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ORIGINAL RESEARCH

Arrhythmia in patients with systemic sclerosis: incidence, risk factors and impact on mortality in a Swedish register-based study

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ABSTRACT

Objectives The objectives of this study are to study the risk of developing cardiac arrhythmia and its subtypes over time in patients with systemic sclerosis (SSc), to assess potential risk factors for arrhythmia in SSc and to explore whether arrhythmia is associated with mortality.

Methods We used nationwide Swedish registers to identify patients with incident SSc 2004–2019 and matched general population comparators (1:10). The primary outcome was incident arrhythmia. Follow-up started at the date of SSc diagnosis and ended at the primary outcome, death, emigration or 31 December 2019. We estimated the incidence of arrhythmia overall and stratified by subtype and explored the relative risk in relation to time since diagnosis using flexible parametric models. We used Cox regression to study risk factors for arrhythmia and the association of arrhythmia with mortality.

Results We identified 1565 patients and 16 009 comparators. The overall incidence of arrhythmia was 255 (95% CI 221 to 295) and 119 (95% CI 112 to 127) per 10 000 person years in patients with SSc and comparators, respectively, corresponding to an IRR of 2.1 (95% CI 1.8 to 2.5). The greatest hazard difference between patients with SSc compared with the comparators was seen in the first year of follow-up (HR for arrhythmia 3.0; 95% CI 2.3 to 3.8). Atrial fibrillation and flutter were the most common arrhythmia subtypes. Male sex, index age and pulmonary arterial hypertension were significant risk factors for arrhythmia in SSc. Incident arrhythmia was significantly associated with mortality (HR 2.2; 95% CI 1.6 to 3.0).

Conclusion SSc is associated with higher incidence of cardiac arrhythmia compared with general population. Arrhythmia seems to be an early manifestation of SSc and is associated with higher mortality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although the association between systemic sclerosis (SSc) and arrhythmia has been studied previously, it is unknown when in relation to SSc diagnosis the risk for developing arrhythmia is increased compared with the general population. We also need to know what impact a newly diagnosed arrhythmia has on mortality.

WHAT THIS STUDY ADDS

⇒ The risk for developing arrhythmia in patients with SSc is highest during the first few years after SSc diagnosis indicating arrhythmia is an early manifestation of SSc. Arrhythmia is associated with higher mortality than patients with SSc without arrhythmia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the importance of active screening for arrhythmia in patients with SSc, particularly early when SSc is diagnosed.

INTRODUCTION

Systemic sclerosis (SSc) is a rare disease of the connective tissue characterised by autoimmunity, vasculopathy and fibrosis. It has the highest mortality among the inflammatory systemic rheumatic diseases.[1 2] SSc-related cardiac manifestations contribute significantly to SSc-related morbidity and mortality[3] and arrhythmia is a frequent cardiac complication of SSc.[4–6] Six per cent of the overall causes of death in patients with SSc have been attributed to arrhythmia.[7] Although the association between SSc and arrhythmia has been studied previously,[5 6 8] there are still important clinical issues related to this cardiac manifestation that need to be addressed. One such question is when in relation to SSc diagnosis the risk is increased compared with the general population. We also need to know what risk factors for arrhythmia we should beware of and what impact a newly diagnosed arrhythmia has on mortality.

We therefore set out to study the development of arrhythmia risk in SSc with respect to time since diagnosis, compared with individuals from the general population,

in a population-based nationwide study on unselected patients with SSc and an age-matched and sex-matched general population comparator cohort. Our aim was to study the absolute and relative risk of arrhythmia overall and in relation to time since SSc diagnosis, stratified into arrhythmia subtypes, as well as to explore risk factors for arrhythmia in SSc and whether arrhythmia is associated with higher mortality.

METHODS

Study design and setting

This is a population-based matched cohort study relying on nationwide registers comprising data obtained from the national tax-funded healthcare system covering all residents in Sweden.

Data sources and participants

We used the National Patient Register (NPR), comprising data on all hospitalisations in Sweden since 1987 and all outpatient non-primary specialist care visits since 2001 coded according to the International Statistical Classification of Diseases and Related Health Problems (ICD) codes.[9] We also used the Total Population Register, to obtain demographic data such as sex, birth year, residential area and so on.[10] To identify baseline comorbidities, we further used the National Prescribed Drug Register (NPDR), comprising data on all dispensed prescriptions to the entire population of Sweden since 1 July 2005 using ATC codes (Anatomical Therapeutic Chemical Classification System).[11] The study population includes patients with incident SSc in Sweden between 2004 and 2019 and 1:10 comparators from the general population matched on sex and birth year.

We considered individuals as incident patients with SSc if they fulfilled the following criteria: (1) registered as living in Sweden, (2) at least two visits where SSc was the main diagnosis (ICD-10: M34.0, M34.1, M34.8, M34.9), (3) the first visit between 1 January 2004 and 31 December 2019, (4) the second visit within 12 months of the first, (5) at least one of the two visits had to be coded in a rheumatology or internal medicine clinic/department, (6) 18 years or older at the date of the second visit, (7) no visits with SSc coded as main or secondary diagnosis prior to study start, to ensure that the included patients truly were incident cases. Index date, start of follow-up, was defined as the date of the second disease-defining visit for patients with SSc; the same date was assigned to the respective comparators. We identified 1:10 comparators from the general population matched on sex and birth year who were alive at the index date of the respective patient with SSc. We excluded individuals who had any visit indicating arrhythmia as main or secondary diagnosis (ICD-10: I44–I49) prior to the index date.

