched Control Subjects and Absolute Risk of All-Cause Mortality Following Heart Failure Diagnosis**



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(A) Absolute risk of HF in SLE patients and matched control subjects from the background population. (B) Absolute risk of all-cause mortality in SLE patients with HF and matched non-SLE control subjects with HF. For all-cause mortality, Kaplan-Meier estimates are presented; for HF, Aalen-Johansen estimates (taking the competing risk of death into account) are presented. HF = heart failure; SLE = systemic lupus erythematosus.

of follow-up (31). In this analysis, the index date was the date of fulfilment of the criteria.

**ETHICS.** This study was approved by the Capital Region of Denmark (approval number: P-2019-348) in accordance with the General Data Protection Regulation. Registry-based studies in which individuals cannot be identified do not require ethical approval in Denmark.

**RESULTS**

Of the 4,271 patients diagnosed with SLE in Denmark between 1996 and 2018, 3,462 patients were included after application of exclusion criteria. Within 6 months after SLE diagnosis, 36.3% of patients redeemed a prescription of prednisolone, 34.4% hydroxychloroquine, 27.9% nonsteroidal anti-inflammatory drugs, 11.5% azathioprine, 5.0% methotrexate, and 3.1% another disease-modifying anti-rheumatic drug (cyclophosphamide, ciclosporin, mycophenolate mofetil, sulfasalazine). Of the 3,462 patients eligible for matching, 3,411 patients were matched with 13,644 control subjects from the background population. Table 1 shows baseline characteristics for the SLE and background population. The median age of the study population was 44.6 years (25th to 75th percentile: 31.9 to 57.0 years), and 14.1% were men.

**HEART FAILURE.** The median follow-up from index until HF diagnosis, death, emigration, or end of the

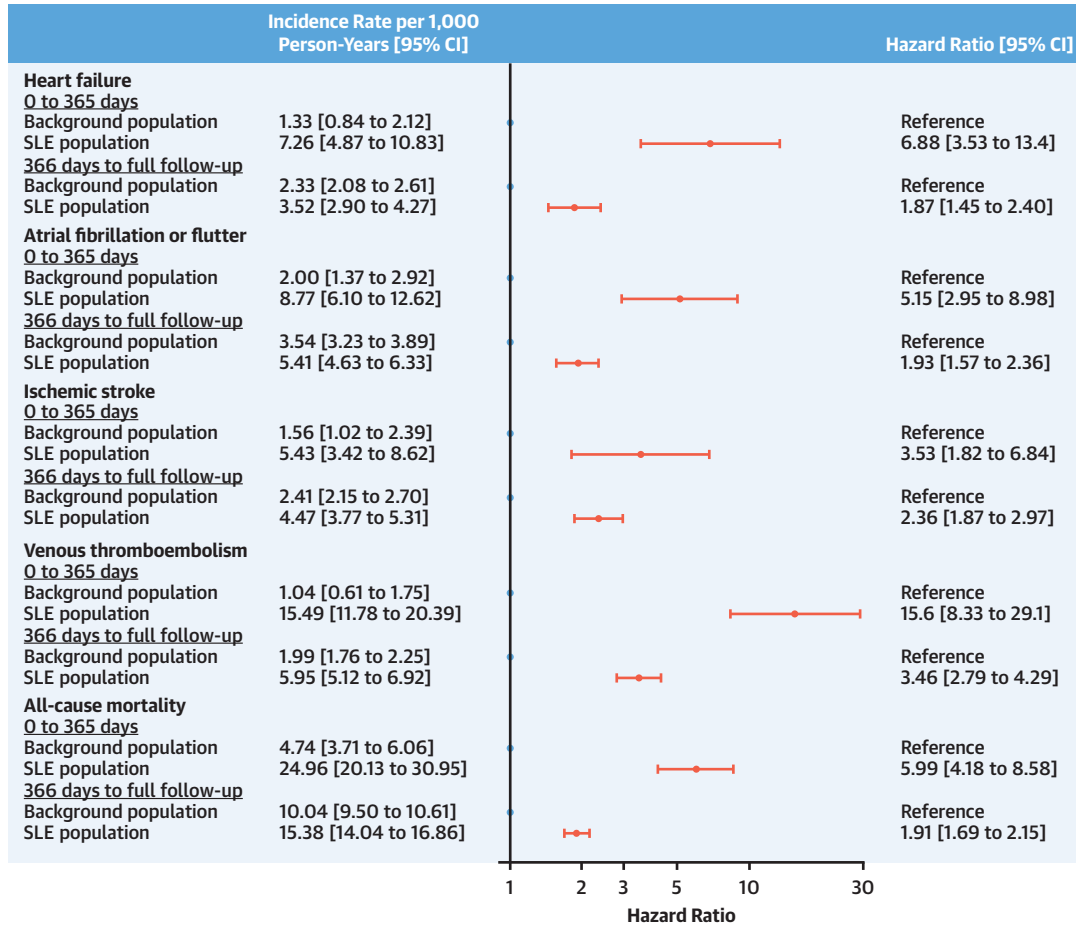
study was 8.5 years (25th to 75th percentile: 4.0 to 14.4 years) and 9.4 years (25th to 75th percentile: 4.6 to 15.3 years) for the SLE and background population, respectively. The Central Illustration shows the absolute risk of incident HF for the groups. The absolute 10-year risk of incident HF was 3.71% (95% CI: 3.02% to 4.51%) for SLE patients and 1.94% (95% CI: 1.68% to 2.24%) for the background population. Figure 1 shows unadjusted incidence rates per 1,000 person-years and adjusted HRs of outcomes. During the first 365 days, the incidence rate of HF per 1,000 person-years was 7.26 (95% CI: 4.87 to 10.83) in SLE patients and 1.33 (95% CI: 0.84 to 2.12) in the background population (adjusted HR: 6.88; 95% CI: 3.53 to 13.41). From day 366 until the end of follow-up, the incidence rate of HF per 1,000 person-years was 3.52 (95% CI: 2.90 to 4.27) in SLE patients and 2.33 (95% CI: 2.08 to 2.61) in the background population (adjusted HR: 1.87; 95% CI: 1.45 to 2.40). Supplemental Table 3 shows HRs according to age group. The rate of incident HF was significantly higher in SLE patients compared with the background population in both time periods irrespective of age. However, patients younger than the median age had higher rates of HF relative to the background population than patients older than the median age in both time periods.

