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ORIGINAL RESEARCH

Cardiovascular Manifestations of Systemic Sclerosis: A Danish Nationwide Cohort Study

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Background—Cardiovascular involvement in systemic sclerosis (SSc) comprises a wide range of manifestations with prevalence and incidence that remain uncertain.

Methods and Results—In the Danish administrative registries between 1995 and 2015, all patients aged ≥18 years with a first diagnosis of SSc were matched by age and sex with controls (1:5) from the general population. Prevalence of cardiovascular diseases at the time of the SSc diagnosis and incidence during follow-up were assessed by in- and outpatient discharge diagnoses. Conditional logistic and Cox proportional hazards regression models were used respectively to calculate odds ratios for prevalent cardiovascular diseases and hazard ratios (HRs) for incident diseases associated with SSc. Patients with SSc (n=2778; 76% women; mean±SD age: 55±15 years) had more established cardiovascular risk factors than their respective controls at baseline, including greater prevalence of hypertension (31.2% versus 21.0%, $P<0.0001$) and treated dyslipidemia (9.8% versus 8.5%, $P=0.02$). SSc was associated with an increased relative risk of developing most cardiovascular diseases, including myocardial infarction (HR: 2.08; 95% CI, 1.65–2.64), peripheral vascular disease (HR: 5.73; 95% CI, 4.63–7.09), pulmonary hypertension (HR: 21.18; 95% CI, 14.73–30.45), mitral regurgitation (HR: 4.60; 95% CI, 3.12–6.79), aortic regurgitation (HR: 3.78; 95% CI, 2.55–5.58), aortic stenosis (HR: 2.99; 95% CI, 2.25–3.97), pericarditis (HR: 8.78; 95% CI, 4.84–15.93), heart failure (HR: 2.86; 95% CI, 2.43–3.37), atrial fibrillation (HR: 1.75; 95% CI, 1.51–2.04), and venous thromboembolism (HR: 2.10; 95% CI, 1.65–2.67). Additional adjustment for medications and comorbidities yielded results similar to the main analyses.

Conclusions—In this nationwide study, SSc was associated with greater risks of distinct cardiovascular diseases for patients than for matched controls, suggesting a significant disease-related adverse impact across the vascular bed and specific cardiac structures. **(*J Am Heart Assoc*. 2019;8:e013405. DOI: 10.1161/JAHA.119.013405.)**

Key Words: atherosclerosis • autoimmune diseases • cardiovascular disease • panvascular • systemic sclerosis

Systemic sclerosis (SSc; also called scleroderma) is a connective tissue disease with substantially increased cardiopulmonary morbidity and mortality.[1] Microvascular impairment is a pathognomonic feature in SSc with manifestations such as Raynaud phenomenon, pulmonary arterial hypertension, and renal crisis being well characterized. Several pathways in SSc vasculopathy (eg, endothelial dysfunction, inflammation, impaired coagulation or fibrinolysis, and oxidative stress) may lead to atherosclerotic manifestations.[2] Moreover, SSc-related vasculopathy combined with immune dysregulation and progressive fibrosis (hallmark features of SSc) are implicated in the pathogenesis of large vessel disease and specific cardiac dysfunction, but the clinical impact remains uncertain.[3–5]

A recent Danish study found SSc to be a significant risk factor for all-cause cardiovascular disease (defined as a composite end point including death due to cardiovascular disease).[6] However, few studies have examined the incidence of individual macrovascular manifestations such as myocardial infarction, stroke, peripheral artery disease, and venous thromboembolism[7–9] and data on the prevalence of valvular heart disease and arrhythmias in SSc are scarse.[10–13] We aimed to investigate the burden of cardiovascular disease

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Accompanying Data S1 and Tables S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013405

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Clinical Perspective

What Is New?

- This nationwide retrospective cohort (n=2778 individuals with systemic sclerosis) study spanning 1995–2015 confirms and quantifies a wide spectrum of cardiovascular complications for systemic sclerosis patients compared with a general-population control group.
- We observed that both well-established manifestations (eg, pulmonary hypertension) and less evaluated cardiovascular complications (eg, myocardial infarction, peripheral vascular disease, aortic and mitral regurgitation) were more prevalent at the time of diagnosis and during follow-up among patients with systemic sclerosis versus controls.

What Are the Clinical Implications?

- The increased prevalence, incidence, and relative risk of cardiovascular manifestations in systemic sclerosis underscore a significant adverse impact of systemic sclerosis across the vascular bed and specific cardiac structures, warranting increased focus on less recognized complications.

in a nationwide sample of patients with incident SSc compared with matched controls. Using the Danish healthcare registers, we specifically estimated the prevalence and incidence of ischemic manifestations (acute myocardial infarction, stroke, peripheral vascular disease), arrhythmias (atrial fibrillation), conduction blocks (atrioventricular and left bundle-branch block) and hitherto unknown risk of device implantation (pacemaker or implantable cardioverter-defibrillator), cardiac valve disease (aortic and mitral stenosis and regurgitation), aortic disease (aortic aneurysm and dissection), and established manifestations including pulmonary hypertension, heart failure, pericarditis, and venous thromboembolism in SSc. We hypothesized that patients with SSc would be at increased risk of cardiac and vascular manifestations across the whole spectrum of cardiovascular diseases.