Exposure, outcome definition and covariates

We defined the exposure as an incident diagnosis of SSc. The primary outcome in the analysis of arrhythmia overall is incident arrhythmia of any subtype (main or secondary diagnosis) coded ICD-10: I44–I49. The primary outcome in the analysis of arrhythmia subtypes was stratified using ICD-10 codes into (1) conduction disorders (I44, I45.0, I45.1, I45.2, I45.3, I45.4, I45.5, I45.8, I45.9, I49.5), (2) atrial fibrillation and flutter (I48), (3) cardiac arrest and ventricular arrhythmia (I46, I47.0, I47.2, I49.0), (4) paroxysmal supraventricular tachycardia (PSVT) (I45.6, I47.1, I47.9) and (5) other (I49.1, I49.2, I49.3, I49.4, I49.8, I49.9). As a secondary analysis, we identified participants who received a permanent pacemaker or implantable cardioverter defibrillator during follow-up using procedure codes available in the NPR introduced by the Swedish Board of Health and Welfare.[12] The used codes are presented in online supplemental data 1. We followed all participants from the index date until the chosen outcome in each analysis or until being censored in case of death, emigration or 31 December 2019, whichever occurred first.

When exploring whether developed arrhythmia during follow-up in patients with SSc is associated with mortality, the primary outcome was death. We followed patients with SSc in this analysis from the index date until death, or until being censored in case of emigration or 31 December 2019, whichever occurred first.

We identified the following comorbidities at baseline: diabetes, hypertension, heart failure, ischaemic heart disease, asthma/chronic obstructive pulmonary disease and renal disease. In patients with SSc, we identified two SSc-related manifestations: pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD). We also identified those who were treated with SSc-related drugs: methotrexate, mycophenolic acid, hydroxychloroquine, phosphodiesterase-5 (PDE5) inhibitors and calcium channel blockers (CCB). Since data from the NPDR are available from 1 July 2005, analyses comprising baseline comorbidities and SSc-related manifestations and drugs will be conducted on participants with index date starting from 1 January 2006. The definition of these comorbidities, manifestations and drugs is presented in online supplemental data 2.

Statistical methods

To describe the baseline characteristics of the study population, we used n (%), means (SD) and medians (IQR), as appropriate. We used time since index date as time scale in all models.

We used the Kaplan-Meier method to estimate the cumulative probability of developing arrhythmia in patients with SSc and their comparators, and the Log-rank test to compare the two groups. We estimated the incidence rate of arrhythmia overall and stratified by arrhythmia subtype using Poisson regression adjusted for sex and age. We estimated incidence rate ratios (IRR) using Poisson regression adjusted for sex and index age to compare the risk of developing arrhythmia between the two groups. To study the absolute and relative risk of arrhythmia over time, we used the flexible parametric models to estimate time-varying hazard and HR by

allowing for time-dependent effect of SSc.[13] To study risk factors for developing arrhythmia in patients with SSc, we used a multivariable Cox regression model comprising the following variables: sex (women as reference), index age (as a continuous variable), baseline comorbidities, PAH, ILD and SSc-related drugs.

To explore whether developed arrhythmia overall during follow-up in patients with SSc is associated with mortality, we used a multivariable Cox regression model comprising sex, index age, the baseline comorbidities mentioned above, PAH as time-varying covariate and arrhythmia as time-varying covariate.[14] We stratified this analysis by arrhythmia subtype to explore the potential association of each subtype with mortality. We used R V.3.6.3 (R foundation for statistical computing, Vienna, Austria) to perform the statistical analyses.

Patient and public involvement

This study is a register-based study. Patients and/or the public were not involved in the design, or conduct, or reporting of this research.

RESULTS

We identified 1722 patients with incident SSc between 2004 and 2019 and 16983 comparators. We excluded 157 (9%) patients with SSc and 974 (6%) comparators who received ICD-10 code indicating arrhythmia prior to the index date (online supplemental figures 1 and 2). The final cohort consisted therefore of 1565 patients with SSc and 16009 matched comparators. The majority of the cohort were women (81% of each of patients with SSc and the comparators). The mean age at index date was 57.6 (SD 14.7) years in patients with SSc and 57.9 (SD 14.8) years in the comparators. The median follow-up in the analysis of arrhythmia overall was 4.9 years (IQR 6.7) in patients with SSc and 6.2 years (IQR 7.1) in their comparators. Table 1 shows baseline characteristics.