**ALL-CAUSE MORTALITY AFTER DIAGNOSIS OF HF.**

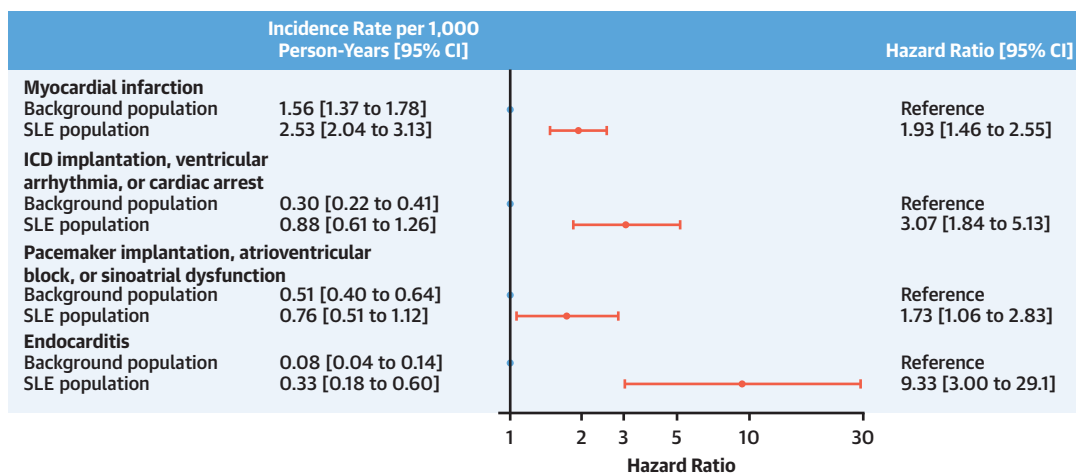
A total of 127 SLE patients developed HF during follow-up; of these, 126 patients were matched with 504 non-SLE patients with HF based on age, sex, and

**FIGURE 1** Unadjusted Incidence Rates and Adjusted Hazard Ratios of Outcomes

**A**



**B**



**(A)** Outcomes for which the proportional hazards assumption was not fulfilled (estimates for 0 to 365 days and 366 days to full follow-up). **(B)** Outcomes for which the proportional hazards assumption was fulfilled (estimates for full follow-up). CI = confidence interval; ICD = implantable cardioverter-defibrillator; SLE = systemic lupus erythematosus.