Methods

Data obtained through the nationwide registers in Denmark can be made available only through research on Danish servers hosted in highly protected research environments where researchers can be granted access and permission with encrypted person identification. Access to raw data can be gained only through collaboration with the authors or other Danish institutions that already have been granted access. Please contact the first author with any questions regarding data access. Additional methods can be found in Data S1.

Study Design

The study is a nationwide cohort study that included all patients with a first-time registration of SSc versus age- and sex-matched controls (1:5) from the Danish healthcare registries between January 1, 1995, and December 31, 2015. The study was conceived in agreement with the recommendations for cohort studies by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative.[14]

Data Sources

For this study we cross-linked the Central Population Registry (using individual-level data) with the National Patient Registry and the National Prescription Registry. The Central Population Registry contains the unique personal identification numbers of all Danish residents along with information on their birth date, sex, and vital status. The National Patient Registry contains information on all in- and out-hospital diagnoses, registered according to the *International Classification of Diseases* (*ICD*) system, using the *Eighth Revision* (*ICD-8*) from 1978 to 1993 and the *Tenth Revision* (*ICD-10*) since 1994. The accuracy and completeness of diagnostic coding in the National Patient Registry has been evaluated as consistently high for a variety of chronic comorbidities and cardiovascular diagnoses,[15–18] and we have previously found a positive predictive value of 94% for the SSc diagnosis in this registry.[19] The National Prescription Registry holds information on all prescription claims since 1995 with all drugs classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Because of reimbursement-driven policy, this registry is considered high quality.[20]

Study Population

In the National Patient Registry, we identified all first-time diagnoses of SSc (*ICD-10* codes M34, except for M34.2) that followed outpatient or inpatient visits between 1995 and 2015. We excluded patients with a prior diagnosis of SSc, defined as an *ICD-10* code of M34 in 1994 or an *ICD-8* code of 734 anytime between 1978 and 1993. The controls consisted of 5 randomly selected age- and sex-matched individuals from the Central Population Registry. An index date was assigned to each control that corresponded to the date of first registration of SSc for his or her respective case, in accordance with the principle of incidence density sampling.[21]

Outcome Variables and Follow-Up

The primary outcome variables were defined by *ICD-8* and *ICD-10* codes, together with procedural codes (obtained via the National Patient Registry) and medication use (obtained

via the ATC Classification System coding in the National Prescription Registry). Table S1 shows the different variables, different registries, and corresponding diagnosis or procedure/surgical codes for each outcome.

Comorbidity and Medications

Baseline comorbidity comprised prevalent conditions at any time before study inclusion. Comorbidity included hypertension, atrial fibrillation, heart failure of any cause, myocardial infarction, ischemic stroke, aortic aneurism and dissection, aortic stenosis and regurgitation, mitral stenosis and regurgitation, conduction block (left bundle-branch block and atrioventricular block), implantation of pacemaker or implantable cardioverter-defibrillator, pericarditis, peripheral vascular disease, pulmonary hypertension, venous thromboembolism, treated dyslipidemia, and diabetes mellitus. Baseline treatment was defined by at least 1 prescription dispensed for each respective drug up to 180 days before the study inclusion date. The following drugs were included: aspirin, NSAIDs, statins, oral anticoagulants, antiplatelet therapy, and glucocorticoids.

Statistical Analysis

Continuous variables are presented as mean±SD, and categorical variables are presented as absolute numbers and percentages. Tests for differences between groups were performed by the Pearson χ^2 or Fisher exact test (categorical data) or by the Student *t* test (continuous data), as appropriate. Time at risk was measured from the index date (date of SSc diagnosis), and individuals were censored at the date of first-time registration of the specific end point, migration, or death. Conditional logistic regression models and Cox proportional hazards regression models were used respectively to calculate the odds ratios (ORs) for prevalent cardiovascular diseases and hazard ratios (HRs) for incident diseases associated with SSc. Separate models were run for each end point. The main models were adjusted for age and sex. In addition, a multivariable Cox regression model (including all comorbidities and treatment in Table 1) was applied to investigate the association of SSc and outcomes after adjustment for various comorbidities and risk factors. Two-sided $P<0.05$ was considered statistically significant for all analyses. All analyses were performed in SAS v9.4 (SAS Institute).

Ethics

All data were anonymized to the investigators. The study was approved by the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-suite 02736). Because the study is retrospective and registry-based using deidentified data, Danish law does not require ethics approval. The Danish procedures for safeguarding patient anonymity prohibit the reporting of outcomes with ≤3 events. The first author had full access to the data and takes responsibility for its integrity and for the data analysis.