Table 1 Baseline characteristics of patients with systemic sclerosis (SSc) and the general population comparators with no prior 10th revision of the International Classification of Diseases code indicating arrhythmia

	Patients with SSc	General population comparators
N	1565	16009
Age at start of follow-up, years, mean (SD)	57.6 (14.7)	57.9 (14.8)
Follow-up, years, median (IQR)	4.9 (6.7)	6.2 (7.1)
Sex		
Women, n (%)	1274 (81%)	12973 (81%)
Men, n (%)	291 (19%)	3036 (19%)
Age at start of follow-up (years), n (%)		
18–49	458 (29%)	4613 (29%)
50–59	357 (23%)	3612 (22%)
60–69	411 (26%)	4149 (26%)
70+	339 (22%)	3635 (23%)
Baseline comorbidities*, n (%)		
Diabetes	85 (6%)	977 (7%)
Hypertension	514 (37%)	3558 (25%)
Heart failure	60 (4%)	144 (1%)
Ischaemic heart disease	91 (7%)	619 (4%)
Asthma/COPD	330 (24%)	2662 (19%)
Renal disease	63 (5%)	358 (3%)

*Baseline comorbidities were identified in only participants with index date starting from 1 January 2006 (1393 patients with SSc and 14246 matched comparators) since data from the drug register are available starting from 1 July 2005.
COPD, chronic obstructive pulmonary disease.

Arrhythmia overall

The cumulative probability of developing arrhythmia was significantly higher in patients with SSc than the comparators (p<0.0001), figure 1. In the SSc cohort, 186 patients (12%) developed arrhythmia during follow-up compared with 1140 individuals of the comparators (7%). The sex-adjusted and age-adjusted incidence rate of arrhythmia overall was 255.0 (95% CI 220.5 to 295.0) per 10000 person years in patients with SSc and 119.3 (95% CI 112.3 to 126.7) per 10000 person years in their comparators, corresponding to an IRR of 2.1 (95% CI 1.8 to 2.5), figure 2. During follow-up, 11 patients with SSc (0.70%) and 103 of the comparators (0.64%) received a permanent pacemaker. Two patients with SSc (0.13%) and 16 of the comparators (0.09%) received an implantable cardioverter defibrillator. Incidence rates of arrhythmia overall were higher in women and men with SSc than their comparators (figure 2); IRR were 2.1 (95% CI 1.7 to 2.5) and 2.3 (95% CI 1.7 to 3.1), respectively.

Of patients with SSc and incident arrhythmia (n=186), more than half of them developed arrhythmia in the first 3 years since the index date, whereas in the matched comparators with incident arrhythmia (n=1140) the distribution over the follow-up period was more even (figure 3). Throughout almost the entire follow-up period, patients with SSc had higher rate of incident arrhythmia overall in comparison to their comparators (figure 4). At the end of the 1st year of follow-up, we noted a 200% higher rate in SSc (HR 3.0; 95% CI 2.3 to 3.8), at the end of the 5th year of follow-up, a 20% higher rate (HR 1.2; 95% CI 0.7 to 1.8), at the end of the 10th year of follow-up, the rate was doubled (HR 2.0; 95% CI 1.5 to 2.7) and at the end of the entire follow-up, the rate was increased by 160% (HR 2.6; 95% CI 1.5 to 4.5).

Risk factors for arrhythmia

Multivariable Cox regression analysis of risk factors for developing arrhythmia overall showed that male sex (HR 1.8; 95% CI 1.2 to 2.6, p=0.002), age at index as a continuous variable (HR 1.05; 95% CI 1.03 to 1.07, p<0.001, per 1 year), and PAH as time-varying covariate (HR 2.8; 95% CI 1.6 to 4.8, p<0.001) were risk factors for developing arrhythmia. The remaining variables were not associated with statistically significant increased risk for arrhythmia overall (table 2).