**TABLE 2 Characteristics of HF Patients With and Without SLE**

	Non-SLE Population (n = 504)	SLE Population (n = 126)	p Value
<b>Demographics</b>			
Age, yrs	65.4 (54.7-74.5)	65.4 (54.7-74.5)	N/A
Male	136 (27.0)	34 (27.0)	N/A
<b>Comorbidities before HF diagnosis</b>			
Ischemic stroke	54 (10.7)	9 (7.1)	0.95
Ischemic heart disease	187 (37.1)	29 (23.0)	0.003
Atrial fibrillation/flutter	128 (25.4)	21 (16.7)	0.04
Hypertension	240 (47.6)	75 (59.5)	0.02
Peripheral artery disease	38 (7.5)	10 (7.9)	0.88
Venous thromboembolism	37 (7.3)	11 (8.7)	0.60
Diabetes	81 (16.1)	13 (10.3)	0.10
Chronic kidney disease			
None	462 (91.7)	101 (80.2)	0.0007
Non-end-stage kidney disease	35 (6.9)	22 (17.5)	
End-stage kidney disease and/or dialysis	7 (1.4)	≤3 (≤2.4)*	
Chronic obstructive pulmonary disease	94 (18.7)	24 (19.1)	0.92
Malignancy	86 (17.1)	22 (17.5)	0.92
Liver disease	26 (5.2)	8 (6.4)	0.60
<b>Medical treatment before HF diagnosis†</b>			
Lipid-lowering medication	161 (31.9)	29 (23.0)	0.05
Acetylsalicylic acid	155 (30.8)	31 (24.6)	0.18
ADP receptor inhibitors	41 (8.1)	13 (10.3)	0.43
Beta-blockers	159 (31.6)	43 (34.1)	0.58
Calcium-channel blockers	103 (20.4)	32 (25.4)	0.22
RAS inhibitors	185 (36.7)	42 (33.3)	0.48
Loop diuretics	175 (34.7)	48 (38.1)	0.48
<b>Medical treatment after HF diagnosis‡</b>			
RAS inhibitors	297 (58.9)	59 (46.8)	0.01
Beta-blockers	278 (55.2)	57 (45.2)	0.05
Mineralocorticoid receptor antagonists	104 (20.6)	24 (19.1)	0.69
Loop diuretics	289 (57.3)	62 (49.2)	0.10
Antiarrhythmic/frequency-regulating medication§	97 (19.3)	16 (12.7)	0.09

Values are median (25th to 75th percentile) or n (%). \*In Denmark, ethics approval is not required for registry-based studies in which individuals cannot be identified; to ensure that data are not identifiable, we are not allowed to report estimates for outcomes where n ≤3. †Within 6 months before HF diagnosis. ‡Within 4 months after HF diagnosis. §Digoxin, amiodarone, dronedarone, flecainide, sotalol.  
HF = heart failure; other abbreviations as in Table 1.

HF presentation (inpatient/outpatient). The median follow-up from HF diagnosis until death, emigration, or end of the study was 3.1 years (25th to 75th percentile: 1.3 to 8.6 years) and 4.4 years (25th to 75th percentile: 1.6 to 8.9 years) for the SLE and non-SLE population, respectively. Table 2 summarizes characteristics for the SLE and non-SLE population with HF. SLE patients with HF had a lower prevalence of ischemic heart disease and atrial fibrillation and higher prevalence of hypertension before HF diagnosis compared with non-SLE control subjects. SLE patients with HF were less likely to receive renin-angiotensin system inhibitors and beta-blockers within 4 months after HF diagnosis compared with non-SLE control subjects. The Central Illustration displays the absolute risk of death according to

groups. The unadjusted all-cause mortality rate per 1,000 person-years was 106.08 (95% CI: 84.06 to 133.86) for SLE patients with HF and 76.10 (95% CI: 66.76 to 86.74) for matched non-SLE HF control subjects. In adjusted Cox regression, SLE patients with HF had a higher all-cause mortality rate than non-SLE HF control subjects (adjusted HR: 1.50; 95% CI: 1.08 to 2.08).