Table 1. Baseline Characteristics of SSc Patients and Controls

Variable	SSc Cases (n=2778)	Controls (n=13 890)	*P* Value
Female sex	2114 (76)	10 570 (76)	
Age, y, mean±SD	55±15	55±15	
Hypertension	867 (31.2)	2915 (21.0)	<0.0001
Atrial fibrillation and atrial flutter	77 (2.8)	189 (1.1)	<0.0001
Heart failure	84 (3)	166 (1)	<0.0001
Myocardial infarction	86 (3.1)	260 (1.9)	<0.0001
Ischemic stroke	69 (1.3)	224 (2.5)	<0.0001
Aortic aneurism	9 (0.3)	25 (0.2)	0.1247
Aortic dissection	≤3	≤3	0.4385
Aortic stenosis	15 (0.5)	35 (0.3)	0.0113
Aortic regurgitation	19 (0.7)	30 (0.2)	<0.0001
Mitral stenosis	≤3	≤3	0.1615
Mitral regurgitation	13 (0.5)	32 (0.2)	0.0276
Conduction block (left bundle-branch or atrioventricular block)	15 (0.5)	28 (0.2)	0.0013
Pacemaker/implantable cardioverter-defibrillator	18 (0.7)	54 (0.4)	0.0572
Pericarditis	28 (1.0)	29 (0.2)	<0.0001
Peripheral vascular disease	121 (4.4)	133 (1.0)	<0.0001
Pulmonary hypertension	22 (0.8)	14 (0.1)	<0.0001
Venous thromboembolism	93 (3.4)	156 (1.1)	<0.0001
Diabetes mellitus	139 (5.0)	585 (4.2)	0.0616
Aspirin	344 (12.4)	1055 (7.6)	<0.0001
NSAIDs	752 (27.1)	1733 (12.5)	<0.0001
Glucocorticoids	379 (13.6)	352 (2.5)	<0.0001
Treated dyslipidemia	273 (9.8)	1177 (8.5)	0.0208
Oral anticoagulant	109 (3.9)	176 (1.3)	<0.0001
Antiplatelet therapy	375 (13.5)	1153 (8.3)	<0.0001

Data are shown as n (%) except as noted. SSc indicates systemic sclerosis.

Results

Study Population

The demographic characteristics and baseline comorbidities for patients with SSc and matched controls are shown in

Table 1. The study population comprised 2778 patients (76% female) with a diagnosis of SSc and 13 890 controls with an overall follow-up time of 8.9 years. A total of 722 (26%) and 1.938 (14%) patients died in the SSc and matched cohorts, respectively, with an age- and sex-adjusted HR for all-cause mortality of 2.68 (95% CI, 2.43–2.94).

The presence of other autoimmune tissue disorders was low but higher among patients with SSc than controls (114 [4.1%] versus 97 [0.7%] for rheumatoid arthritis, 41 [1.5%] versus 8 [0.06%] for systemic lupus erythematosus, and 48 [1.7%] versus 4 [0.03%] for mixed connective tissue disease; all P <0.0001). Cardiovascular risk factors such as hypertension (OR: 1.82; 95% CI, 1.66–2.01) and treated dyslipidemia (OR: 1.21; 95% CI, 1.04–1.40) were more frequent in the SSc cohort compared with control participants. The prevalence of most cardiovascular disorders was found to be higher in the SSc cohort than in the matched population. Very few SSc patients had either aortic disease (≤9) or mitral stenosis (≤3) at baseline.

Incidence rates for new-onset cardiovascular manifestations are presented in Table 2. Table 2 also shows the total number of events in each cohort in patients with SSc and controls for all outcomes. SSc patients had higher risks (Figure) of developing myocardial infarction (HR: 2.08; 95% CI, 1.65–2.64), ischemic stroke (HR: 1.28; 95% CI, 1.04–1.58), peripheral vascular disease (HR: 5.73; 95% CI, 4.63–7.09), atrial fibrillation (HR: 1.75; 95% CI, 1.51–2.04), heart conduction block (atrioventricular and left bundle-branch; HR: 1.73; 95% CI, 1.14–2.62), pulmonary hypertension (HR: 21.18; 95% CI, 14.73–30.45), heart failure (HR: 2.86; 95% CI, 2.43–3.37), pericarditis (HR: 8.78; 95% CI, 4.84–15.93), mitral regurgitation (HR: 4.60; 95% CI, 3.12–6.79), aortic regurgitation (HR: 3.78; 95% CI, 2.55–5.58) and stenosis (HR: 2.99; 95% CI, 2.025–3.97), and venous thromboembolism (HR: 2.10; 95% CI, 1.65–2.67). The proportions of patients with incident myocardial infarction who were revascularized within 30 days (either by coronary artery bypass grafting surgery or percutaneous coronary

Table 2. Incidence of Various Cardiovascular Comorbidities and Conditions During Follow-Up