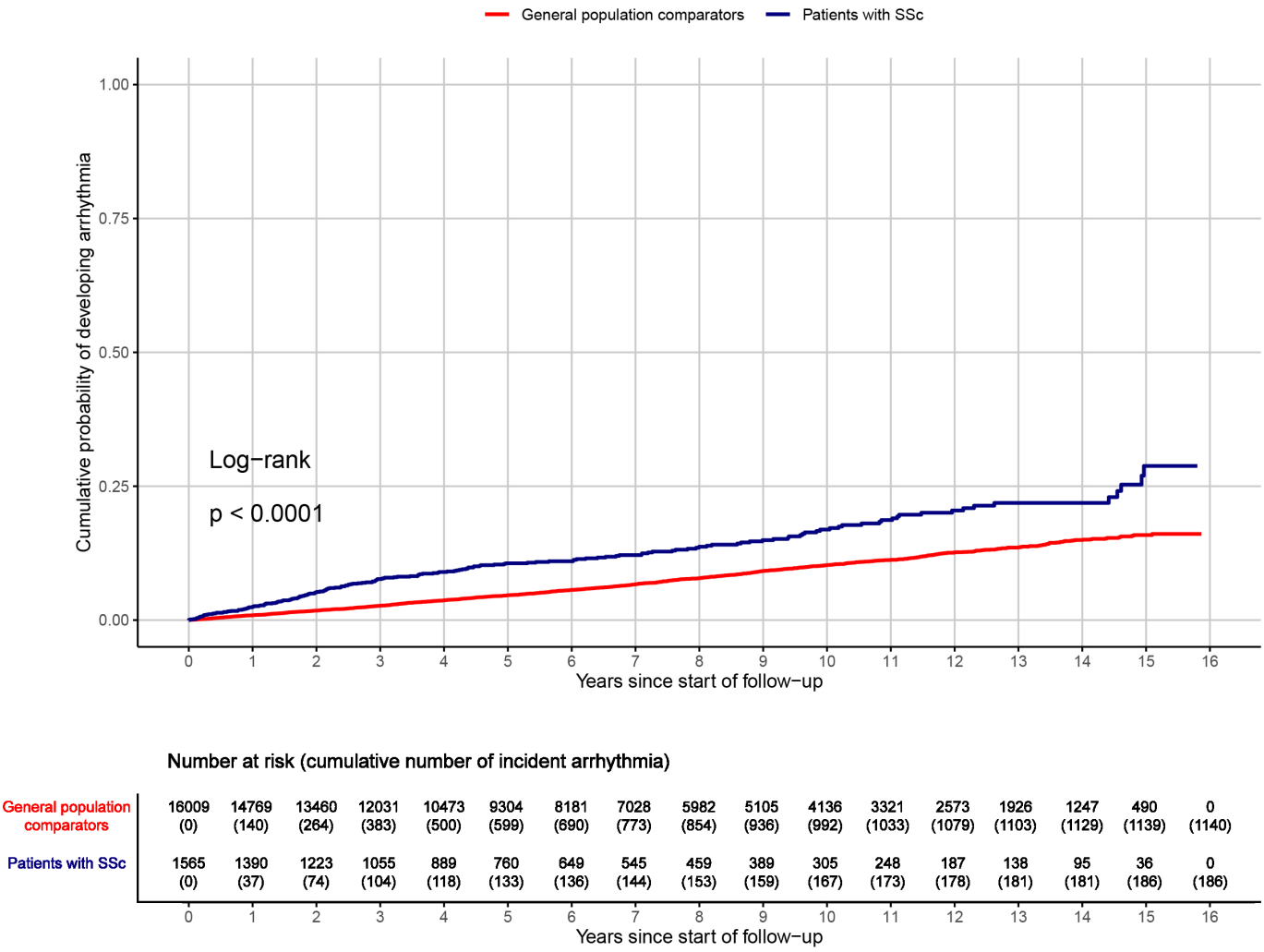

Figure 1 Cumulative probability of developing any arrhythmia in patients with systemic sclerosis (SSc) and the general population comparators.

Arrhythmia subtypes

The incidence rates of all arrhythmia subtypes, defined above, were higher in patients with SSc than in the matched comparators (figure 2). Atrial fibrillation and flutter were noticeably the most common arrhythmia subtype in both groups; the incidence rate in patients with SSc was 186.7 (95% CI 156.9 to 222.2) per 10 000 person years and 89.2 (95% CI 83.1 to 95.8) per 10 000 person years in the comparators. IRRs were statistically significant in all arrhythmia subtypes; 2.1 (95% CI 1.4 to 3.1) for conduction disorders, 2.1 (95% CI 1.7 to 2.5) for atrial fibrillation and flutter, 3.2 (95% CI 2.1 to 4.9) for cardiac arrest and ventricular arrhythmia, 2.3 (95% CI 1.3 to 3.9) for PSVT and 2.4 (95% CI 1.6 to 3.6) for other arrhythmias. The distribution of each arrhythmia subtype across age groups is presented in online supplemental figure 3.

The association between arrhythmia and mortality in patients with SSc

Of the 1393 patients with SSc starting from 1 January 2006, 281 (20%) were deceased during the follow-up period. Of those who deceased, 74 patients (26% of total deaths) had developed arrhythmia prior to death. Multivariable Cox regression analysis comprising sex, index age, baseline comorbidities, PAH and arrhythmia showed that incident arrhythmia overall was associated with increased risk of death in patients with SSc (HR 2.2; 95% CI 1.6 to 3.0, p<0.001). Atrial fibrillation and flutter (HR 2.2; 95% CI 1.6 to 3.1) and cardiac arrest and ventricular arrhythmia (HR 5.7; 95% CI 2.5 to 13.1) were significantly associated with increased risk of death (table 3).

DISCUSSION

In this study, we demonstrated that SSc was associated with higher incidence rate of arrhythmia compared with general population and that the risk for developing arrhythmia in patients with SSc was highest early after index. Developing arrhythmia was associated with significantly worse prognosis. However, our study did not aim to establish causality between SSc and arrhythmia, or between arrhythmia and death. Our findings should be