**SECONDARY ADVERSE CARDIOVASCULAR OUTCOMES.**

Table 3 shows the number of events for each outcome for the SLE and background population. Absolute risks of secondary outcomes are depicted in Figure 2 and Supplemental Figure 1. Absolute 10-year risks of outcomes were: atrial fibrillation/flutter, 4.35% (95% CI: 3.61% to 5.18%) for SLE patients, 2.82% (95% CI: 2.50% to 3.16%) for the background population; ischemic stroke, 3.75% (95% CI: 3.06% to 4.54%) for SLE patients, 1.92% (95% CI: 1.66% to 2.20%) for the background population; myocardial infarction, 2.17% (95% CI: 1.66% to 2.80%) for SLE patients, 1.49% (95% CI: 1.26% to 1.75%) for the background population; venous thromboembolism, 6.03% (95% CI: 5.17% to 6.98%) for SLE patients, 1.68% (95% CI: 1.44% to 1.95%) for the background population; the composite of ICD implantation, ventricular arrhythmia, and cardiac arrest, 0.89% (95% CI: 0.58% to 1.31%) for SLE patients, 0.30% (95% CI: 0.20% to 0.43%) for the background population; the composite of pacemaker implantation, atrioventricular block, and sinoatrial dysfunction, 0.59% (95% CI: 0.36% to 0.94%) for SLE patients, 0.45% (95% CI: 0.33% to 0.60%) for the background population; endocarditis, 0.31% (95% CI: 0.15% to 0.57%) for SLE patients, 0.05% (95% CI: 0.02% to 0.13%) for the background population; all-cause mortality, 14.11% (95% CI: 12.78% to 15.52%) for SLE patients, 7.97% (95% CI: 7.43% to 8.52%) for the background population. Figure 1 shows unadjusted incidence rates per 1,000 person-years and adjusted HRs of outcomes. Compared with the background population, SLE patients had higher rates of all outcomes; for HF, atrial fibrillation/flutter, ischemic stroke, venous thromboembolism, and all-cause mortality, HRs were highest within the first 365 days after diagnosis. Supplemental Table 3 shows HRs according to age group. Generally, rates of outcomes were higher in SLE patients compared with the background population irrespective of age. Patients younger than the median age had higher rates of outcomes relative to the background population than patients older than the median age.

**SENSITIVITY ANALYSES.** We found results similar to the main analysis after restricting the primary

outcome to primary HF diagnoses (0 to 365 days: HR: 6.66 [95% CI: 3.05 to 14.57], >365 days: HR: 1.85 [95% CI: 1.35 to 2.52]) and inpatient HF diagnoses (0 to 365 days: HR: 6.05 [95% CI: 2.87 to 12.78], >365 days: HR: 1.89 [95% CI: 1.43 to 2.50]). We also found results similar to the main analysis after including incident myocardial infarction (0 to 365 days: HR: 4.12 [95% CI: 1.80 to 9.40], >365 days: HR: 1.88 [95% CI: 1.46 to 2.42]) and incident myocardial infarction, atrial fibrillation, and ICD implantation/ventricular arrhythmia/cardiac arrest (0 to 365 days: HR: 3.81 [95% CI: 1.65 to 8.81], >365 days: HR: 1.86 [95% CI: 1.44 to 2.40]) as time-dependent covariates in the Cox regression for HF. Exclusion of patients who were diagnosed with HF or died within the first 14 days after index also yielded results similar to the main analysis (0 to 365 days: HR: 4.28 [95% CI: 2.05 to 8.92], >365 days: HR: 1.87 [95% CI: 1.45 to 2.40]). Furthermore, we repeated analyses in the subgroup of patients who fulfilled previously validated stricter criteria for SLE (31). Using these criteria, we identified 2,407 SLE patients (2,095 patients after application of exclusion criteria). A total of 1,914 were matched with 7,656 control subjects. This analysis yielded results similar to the main analysis (Supplemental Table 4) with 1 exception: unlike in the main analysis, the rate of the composite of pacemaker implantation, atrioventricular block, and sinoatrial dysfunction was not significantly increased in SLE patients compared with control subjects.

## DISCUSSION

This nationwide cohort study on long-term adverse cardiovascular outcomes in SLE yielded 3 major findings. First, SLE patients had a higher long-term risk of incident HF compared with matched control subjects. Second, a history of SLE was associated with higher all-cause mortality among patients developing HF. Third, SLE patients had higher long-term risks of other adverse cardiovascular outcomes compared with matched control subjects.