Variable	SSc Cases (n=2778)		Controls (n=13 520)	
	Incident Cases	Incidence Rate Per 100 Person-Years	Incident Cases	Incidence Rate Per 100 Person-Years
Hypertension	1320	15.21 (14.42–16.06)	5081	6.96 (6.77–7.16)
Atrial fibrillation	235	0.92 (0.81–1.04)	713	0.54 (0.50–0.58)
Heart failure	229	0.92 (0.81–1.05)	451	0.34 (0.31–0.37)
Myocardial infarction	100	0.39 (0.32–0.48)	252	0.19 (0.17–0.22)
Ischemic stroke	112	0.43 (0.36–0.52)	439	0.33 (0.31–0.37)
Aortic aneurism	21	0.08 (0.05–0.12)	74	0.05 (0.04–0.07)
Aortic dissection	≤3	NA	12	0.01 (0.005–0.02)
Aortic stenosis	77	0.29 (0.23–0.36)	133	0.10 (0.08–0.12)
Aortic regurgitation	44	0.16 (0.12–0.22)	58	0.04 (0.03–0.05)
Mitral stenosis	6	0.02 (0.01–0.05)	≤3	NA
Mitral regurgitation	49	0.18 (0.14–0.24)	53	0.04 (0.03–0.05)
Conduction block (left bundle- branch or atrioventricular block)	30	0.11 (0.08–0.16)	91	0.07 (0.05–0.08)
Pacemaker or implantable cardioverter-defibrillator	48	0.18 (0.13–0.23)	137	0.10 (0.08–0.12)
Pericarditis	30	0.11 (0.08–0.16)	18	0.01 (0.01–0.02)
Peripheral vascular disease	184	0.75 (0.65–0.87)	182	0.14 (0.12–0.16)
Pulmonary hypertension	153	0.58 (0.49–0.68)	36	0.02 (0.02–0.04)
Venous thromboembolism	95	0.37 (0.30–0.46)	232	0.17 (0.15–0.20)

NA indicates not assessed; SSc, systemic sclerosis.

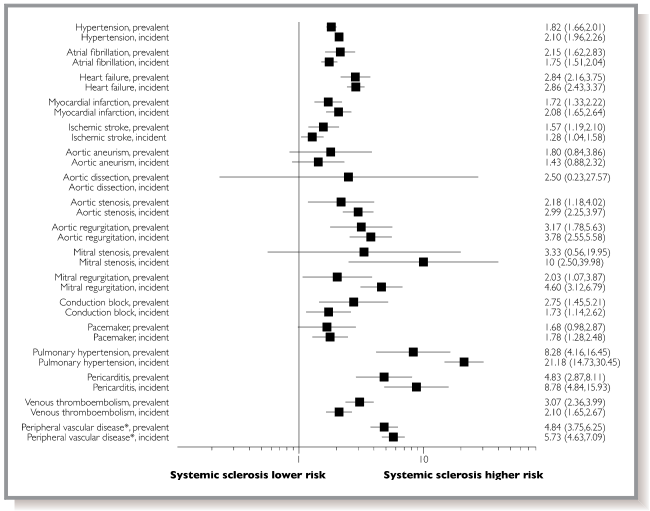

Figure. Forest plot. Odds ratio (prevalent disease) or hazard ratio (incident disease) for various cardiovascular conditions associated with systemic sclerosis, adjusted for age and sex. Relative risks are expressed as odds ratios for prevalent diseases and hazard ratios for incident diseases. *Defined as atherosclerosis in peripheral artery or aorta.

intervention) were similar for SSc cases and controls (31% versus 35%; P=0.44).

Further adjustment for medications (aspirin, NSAIDs, glucocorticoids, statins, oral anticoagulants, and platelet inhibitors) and comorbidities yielded results similar to the main analyses (Table S2), except for ischemic stroke (HR: 1.13; 95% CI, 0.90–1.42).

Validation

To increase the likelihood of causality underlying our observations, we used the 2 known genetic variants associated with SSc from prior genome-wide association studies, *rs3894194* and *rs4134466*, as instrument variables to look for associations with various cardiovascular disorders in the UK Biobank.[22,23] Multiple disorders, including myocardial infarction, heart failure, aneurisms, arrhythmias, and peripheral vascular disease were associated with the single-nucleotide polymorphisms at P<0.05 (Table S3). In addition, evidence suggested a causal association with nonrheumatic mitral valve disease (P=0.058).

Discussion

In this nationwide cohort study comprising all Danish SSc patients from 1995 to 2015 and matched controls, we confirm well-known associations between SSc and pulmonary hypertension, pericarditis, and atrial fibrillation. In addition, we show that less evaluated cardiovascular complications (ischemic manifestations, valvular disease, venous thromboembolism) are both more prevalent at the time of SSc diagnosis and occur at higher incidence rates after diagnosis in SSc patients compared with matched controls. In contrast to the established cardiovascular manifestations of SSc (eg, pericarditis), the increased risks associated with several of the less well-recognized diseases were moderate. However, given the overall higher prevalence and incidence rates of the many cardiovascular manifestations, increased attention to the risk of cardiovascular diseases in SSc patients is warranted.