	Patients with SSc (n = 1565)		General population comparators (n = 16009)		
	Number of cases	Incidence rate[a] with 95% CI	Number of cases	Incidence rate[a] with 95% CI	Incidence rate ratio (IRR) with 95% CI
All arrhythmias	186	255.0 (220.5-295.0)	1140	119.3 (112.3-126.7)	**2.1 (1.8-2.5)**
Stratified by sex					
Women	132	219.9 (185.1-261.2)	816	105.8 (98.5-113.6)	**2.1 (1.7-2.5)**
Men	54	406.7 (309.1-535.1)	324	177.2 (158.2-198.5)	**2.3 (1.7-3.1)**
Stratified by arrhythmia subtype					
Conduction disorders	27	34.0 (23.3-49.6)	164	16.3 (13.9-19.0)	**2.1 (1.4-3.1)**
Atrial fibrillation and flutter	132	186.7 (156.9-222.2)	832	89.2 (83.1-95.8)	**2.1 (1.7-2.5)**
Cardiac arrest and ventricular arrhythmia	28	33.6 (23.2-48.5)	108	10.4 (8.6-12.6)	**3.2 (2.1-4.9)**
Paroxysmal supraventricular tachycardia	16	17.1 (10.5-27.9)	83	7.5 (6.1-9.4)	**2.3 (1.3-3.9)**
Other	31	33.6 (23.7-47.7)	152	13.9 (11.8-16.3)	**2.4 (1.6-3.6)**

a per 10 000 person-years

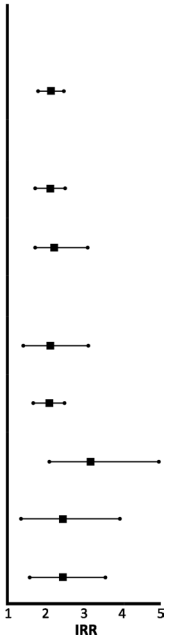

Figure 2 Incidence rate of arrhythmia overall and stratified by arrhythmia subtype in patients with systemic sclerosis (SSc) and the general population comparators using Poisson regression adjusted for sex and age (as a continuous variable). Incidence rate ratios were calculated using Poisson regression adjusted for sex and age.

interpreted with caution, considering the register-based study design and the potential residual confounding from unmeasured variables.

The exact pathophysiology and aetiology of arrhythmia in SSc is yet to be understood, but several mechanisms have been suggested. They include microvascular injuries due to recurrent vasospasm, fibrosis engaging the myocardial tissue and structural changes, such as ventricular dilatation and diastolic dysfunction, leading to secondary arrhythmias.[8] The inflammatory burden of SSc, particularly myocarditis, has also been suggested to be implicated in the pathogenesis of arrhythmia in SSc.[15] However, it is also important to consider the abundant use of nifedipine as well as other vasoactive drugs in patients with SSc which may induce tachyarrhythmias. Our study focused on the incidence of new-onset arrhythmia in patients with SSc after the diagnosis of SSc was made. The incidence rate of arrhythmia overall was 255.0 per 10 000 person years. The risk for developing arrhythmia compared with the comparators was highest during the first few years after the index date and declined thereafter over time, but remained significant throughout almost the entire follow-up period (figure 4). More than half of arrhythmias in patients with SSc occurred during the first 3 years since the index date which indicates that arrhythmia is an early manifestation of SSc (figure 3).

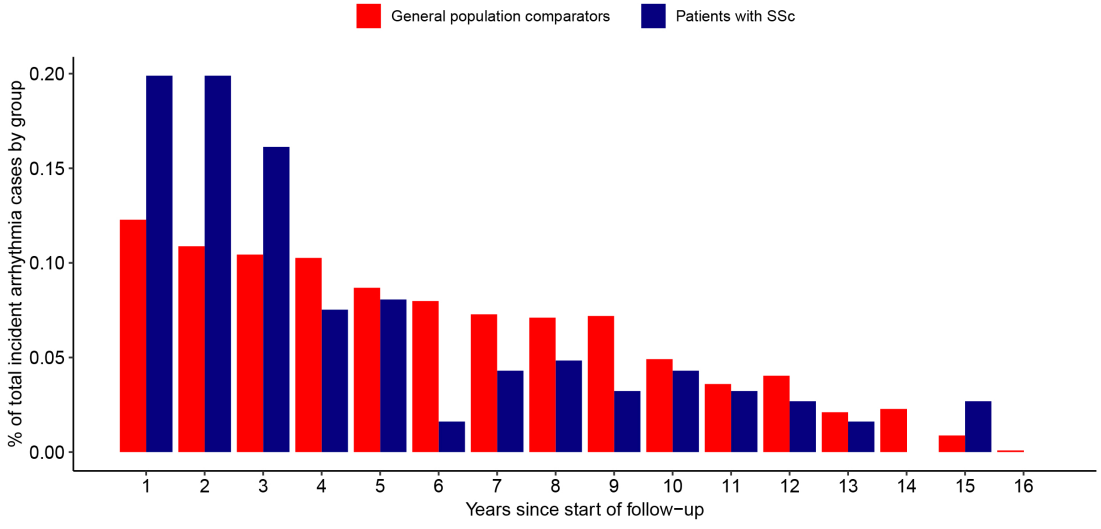

Figure 3 The distribution of total incident arrhythmias in patients with systemic sclerosis (SSc) and the general population comparators in % over years since start of follow-up.