**HEART FAILURE.** In the present study, SLE patients had a higher long-term risk of incident HF compared with matched control subjects from the background population. Although the rate was highest within the first 365 days after SLE diagnosis, it remained elevated compared with matched control subjects beyond the first 365 days. Similar to our study, other cohort studies have found that SLE patients have a higher risk of developing HF compared with the general population (9,10). Previous studies have compared risks with the general population without

**TABLE 3** Number of Events for Each Outcome

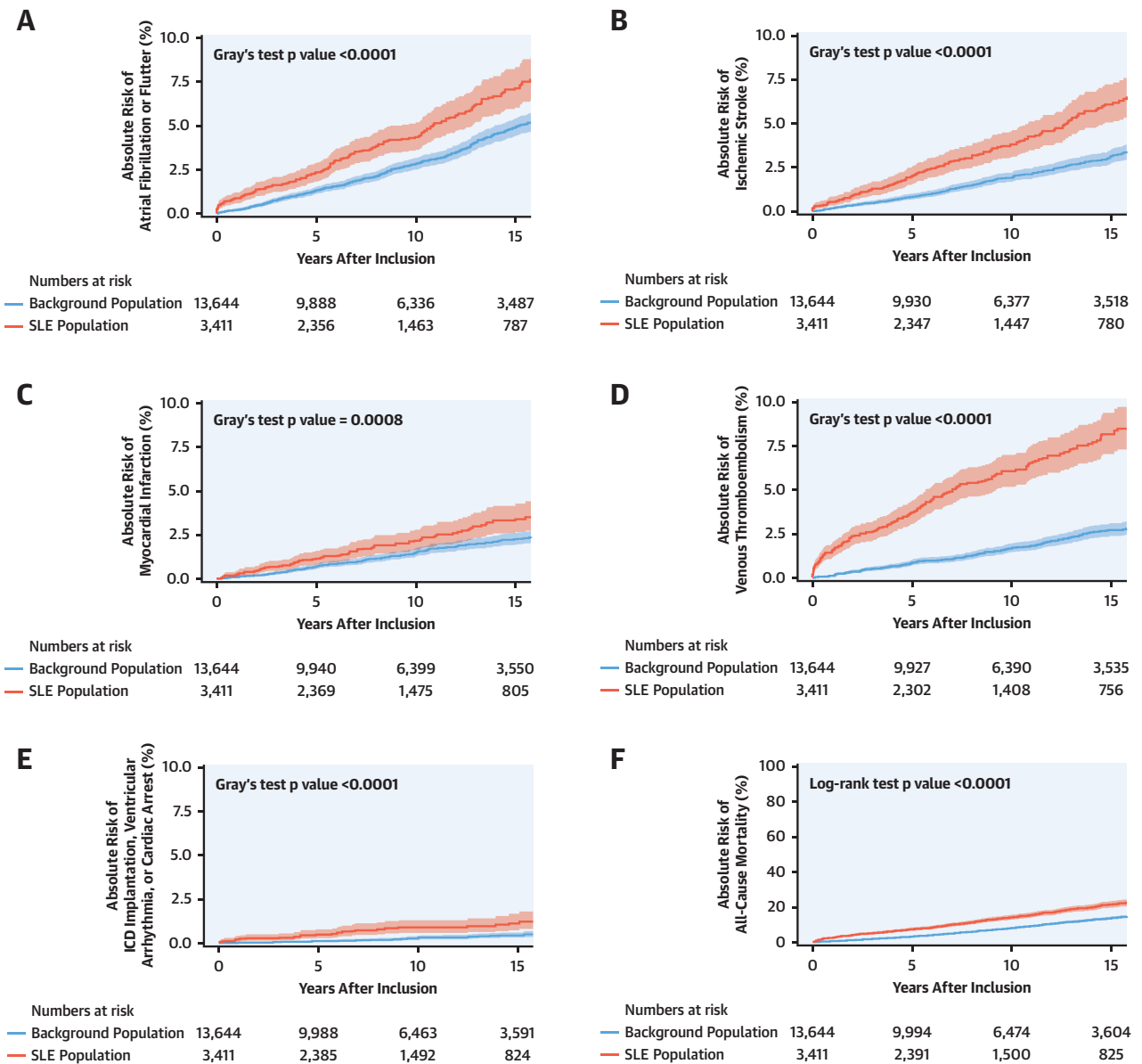
	Background Population (n = 13,644)	SLE Population (n = 3,411)
Heart failure	311 (2.3)	127 (3.7)
Atrial fibrillation or flutter	469 (3.4)	187 (5.5)
Ischemic stroke	323 (2.4)	148 (4.3)
Acute myocardial infarction	218 (1.6)	83 (2.4)
Venous thromboembolism	264 (1.9)	220 (6.5)
ICD implantation, ventricular arrhythmia, or cardiac arrest	42 (0.3)	29 (0.9)
Pacemaker implantation, atrioventricular block, or sinoatrial dysfunction	71 (0.5)	25 (0.7)
Endocarditis	11 (0.1)	11 (0.3)
All-cause mortality	1,338 (9.8)	543 (15.9)