Atherosclerotic Cardiovascular Disease

Systemic inflammatory autoimmune diseases are associated with premature atherosclerosis. Although the degree of overt systemic inflammation and renal involvement may be less profound in SSc than in, for example, systemic lupus (which is well known to be associated with atherosclerosis, especially in the presence of nephropathy),[24,25] we hypothesize that part of the observed association may be due to inflammation in SSc.[26,27] A few studies of limited size have suggested that patients with SSc have similar or lower prevalence of traditional cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes mellitus compared with controls.[7,28,29] In contrast, our study observed higher prevalence of hypertension, treated dyslipidemia, and diabetes mellitus in patients with SSc than controls. Similar to our findings, registries have pointed toward increased prevalence of coronary heart disease in SSc patients compared with controls,[30] with recent studies showing a 2.0- to 3.5-fold increased relative risk of myocardial infarction.[7,28,31]

Peripheral vascular disease in SSc has recently come into focus with the use of angiography and subclinical markers such as pulse wave velocity, ankle brachial index, and systolic/diastolic interarm difference.[32–34] Few studies have been conducted, but a recent case–control study comprising 858 individuals with SSc found incidence rates (7.6/1000 person-years) and HRs (4.57; 95% CI, 2.99–7.01) similar to ours.[7] Aortic disease (aneurysm or dissection) involvement has been reported in only a few case reports,[35] and our study confirms it being uncommon in SSc. Cerebral vascular involvement in patients with SSc has been studied previously by assessing carotid intima media thickness, and findings have been inconclusive findings,[36,37] although higher prevalence of intracerebral calcifications[38] and white matter hyperintensities[39] has been suggested in patients with SSc compared with age- and sex-matched controls. In contrast to a few prior smaller studies,[40,41] some recent studies have shown a slightly increased risk of ischemic stroke (HR: 1.44–2.56) in patients with SSc compared with controls.[7,31,42] Our findings of an increased crude risk of ischemic stroke partially mirror findings of a disproportionately lower relative risk of

ischemic cerebral disease compared with the risk of ischemic heart disease and peripheral vascular disease, albeit insignificant in the fully adjusted model.

Arrhythmias and Conduction Defects

Arrhythmias and cardiac conduction defects are common in SSc, presumably because of myocardial ischemic, fibrotic, and inflammatory lesions.[43] In selected SSc cohorts, electrophysiological abnormalities have been reported in 25% to 85% of patients and transient atrial arrhythmias reported in 20% to 30%.[12,44] Our study confirms an increased prevalence (2.8%) at the time of diagnosis and almost 2-fold increased relative risk of atrial fibrillation for SSc patients during follow-up; a similar 2-fold risk of implantation of pacemakers and cardioverter-defibrillators was found in the SSc cohort.

Pulmonary Hypertension and Heart Failure

Pulmonary hypertension and resulting right-sided heart failure is a significant cause of morbidity and mortality in SSc.[45] In contrast, echocardiographically diagnosed left ventricular systolic dysfunction is infrequently seen (≈5%),[46] although diastolic dysfunction may contribute more to mortality than recognized previously.[47] Of note, subclinical myocardial abnormalities are detected more often by tissue Doppler or magnetic resonance imaging than with conventional echocardiography, in line with the typically gradual and subtle disease progression over time.[48] The prevalence of pulmonary hypertension is estimated to be ≈7%,[49] and incidence estimates have been reported to be 1.37 to 1.85/100 person-years, based on modalities such as echocardiography and right heart catheterization.[50,51] Our register-based prevalence at time of diagnosis and incidence rate estimates of 0.58/100 person-years (95% CI, 0.6–0.8) are lower than expected. Because the manifestation is insidious, our findings could be explained in part by the study design, the time span applied, and the modalities required (echocardiography, right heart catheterization), making it likely that SSc-related pulmonary hypertension may be underdiagnosed and underreported in the National Patient Registry. However, the 21-fold increased relative risk of pulmonary hypertension (HR: 21.18; 95% CI, 14.73–30.45) during follow-up underscores the well-known association between SSc and pulmonary hypertension.

Pericarditis

Pericardial involvement in SSc was first described in autopsy studies[52] and may occur in 2 patterns.[53] Consistent with prior autopsy studies, pericardial involvement has been characterized through modalities like echocardiography[10,54] and magnetic resonance imaging[55] as being an indolent chronic process, often with smaller pericardial effusions that are not always clinically apparent. However, it can also present as an acute disorder with symptomatic pericarditis for which larger effusions are known to be associated with poorer prognosis.[53,56,57] Literature on the prevalence and risk of symptomatic pericarditis is scarce. We found that overt pericarditis leading to clinical registration occurred in 1% of SSc patients at time of diagnosis, with a 6-fold increased relative risk during follow-up. Nevertheless, the absolute numbers are low, indicating that clinical symptomatic pericarditis remains a rare complication.