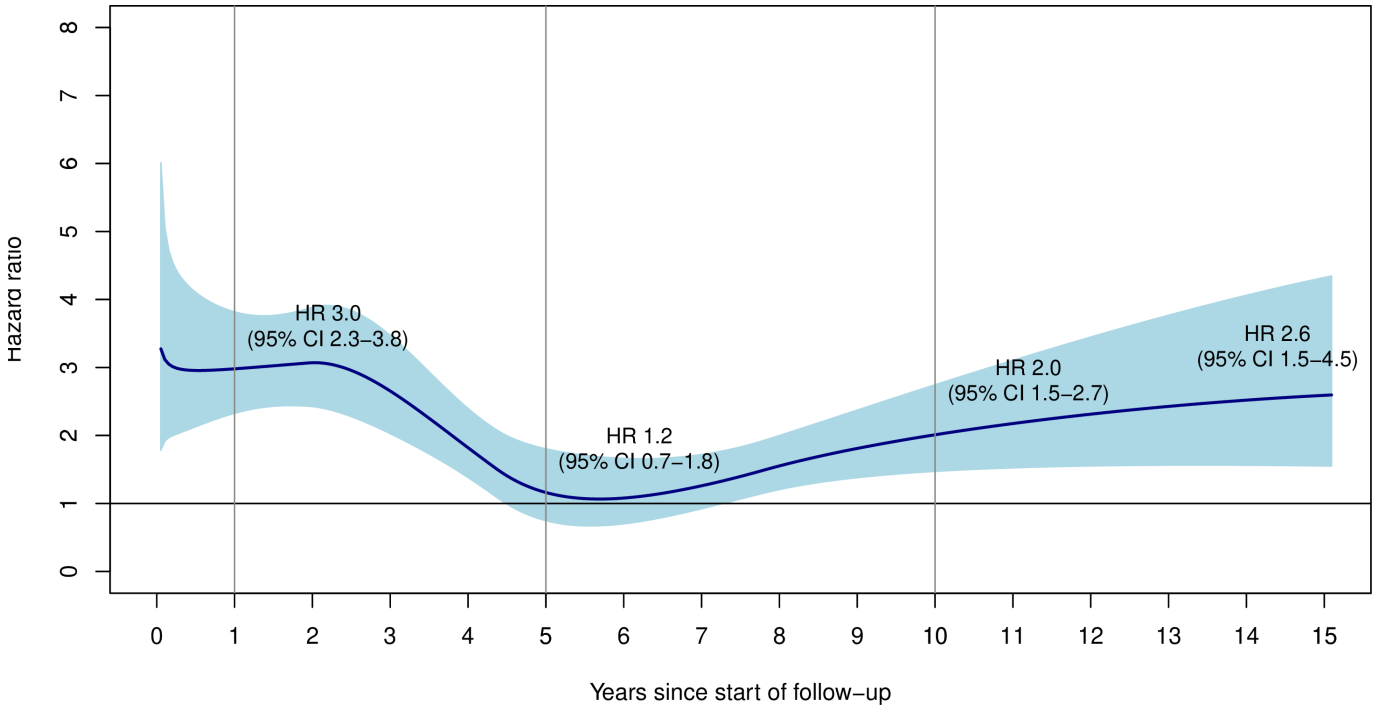

Figure 4 HR of incident arrhythmia in patients with systemic sclerosis (SSc) compared with the general population comparators using flexible parametric models, adjusted for sex and age as a continuous variable (sex=men and index age=58 years) with degree of freedom=3 and allowing for time-dependent effect of SSc.

Patients when diagnosed with SSc usually undergo a comprehensive set of examinations to detect organ manifestations including echocardiography and ECG which in turn may reveal arrhythmias during the first few months after diagnosis. A similar workup is not performed on individuals from the general population. This could partly explain why the incidence rate is highest early after index in patients with SSc but not in the general population. However, the risk remains elevated compared with the general population throughout follow-up, which cannot be explained only by a more thorough screening in SSc.

Table 2 Multivariable Cox regression model of risk factors for developing arrhythmia overall in patients with systemic sclerosis (SSc) comprising sex (women as reference), index age (as a continuous variable) and baseline comorbidities, in addition to pulmonary arterial hypertension (PAH), interstitial lung disease (ILD) and SSc-related drugs as time-varying covariates

Variable	SSc population (n=1393)	HR (95% CI)
Age (continuous)	–	**1.05 (1.03 to 1.07)**
Sex (women as reference)	1146	**1.8 (1.2 to 2.6)**
Diabetes	85	0.9 (0.5 to 1.8)
Hypertension	514	1.4 (1.0 to 2.1)
Heart failure	60	1.3 (0.6 to 2.5)
Ischaemic heart disease	91	0.9 (0.5 to 1.5)
Asthma/COPD	330	0.9 (0.6 to 1.3)
Renal disease	63	1.6 (0.8 to 3.0)
PAH	151	**2.8 (1.6 to 4.8)**
ILD	209	0.6 (0.3 to 1.1)
Methotrexate	250	0.7 (0.4 to 1.3)
Mycophenolic acid	301	1.2 (0.7 to 1.9)
Hydroxychloroquine	134	1.0 (0.5 to 2.1)
PDE5 inhibitors	264	1.2 (0.7 to 2.0)
CCB	950	0.9 (0.6 to 1.3)

Bold font indicates statistically significant values.
CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; PDE5, inhibitors phosphodiesterase-5 inhibitors.