Values are n (%).  
 ICD = implantable cardioverter-defibrillator; other abbreviations as in Table 1.

matching (9) or only matched based on age and sex (10); thus, our study expands previous research by showing a higher risk in SLE patients compared with control subjects matched more thoroughly by sex, age, and comorbidity on a nationwide level. An American cohort study found that the incidence of HF was 2.7-fold higher than in the general population; however, this study was limited by its short mean follow-up of 1.9 years and exclusion of patients >65 years (10). In our study, the median age at HF diagnosis for SLE patients was 65 years, indicating that older patients should not be excluded in studies addressing the risk of HF in SLE patients. Although the rate of HF was higher in SLE patients compared with matched control subjects across age groups, patients younger than the median age had a higher relative rate of HF than older patients. This is in accordance with previous findings that relative risks of cardiovascular disease are highest in younger SLE patients compared with comparison groups without SLE (7,32). Furthermore, we found that among patients developing HF, a history of SLE was associated with higher mortality. Given the high morbidity and mortality associated with HF generally (19,33,34), our findings stress the importance of cardiac assessment in SLE patients and early diagnosis and treatment of cardiovascular manifestations, including HF. This may be especially important in younger patients who might seem least at risk, but who had higher relative rates of these adverse outcomes compared with older patients. The finding of higher rates within the first year suggests that some SLE patients show HF symptoms early after SLE diagnosis, underlining the need for early cardiac monitoring.

Although we cannot draw conclusions regarding HF pathophysiology in our SLE population, there are several interesting observations to be noted. At HF

**FIGURE 2** Absolute Risks of Secondary Outcomes in SLE Patients and Matched Control Subjects From the Background Population



(A) Atrial fibrillation/flutter. (B) Ischemic stroke. (C) Myocardial infarction. (D) Venous thromboembolism. (E) Composite of ICD implantation, ventricular arrhythmia, and cardiac arrest. (F) All-cause mortality. For all-cause mortality, Kaplan-Meier estimates are presented; for all other outcomes, Aalen-Johansen estimates (taking the competing risk of death into account) are presented. Abbreviations as in Figure 1.

diagnosis, SLE patients with HF had a lower prevalence of ischemic heart disease and atrial fibrillation and a higher prevalence of hypertension compared with non-SLE control subjects with HF. This is in line with other studies reporting that hypertension is an important risk factor for HF in SLE (35), and that only 21% of HF cases in SLE are attributable to coronary

artery disease (36). After including incident myocardial infarction as a time-dependent covariate in the Cox regression for HF, rates of HF remained elevated in SLE compared with matched control subjects, indicating that myocardial infarction cannot explain the whole association between SLE and HF. Besides traditional risk factors, there are several possible

mechanisms that might underly the development of HF in SLE patients, including active SLE with other cardiovascular manifestations, which can lead to HF (vasculitis, arrhythmias, conduction disturbances, or myocarditis, which may especially occur in untreated patients [37]); and use of glucocorticoids and nonsteroidal anti-inflammatory drugs, which may increase the risk of HF (11), and use of hydroxychloroquine, which has been reported to be associated with cardiotoxicity, cardiovascular mortality, and development of HF (38-40). Clinicians should be aware of these adverse effects of when treating patients with SLE. Furthermore, end-stage kidney disease is an important cause of cardiovascular disease in SLE patients; although end-stage kidney disease was not highly prevalent in our population, timely referral of these patients for transplant is essential to improve cardiovascular outcomes (41). Our findings suggest that development of HF in SLE may, at least partly, be attributed to nonischemic and nonarrhythmic causes. Although these are only speculations, our findings underline the need for more studies examining possible etiologies of HF in SLE. Furthermore, although we did not have data on the subtype of HF (HF with reduced or preserved ejection fraction), SLE patients with HF were less likely to receive guideline-recommended therapy for HF with reduced ejection fraction than non-SLE patients with HF. In Denmark, a diagnosis of HF combined with renin-angiotensin-system inhibitor and beta-blocker treatment by 120 days post-discharge can be used to identify patients with HF with reduced ejection fraction (42). Although speculative, these findings may suggest that SLE patients with HF to a greater extent develop HF with preserved ejection fraction. This has also been suggested by a previous study that showed that HF with preserved ejection fraction is the predominant form of HF in SLE (43).