Cardiac Valve Disease

Cardiac valve disease has not gained much attention even though early autopsy studies described minor valvular lesions in patients with SSc.[52] A few echocardiographic studies have reported an association between SSc and, particularly, valvular regurgitation,[10,11,58] but the risk of incident valve disease has not been studied previously. In our study, we found a 3-fold increased relative risk of aortic stenosis, a 4-fold increased relative risk of aortic regurgitation, and an almost 5-fold increased relative risk of mitral regurgitation. The relative risk of mitral stenosis was similarly found to be increased 10-fold but limited by a small number of cases and a wide CI. In accordance with a recent Swedish study,[59] our findings illustrate that cardiac valve disease can develop during the natural history of disease and thus be regarded as a specific SSc-related complication.

Venous Thromboembolism

Autoimmune disorders are recognized as risk factors for venous thromboembolism, presumably because of chronic inflammation and hypercoagulability.[60] Prior studies imply an increased risk of venous thrombosis; for instance, a recent meta-analysis based on 5 studies, although hampered by high statistical heterogeneity, reported a pooled risk ratio of 2.51 (95% CI, 1.79–3.54).[9] Our observations of doubled risk are in line with these earlier reports, adding weight to the association between SSc and venous thromboembolism. The mechanistic link, however, cannot be determined from our study. It is possible that although the prevalence of rheumatoid arthritis, systemic lupus erythematosus, and mixed connective tissue disorders was small (<5%) in our study cohort, some of the observed association between SSc and venous thromboembolism (and potentially other cardiovascular disorders) was driven by the presence of these and other autoimmune comorbidities.

Study Strengths and Weaknesses

Danish registries are considered accurate and complete and can contribute to the study of rare diseases.[61] Because

almost all patients in Denmark with SSc are followed in specialized departments of rheumatology or dermatology, selection and recall bias as a source of error is low given the nationwide administrative setup. However, a detection bias of cardiovascular diseases may have occurred in the SSc cohort because of the regular specialized care and surveillance (eg, valvular diseases may have been detected because of more frequent echocardiography). Bias could also be introduced if SSc patients had diagnoses coded more often than controls because of a more thorough coding practice by their treating physicians. However, because of the Danish reimbursement policy, physicians should code only clinically significant conditions of importance to the specific contact (eg, valve disorders should be coded only if they require follow-up), making such bias less likely. Our observations were also strengthened by genetic evidence suggesting a causal relationship between SSc and many of the cardiovascular manifestations, underscoring that surveillance and coding practices might not be solely responsible for the observed associations. The main strength of the study includes the high number of cases and the long duration of follow-up. Considering the high validity in the National Patient Registry of the exposure and outcome variables used in this study,[15–17,19] the potential for inaccurate diagnosis and consequently misleading calculations should be low; however, it should be acknowledged that a few diagnoses (eg, pulmonary hypertension) have never been validated. Furthermore, the diagnoses could not be used to subclassify the disease severity (eg, severity of an aortic stenosis). In the multivariable analysis, several end points had a relatively low number of incident cases, and the rule of thumb that the number of events should be at least 10 times the number of covariates was not met for all end points. Therefore, caution is advised when interpreting the results from the multivariable analysis. Of note, our study spans a time period in which the classification criteria of SSc have evolved,[62–64] and the increasing use of serological markers and capillaroscopy, for example, have yielded increases in the number of patients fulfilling disease criteria.[65–67] It is likely that our cohort contained a larger proportion of early and mild disease compared with earlier cohorts, although we did not have information allowing us to differentiate distinct phenotypes of SSc with regard to extent of skin involvement or serological features known to be associated with mortality in SSc.[68] Moreover, residual confounding cannot be refuted because valid information on lifestyle parameters (eg, tobacco, alcohol, body mass index, physical activity level) is not available in the registries used for this study. Our cohort was based on a homogeneous ethnic northern European population, making extrapolation to other ethnicities difficult.

Conclusions

The magnitude of cardiovascular manifestations estimated in our study suggests a significant disease-related adverse impact across the vascular bed and specific cardiac structures, warranting an increased focus on less recognized complications. The limited understanding of the pathology and dynamics behind our multifaceted findings reflects an unmet need for characterization of key determinants of risk and causal factors of cardiovascular complications in SSc. Our findings require more research; however, our study supports a multidisciplinary approach for the assessment of cardiovascular disease and its treatment in patients with SSc.

Author Contributions

Butt, Andersson, Jacobsen, and Jeppesen conceived and designed the study. All authors acquired, analyzed, and/or interpreted data. Butt drafted the article. Butt and Andersson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically revised the article for important intellectual content. All authors approved the final version to be submitted for review.

Disclosures

None.

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Supplemental Material

Data S1.

