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Primary myocardial disease in scleroderma – a comprehensive review of the literature to inform the UK Systemic Sclerosis Study Group cardiac working group

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Short title: Primary myocardial disease in SSc

Abstract

Cardiac disease is prevalent in Systemic Sclerosis (SSc) and associated with a poor prognosis. Differentiating primary myocardial disease (SSc-cardiomyopathy) from ischaemic heart disease (IHD) is difficult, and the disease phenotype most at risk is unclear. A comprehensive literature review was performed to inform the UK Systemic Sclerosis Study Group for cardiac disease tasked with producing a best practice pathway for the management of cardiac disease in SSc. This review describes the prevalence of SSc-cardiomyopathy, its associated greater mortality, and various manifestations, for example, heart failure, arrhythmias and diastolic dysfunction. The limited evidence suggests SSc-cardiomyopathy is associated with other poor prognostic indicators such as diffuse cutaneous disease, positive SSc-specific serology, black ethnicity, older age at disease onset,

tendon friction rubs, abnormal nail-fold capillaroscopy and worse quality of life scores.

Differentiating SSc-cardiomyopathy from IHD requires well planned studies. Non-invasive investigative techniques are improving the understanding of its pathophysiological basis.

Key words: systemic sclerosis, scleroderma, SSc-cardiomyopathy, primary myocardial disease, cardiac disease

Key messages

SSc-cardiomyopathy is prevalent in SSc and is associated with poor SSc prognostic indicators.

Advancing non-invasive investigative techniques are helping to inform the pathophysiology of SSc-cardiomyopathy.

Differentiating SSc-cardiomyopathy from ischaemic heart disease requires well planned future studies.

Introduction

Cardiac disease in systemic sclerosis (SSc, Scleroderma), distinct from pulmonary vasculopathy and its associated cardiac effect, carries a significant mortality risk, and manifests in various ways, such as myocarditis and conduction abnormalities [1, 2]. The SSc disease phenotype most at-risk of SSc-cardiomyopathy is relatively under explored, leaving uncertainty in disease management; compounded by the difficulty in sometimes differentiating primary myocardial disease (herewith termed SSc-cardiomyopathy) from that of macrovascular cardiovascular disease (CVD).

Recently, the UK Systemic Sclerosis Study Group initiative (UKSSSG) producing the expert consensus best practice management for SSc, commissioned best practice guidelines for the detection and management of myocardial disease in SSc in the UK. The purpose of this comprehensive literature

review was to inform these guidelines with a focus on the prevalence and nature of SSc-cardiomyopathy, its associated mortality and prognosis, and associations with disease phenotype. This would in addition serve to highlight knowledge gaps to help determine a future research agenda.

Search strategy**Methods**

Remit of literature search

The UKSSSG cardiac group outlined the requirements for the literature search, namely to answer the following questions: What is the prevalence of primary myocardial disease in SSc, and how does it present?; To what extent is primary myocardial disease associated with greater mortality in SSc?; Is primary myocardial disease associated with a specific disease subtype or serology? ; and Do poor prognosis SSc clinical features associate with increased evidence of primary myocardial disease?

Literature search

In September 2012, EMBASE, MEDLINE, and the Cochrane database were searched from 1946 with the help of an experienced librarian. The search terms scleroderma, systemic sclerosis and CREST were used, in combination with myocardial, cardiac, cardiovascular, conduction defect or arrhythmia. MeSH terms and subject headings were used for all. The references of relevant and recent reviews, American College of Rheumatology, European League Against Rheumatism and Scleroderma World Congress abstracts from 2010 to 2012, were checked to ensure no other original relevant articles were missed. Therapeutic intervention studies were outside of the search remit.

Eligibility criteria and data extraction

Studies not published in English, not in adults and non-original articles were not included. Unless providing any additional information, publications already included in obtained meta-analyses/systematic reviews were excluded to avoid repetition. Studies were dismissed if

insufficient detail was supplied for a thorough analysis. Case series were excluded. To avoid a biased perspective of the case study analysis, publications referring to scleroderma in specific cohorts, for example, those with sine scleroderma, were excluded.

Studies with the following were excluded (1) Reports not covering scleroderma and cardiac disease (2) Articles purely referring to macrovascular (atherosclerotic) disease (3) Genetic studies (4) Publications referring to the use of soluble biomarkers due to their lack of validity, relative lack of use and/or availability in rheumatological practice; this included N Terminal-pro-Brain Natriuretic Peptide (NT-pro-BNP) (although perhaps this is now more accessible) that is also mainly applied in pulmonary hypertension studies, which was outside remit (5) Less routinely used (nuclear medicine) imaging techniques, and angiography (specific to the assessment of ischaemic heart disease (IHD)) (6) (Unless stated) Studies reporting less than 60 patients were excluded, however, due to the paucity of data, studies of 30 or more patients were considered for the cardiac MRI, conduction and autonomic analyses.