Table 3 Multivariable Cox regression model of the association between arrhythmia and mortality in patients with systemic sclerosis (SSc) comprising sex (women as reference), index age (as a continuous variable) and baseline comorbidities, in addition to pulmonary arterial hypertension as time-varying covariate

	SSc population (n=1393)		
Arrhythmia	**Patients with incident arrhythmia (n)**	**Arrhythmia prior to death (n)**	**HR (95% CI)**
Arrhythmia overall	150	74	**2.2 (1.6 to 3.0)**
Conduction disorders	19	10	1.1 (0.6 to 2.3)
Atrial fibrillation and flutter	108	60	**2.2 (1.6 to 3.1)**
Cardiac arrest and ventricular arrhythmia	21	15	**5.7 (2.5 to 13.1)**
PSVT	12	2	1.5 (0.4 to 6.3)
Other	25	3	1.1 (0.4 to 3.6)

Arrhythmia was treated as time-varying covariate in the model.
Bold font indicates statistically significant values.
PSVT, paroxysmal supraventricular tachycardia.

There are differences in the literature between studies investigating arrhythmia in SSc with regard to study population, design and definition of arrhythmia. Our estimates should therefore be compared with other studies with caution considering those issues. A higher prevalence of abnormal ECG (28% vs 17%) and 24-hour Holter monitoring (38% vs 17%) was reported in patients with SSc in Stockholm compared with matched healthy comparators in a previous study. In both groups, the most common finding on Holter was frequent ectopic beats.[16] A single-centre study in China[17] on patients with incident SSc between 2009 and 2015 found that 4% of patients with SSc had arrhythmia at diagnosis, and 3% developed incident arrhythmia during follow-up (compared with 9% and 12%, respectively, in our cohort). A higher prevalence at baseline of 15% was reported in a study from the USA on an early SSc cohort where patients were enrolled within 5 years of onset of the first non-Raynaud's phenomenon symptom.[18] In a retrospective review of Spanish patients diagnosed with SSc in a single centre between 1976 and 2011, 23% of the patients had conduction alterations (defined as atrial fibrillation, ventricular ectopic beats, atrial flutter, supraventricular paroxysmal tachycardia, bundle and fascicular block, AV-block, ventricular tachycardia).[19] With regard to device implantation, our study comprised a rather small cohort to be able to detect significant differences between patients with SSc and the comparators in the proportion of those who received a pacemaker (0.70% vs 0.64%) or implantable cardioverter defibrillator (0.13% vs 0.09%). A Danish nationwide register-based study[6] with similar design as our study where patients with SSc were matched to comparators from the general population (1:5) found that during follow-up 1.7% of patients with SSc received either pacemaker or ICD compared with 1% of the comparators. That study covered, however, a longer follow-up period, 1995–2015 compared with 2004–2019 in our study, and a larger cohort of patients with SSc; 2778 compared with 1565 in our study.

Conduction disorders have been suggested to occur due to myocardial fibrosis disrupting the transmission of electrical impulses in the cardiac conduction system.[8] The incidence rate of conduction disorders in our study was significantly higher in patients with SSc. Similarly, a population-based cohort study of patients with incident SSc 1980–2016 and sex-matched and age-matched comparators in the USA[20] reported a higher cumulative incidence of conduction disorders (AV-block, right bundle branch block *RBBB*, left bundle branch block, bifascicular block and prolonged QT) than in the comparators, using ECG and Holter monitoring.

SSc has consistently been reported to be associated with increased risk of atrial fibrillation. A large population-based study in the UK found that SSc had the most significant association with new-onset atrial fibrillation among other autoimmune diseases, including gastrointestinal disorders, rheumatic diseases and neurological disorders.[21] Similar findings were reported by a large register-based study in South Korea.[22] In our study, SSc was significantly associated with atrial fibrillation and flutter combined which were the most common arrhythmia subtype in patients with SSc, findings that are in line with another study where atrial fibrillation was the most common.[19] The above-mentioned Danish study with similar design and outcome definition as our study reported lower incidence estimates than what we found. They partly used the same ICD codes to identify prevalence at baseline and incidence of cardiovascular manifestation in patients with SSc between 1995 and 2015, with the addition of ICD-8 codes in the early part of the study period.[6] The incidence estimates in our study were noticeably higher than in the Danish study in both patients with SSc (186.7 vs 92 per 10 000 person years) and the comparators (89.2 vs 54 per 10 000 person years). Possible explanations to that difference include higher mean age at index in our cohort (57.6 vs 55 years), different time periods and different ICD versions (2004–2019 vs 1995–2015), and potential differences in screening practices. Nonetheless, the Danish study showed that patients with SSc had 75% higher risk (HR 1.75) of developing arrhythmia than the comparators, which is comparable to our overall estimate (IRR 2.1).