Supplemental Methods

For the present study we cross-linked the Central Population Registry (using individual-level data) with the National Patient Registry and the National Prescription Registry. The Central Population Registry contains the unique personal identification numbers of all Danish residents along with information on their birthdate, gender, and vital status. The National Patient Registry contains information on all in- and out-hospital diagnoses, registered according to the International Classification of Diseases (ICD) system; revision 8 in 1978-1993 and the 10th revision since 1994. The accuracy and completeness of diagnostic coding in the National Patient Registry has been evaluated as consistently high for a variety of chronic comorbidities and cardiovascular diagnoses [1-4], and we have previously found a positive predictive value of 94% for the SSc diagnosis in this registry.[5] The National Prescription Registry holds information on all prescription claims since 1995 with all drugs being classified according to the Anatomical Therapeutical Chemical classification system. Due to the reimbursement-driven policy, this registry is considered of high quality.[6]

Study population

In the National Patient Registry, we identified all first-time diagnoses of SSc (ICD-10 codes M34 [except for M34.2]) that followed outpatient or inpatient visits between 1995 and 2015. We excluded patients with a prior diagnosis of SSc defined as an ICD-10 code of M34 in 1994 or an ICD-8 code of 734 anytime between 1978 and 1993. The controls consisted of five randomly selected age- and sex-matched individuals from the Central Population Registry. An index date was assigned to each control, which corresponded with the date of first registration of SSc for their respective case, in accordance with the principle of incidence density sampling.[7]

Outcome variables and follow up

The primary outcome variables were defined by ICD-8 and ICD-10 codes, together with procedural codes (obtained via the National Patient Registry) and medication use (obtained via the Anatomical Therapeutic Chemical (ATC) Classification System coding in the National Prescription Registry). **Supplemental Table S1** shows the different variables, different registries, and the corresponding diagnosis or procedure/surgical codes for each outcome.

Comorbidity and Medications

Baseline comorbidity was assessed as a prevalent condition at any time before study inclusion. Comorbidity included hypertension, atrial fibrillation, heart failure of any cause, myocardial infarction, ischemic stroke, aortic aneurism and dissection, aortic stenosis and regurgitation, mitral stenosis and regurgitation, conduction block (left bundle branch block and atrioventricular block), implantation of pacemaker or implantable cardioverter defibrillator, pericarditis, peripheral vascular disease, pulmonary hypertension, venous thromboembolism, treated dyslipidemia, and diabetes. Baseline treatment was defined by at least one prescription dispensed for each respective drug up to 180 days before the study inclusion date. The following drugs were included: aspirin, nonsteroidal anti-inflammatory drugs, statins, oral anticoagulants, anti-platelet therapy and glucocorticoids.

Statistics

Continuous variables are presented as mean with standard deviation, categorical variables as absolute number and percentages. Tests for differences between groups were performed by the Pearson's Chi-squared/Fischer's exact test (categorical data) or by the Student t test (continuous data) where appropriate. Time at risk was measured from index date (date of SSc diagnosis) and

individuals were censored at the date of first-time registration of the specific endpoint, migration or upon death. Conditional logistic regression models and Cox proportional hazards regression models were used to calculate the odds ratios (OR) for prevalent cardiovascular diseases and hazard ratios (HR) for incident diseases associated with SSc, respectively. Separate models were run for each endpoint. The main models were adjusted for age and sex. In addition, a multivariable Cox regression model (including all comorbidities and treatment in **Table 1**) was applied to investigate the association of SSc and outcomes after adjustment for various comorbidities and risk factors. Two-sided p-values <0.05 were considered statistically significant for all analyses. All analyses were performed in SAS version 9.4 (Cary, NC, USA).

Table S1. Variables and sources. Diagnoses (ICD-8 and ICD-10) and medication (ATC) codes used.

Disease/condition	Definition (Register)	Variables
Hypertension	ATC (National Prescription Registry)	ATC: C02A, C02B, C02C, C02DA, C02DB, C02DD, C02DG, C02L, C03A, C03B, C03D, C03E, C03X, C04, C05, C07A, C07B, C07C, C07D, C07F, C08, C08G, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09CA52
Ischemic stroke	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 433, ICD-10 I63-64
Acute myocardial infarction	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 410, ICD-10 I21-22
Ischemic heart disease	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 410-414, ICD-10 I20-25
Heart failure	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 425, 4270-1, ICD-10 I42, I50, I110
Aortic aneurism (abdominal or thoracic)	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 441, ICD-10 I711-I719
Aortic dissection (abdominal or thoracic)	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-10 I71.0
Aortic stenosis	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-10 I35.0, I35.2
Aortic regurgitation	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-10 I34.0, I34.1
Mitral valve stenosis	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-10 I34.2
Mitral valve regurgitation or prolapse	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-10 I34.0-I34.1
Atrial fibrillation	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 4274, ICD-10 I48
Conduction block (left bundle branch or atrioventricular block)	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 4273, ICD-10 I44
Pericarditis	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 420, 421, ICD-10 I30-I32
Peripheral artery disease and atherosclerosis in aorta	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 440, ICD-10 I70, I74
Pulmonary hypertension	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 426, ICD-10 I27
Deep venous thrombosis or pulmonary embolism	ICD8 or ICD10 diagnostic codes (National Patient Registry)	ICD-8 450, 451, ICD-10 I26, I80, I82 (excl. I80.0, I80.8, I82.0)