#### **SECONDARY ADVERSE CARDIOVASCULAR OUTCOMES.**

SLE was also associated with a higher long-term risk of other cardiovascular outcomes compared with matched control subjects. As for HF, rates of several outcomes (atrial fibrillation, ischemic stroke, venous thromboembolism, all-cause mortality) were highest within the first 365 days. Although rates of outcomes were increased in SLE patients compared with control subjects across age groups, younger patients had higher relative rates than older patients. The finding that SLE is associated with a higher risk of atrial fibrillation is in accordance with previous cohort studies with shorter follow-up than our study (12,13). Venous thromboembolism was the most common

cardiovascular manifestation in SLE patients in our cohort, especially within the first 365 days. Other studies have shown that SLE patients have increased risks of atherosclerotic cardiovascular events (including stroke and myocardial infarction) and venous thromboembolism (4-8); our study also showed an increased risk of ischemic stroke, myocardial infarction, and venous thromboembolism compared with matched control subjects. SLE with antiphospholipid syndrome is associated with a higher risk of several manifestations, including thrombosis and valve disease, compared with SLE without antiphospholipid syndrome (44). Early diagnosis and management of antiphospholipid syndrome is important to prevent early death and reduced quality of life (1). Although ventricular arrhythmias and conduction disturbances are rarely reported in SLE (15,16), we found that SLE patients had higher risks of arrhythmic outcomes compared with matched control subjects. Importantly, hydroxychloroquine is suggested to be associated with conduction disturbances and arrhythmias (38,45), and it is contraindicated in patients with existing cardiac arrhythmias (38). Furthermore, SLE patients had an increased risk of endocarditis, which is in accordance with previous findings (17). We did not have information on the type of endocarditis, but SLE patients have an increased risk of both noninfective and infective endocarditis (17,18). Because many cases of Libman-Sacks endocarditis are asymptomatic (18), we may have underestimated the occurrence of noninfective endocarditis in the SLE cohort.

**STUDY STRENGTHS AND LIMITATIONS.** The main strength of the present study is the nationwide design with completeness of data and no loss to follow-up in a large, unselected cohort of SLE patients. The follow-up is substantially longer than in previous studies. Furthermore, all sensitivity analyses (including restricting the definition of SLE to improve the validity of the diagnosis) yielded results similar to the main analyses. There are several limitations that deserve acknowledgement. Because of the observational nature of the study, we cannot assess cause-effect relationships. Despite thorough matching and adjustment for potential confounders, the possibility of residual confounding cannot be excluded. There are significant ethnic variations in the phenotype and epidemiology of SLE (1,2); most of the Danish population is White, and caution must therefore be taken when comparing our results with more heterogeneous populations with regards to ethnicity. Some less commonly used immunosuppressants can be

dispensed at hospitals as special services and may therefore be underrepresented in the registries. We did not have data on certain important covariates, including body mass index, smoking, anti-phospholipid status, blood pressure, HF etiology, ICD indication, left ventricular ejection fraction, natriuretic peptides, and New York Heart Association functional class.

## CONCLUSIONS

In this nationwide cohort study, we found that SLE patients had a higher associated risk of HF and other adverse cardiovascular outcomes compared with matched control subjects from the background population. Among patients developing HF, a history of SLE was associated with higher mortality.

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All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** During long-term follow-up, patients with SLE face a higher risk of heart failure and other adverse cardiovascular outcomes than matched control subjects. Mortality associated with heart failure is also greater among patients with SLE compared with patients without SLE who have heart failure.

**TRANSLATIONAL OUTLOOK:** Research is needed to develop management strategies for patients with SLE to reduce the risk of heart failure and other adverse cardiovascular outcomes.

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**KEY WORDS** cardiovascular outcomes, heart failure, systemic lupus erythematosus

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**APPENDIX** For supplemental tables and a figure, please see the online version of this paper.