The multivariable Cox regression in the present study revealed that increasing age at index, male sex and PAH were significantly associated with developing arrhythmia in patients with SSc. In contrast, male sex was not found to be an independent risk factor for conduction disorders and rhythm disorders in a cohort study from the USA.[20] This could be due to the small sample size (64 patients) and the study being underpowered to detect potential association. The authors reported age as a risk factor for conduction disorders but not for rhythm disorders (atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular tachycardia and ventricular ectopic beats). Other studies reported correlation between hs-cTnT and NT-proBNP levels and the number of supraventricular ectopic beats and ventricular ectopic beats identified on Holter monitoring.[23]

In our study, we have analysed the impact of new-onset arrhythmia on mortality in patients with SSc. In a multivariable Cox regression model adjusted for sex, age, baseline comorbidities and PAH, we found that developing arrhythmia overall after SSc diagnosis was a significant risk factor for death (HR 2.2). Among arrhythmia subtypes, atrial fibrillation and flutter in addition to cardiac arrest and ventricular arrhythmia were significant risk factors for death. The prognostic value of arrhythmia as a risk factor for poor outcome has been reported in several studies in the literature but either at baseline or in a cross-sectional study design. Kostis *et al* reported that ventricular ectopy was associated with mortality and sudden death during follow-up.[24] Frequent ventricular ectopic beats on Holter in an Italian cohort were also found to be associated with life-threatening arrhythmic complications including sudden cardiac death and ventricular tachycardia/fibrillation during follow-up.[23] "Clinically significant arrhythmia on ECG" and RBBB at baseline in a cohort enrolled within 5 years of the onset of the first non-Raynaud's phenomenon symptom was found to be a predictor of mortality.[18 25] Likewise, having arrhythmia when SSc diagnosis was made was found to be a prognostic factor for mortality in a Chinese cohort (HR 4.7).[17] A register-based study from the USA explored adult hospitalisations with atrial fibrillation as main diagnosis with and without SSc as a secondary diagnosis using ICD codes. That study found that patients who had coexisting SSc diagnosis had more than three times the odds of inpatient mortality in comparison to patients without SSc, adjusted for confounders.[26] The mechanism between arrhythmia and mortality is probably partly due to sudden cardiac death and partly that several different types of arrhythmias lead to or exacerbate heart failure.[27 28]

A major strength of the present study is that it comprised a large population-based unselected cohort of all patients with SSc in Sweden, not just patients from tertiary care, allowing us to report robust estimates on the occurrence of arrhythmia and to conduct several subanalyses including assessing arrhythmia subtypes, risk factors for arrhythmia and the association between arrhythmia and mortality, in a population that is highly representative for the SSc population in Northern Europe. The high and equal access to care, and longtime use of healthcare registers in Sweden is also a strength of the study, providing us with high-quality data collected in an unbiased fashion. Medical emergencies, such as ventricular tachycardia, high-rate PSVT and high-rate atrial fibrillation, that usually are managed in hospital or in outpatient non-general practitioner specialised care, are therefore most likely captured in both patient without any chronic disease and in patients with chronic diseases such as SSc equally and well.

However, using register data based on ICD codes to identify and detect disease has its limitations. There are, for example, no ICD codes in use today that with high resolution capture the complexity of SSc and its heterogeneity. We are therefore unable to provide clinical details such as disease subtype, disease phenotype and autoantibody profile of our patients. These data are important in clinical practice and lack thereof is therefore a limitation. In patients with SSc, benign and asymptomatic arrhythmias, such as ventricular ectopic beats, are most likely captured in the NPR through the extensive screening our patients go through. In the comparators, these benign outcomes might have either gone undetected, due to lack of extensive screening, or been identified in primary care and therefore have not been identified in this study. This could lead to differential misclassification of outcome and would lead to overestimation of the true association between exposure and outcome. On the other hand, it is also possible that benign arrhythmias sometimes are left uncoded by the physician, despite being detected, something that would impact patients with SSc and comparators equally resulting in non-differential misclassification of outcome which would bias the association towards the null. Therefore, the association between exposure and outcome presented in our report could be slightly overestimated or slightly underestimated. We do not have information on whether arrhythmia was diagnosed using ECG, Holter monitoring or other diagnostic modalities since this study is register based not relying on medical charts review or prospective collection of data in our own clinics. Using ICD codes to identify clinically relevant arrhythmias in the NPR however has high validity, the validity of atrial fibrillation and flutter diagnosis, for instance, in the NPR is high with a positive predictive value (PPV) of 97% compared with medical charts.[29] Another limitation of this study is the lack of data on traditional cardiovascular risk factors, including smoking status, body mass index and so on. How these unmeasured variables would impact the estimation of the association is difficult to speculate in but would have been interesting to explore.

In conclusion, this study demonstrates that patients with SSc have significantly higher incidence rate of arrhythmia compared with the general population. The risk for developing arrhythmia is highest during the first few years after SSc diagnosis indicating that arrhythmia is an early manifestation of SSc. Its significant association

with higher mortality in patients with SSc highlights the importance of active screening for arrhythmia in SSc.

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