Cardiac pacemaker	Procedure and surgical code (National Patient Registry)	BFCA0, BFCA6, KFPE00, KFPE10, KFPE20, KFPE96, KFPF00, KFPF10, KFPF20, KFPF96
Implantable Cardioverter Defibrillator	Procedure and surgical code (National Patient Registry)	BFCB0, BFCB6, KFPG
Diabetes	ATC (National Prescription Registry)	ATC: A10
Aspirin	ATC (National Prescription Registry)	B01AC06
NSAID (nonsteroidal anti-inflammatory drugs)	ATC (National Prescription Registry)	M01A
Treated dyslipidemia	ATC (National Prescription Registry)	C10AA
OAC (oral anticoagulant)	ATC (National Prescription Registry)	B01
Anti-platelet therapy	ATC (National Prescription Registry)	B01AC
Glucocorticoids	ATC (National Prescription Registry)	H02AB

Hypertension was defined by use of at least 2 antihypertensive drugs according to a validated algorithm[4], diabetes was defined by use of a glucose-lowering drug while treated dyslipidemia was defined as the use of statins. ATC; anatomical therapeutic chemical classification system. ICD-10; International Classification of Diseases 10th revision.

Table S2. Hazard ratio (HR) and 95% confidence interval (CI) for incident disease (fully adjusted model).

Outcome	HR
Hypertension	1.90 (1.76-2.05)
Atrial fibrillation	1.57 (1.33-1.86)
Heart failure	2.43 (2.02-2.91)
Myocardial infarction	1.91 (1.47-2.47)
Ischemic stroke	1.13 (0.90-1.42)
Aortic aneurism	1.18 (0.70-2.07)
Aortic dissection	NA
Aortic stenosis	2.85 (2.07-3.93)
Aortic regurgitation	2.49 (1.56-3.97)
Mitral stenosis	NA
Mitral regurgitation	4.43 (2.75-7.12)
Conduction block (LBBB/AVB)	1.59 (1.00-2.55)
Pacemaker/Implantable cardioverter defibrillator	1.63 (1.12-2.37)
Pericarditis	8.31 (3.74-18.46)
Peripheral vascular disease	5.54 (4.37-7.02)
Pulmonary hypertension	21.06 (13.78-32.19)
Venous thromboembolism	1.92 (1.48-2.49)
Diabetes	0.93 (0.75-1.15)

Fully adjusted HR was adjusted for medications (ASA, NSAID, Glucocorticoids, statins, OAC and platelet inhibitors) and co-morbidities, as specified in Table 1.

Table S3. Associations of *rs3894194* and *rs4134466* with cardiovascular phenotypes at p<0.10 from the UK Biobank based gene atlas.

Variant	Eff. Allele	Trait	Beta	p-value
rs3894194, odds ratio 0.85 (0.81 to 0.90), p=6.6e-10 in original GWAS of systemic sclerosis				
rs3894194	G	I70-I79 Diseases of arteries, arterioles and capillaries	-0.00091	0.0011
rs3894194	G	I50 Heart failure	-0.00072	0.0026
rs3894194	G	I30-I52 Other forms of heart disease	-0.0015	0.0046
rs3894194	G	I77 Other disorders of arteries and arterioles	-0.00032	0.0095
rs3894194	G	I74 Arterial embolism and thrombosis	-0.00024	0.018
rs3894194	G	I21 Acute myocardial infarction	-0.00066	0.020
rs3894194	G	Essential hypertension	0.00028	0.043
rs3894194	G	Heart attack/myocardial infarction	-0.00061	0.045
rs3894194	G	I73 Other peripheral vascular diseases	-0.00039	0.051
rs3894194	G	I34 Nonrheumatic mitral valve disorders	-0.00030	0.058
rs3894194	G	I71 Aortic aneurysm and dissection	-0.00023	0.059
rs3894194	G	I95 Hypotension	-0.00041	0.069
rs3894194	G	I72 Other aneurysm	-0.00013	0.072
rs3894194	G	K55 Vascular disorders of intestine	0.00018	0.080
rs4134466, odds ratio 0.85 (0.80 to 0.89), p=1.4e−10 in original GWAS of systemic sclerosis				
rs4134466	G	I70 Atherosclerosis	-0.00035	0.0033
rs4134466	G	I72 Other aneurysm	-0.00019	0.0075
rs4134466	G	I70-I79 Diseases of arteries, arterioles and capillaries	-0.00074	0.0090
rs4134466	G	Peripheral vascular disease	-0.00028	0.015
rs4134466	G	Heart arrhythmia	-0.00052	0.044
rs4134466	G	I61 Intracerebral haemorrhage	-0.00017	0.050
rs4134466	G	I51 Complications and ill-defined descriptions of heart disease	-0.00040	0.059
rs4134466	G	I30-I52 Other forms of heart disease	-0.00095	0.069
rs4134466	G	heart attack/myocardial infarction	-0.00056	0.072
rs4134466	G	I47 Paroxysmal tachycardia	0.00033	0.082
rs4134466	G	I45 Other conduction disorders	-0.00026	0.094

Data obtained from pheWAS summary results statistics at http://geneatlas.roslin.ed.ac.uk/phewas/, accessed March 27, 2019.[8]

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