In an effort to avoid inclusion of undifferentiated/other connective tissue diseases (CTDs), case studies reporting prevalence of cardiac disease were only included if patients achieved the 1980 ACR criteria for SSc [3] (if published post 1980) or LeRoy criteria for SSc [4]; a criterion applied to echocardiography studies also.

One author (LAB) screened the results and undertook a detailed review. To avoid duplicate reporting, publications were dismissed if another from the same centre was already included, with the most recent and largest cohort kept. Any ambiguity was resolved following discussion with MHB.

Results

Figure 1 summarises the literature search of which 87 publications remained for analysis.

What is the prevalence of primary myocardial disease in SSc, and how does it present?

Data from case studies

The literature search detected 18 cross-sectional and prospective case studies (see Table 1) describing 4854 patients with SSc. The prevalence of cardiac involvement differed greatly across the studies, from 7% to 39% [5, 6] although there was significant heterogeneity in the definitions of cardiac disease.

Most notable publications included Ferri et al who described 30% of 1012 Italian patients with SSc [56% with limited cutaneous SSc (lcSSc), mean (SD) disease duration 5.1 (7.3) years] had at least one of the following symptoms: pericarditis, congestive heart failure (CCF), severe arrhythmias and/or atrioventricular (AV) conduction abnormalities at diagnosis, rising to 35% at follow-up (mean (SD) duration 7.1 (5.7) years) [7]. A Hungarian study reported 33% of 114 patients with SSc [70% lcSSc, mean disease duration 10.7 years] had cardiac involvement. In this study, the authors defined cardiac involvement as AV and intra-ventricular conduction disturbances, signs of myocardial ischaemia on electrocardiograph (ECG), CCF [with normal fundus by ophthalmoscopic examination (although the basis for this is unclear)], and pericarditis (without uraemia) (all evaluated using clinical symptoms, ECG and occasionally echocardiography) [8]. A more modest prevalence was found in a Japanese cohort of (n=211) where only 7.1% of patients with SSc had cardiac involvement; defined as any of the following: symptomatic pericarditis, clinical evidence of LV CCF, or arrhythmia requiring treatment[5]. Sampaio-Barros et al defined cardiac involvement as developing CCF, arrhythmia or a conduction defect requiring treatment (11.7% of 947 SSc patients affected) [9], whereas Riccieri et al also included pericarditis in the definition (18% of 92 SSc patients affected) [10].

Only one study referred to the modified Medgser severity scale [11], which classifies severity of organ involvement (Table 2), and is predictive of mortality [12]. The study reported 12.6% of 103 patients [66% lcSSc] had mild cardiac involvement, 7.8% moderate, 1.9% severe and none had end-stage cardiac disease [13]. Steen and Medgser reported 15% of 913 patients with dcSSc in a prospective study developed severe heart disease which they defined as cardiomyopathy with decrease in LV ejection fraction (LVEF) and symptoms of CCF, symptomatic pericarditis (pericardial pain), cardiac decompensation from effusion, or arrhythmia attributable to SSc requiring treatment [14]. They also commented that those who developed severe cardiac involvement were more likely to do so in the first three years of disease onset.

Where details were given, the nature of cardiac disease reported varied. Palpitations were commonly recorded [15], along with pericarditis and pericardial effusions [16, 17]. Many studies reported abnormalities in conduction, from bundle branch block [15, 18] to arrhythmias requiring intervention [16]; others merely reported any abnormality in ECG [19-21]. Further manifestations included cardiomegaly [15, 18], diastolic dysfunction [22, 23] and abnormal LVEF [22, 23].

No case study differentiated SSc-cardiomyopathy from IHD when reporting cardiac morbidity. Eloranta et al actually included myocardial infarction in their definition of cardiac involvement, reporting 39% of their 70 SSc patient cohort having cardiac involvement [6].

Data from studies using investigative tools

Electrophysiology

Electrophysiology (EP) studies in SSc commonly report cardiac abnormalities, including conduction defects, arrhythmias and autonomic dysfunction (see Supplementary Table S1, available at *Rheumatology* online); in up to 51% of cases [24-28]. Notable studies include that by Draeger et al who presented the results of ECGs analysed by cardiologists in 265 patients with early SSc in the

GENISOS (Genetics versus Environment in Scleroderma Outcome Study) cohort; 51% of patients had abnormalities [24]. A Swedish study determined 28% of 110 patients with SSc compared to 17% of 105 age/gender matched controls ($p=0.05$) had abnormal ECGs, with 15% suffering conduction abnormalities (5% in control ECGs, $p<0.01$) [27]. Forty-nine patients underwent 24 hour ambulatory monitoring; abnormal in 28% compared to 17% controls, $p=0.05$) mainly due to extra-systoles. However, 12% of the cohort had known IHD. Attempts have been made to reduce confounding from IHD; Kostis et al described SSc patients free of CVD; 43% of 183 patients with SSc had abnormal ECGs; including 20% with conduction defects [26]. Twenty-four hour ambulatory monitoring in these patients found premature atrial contractions in 61%, supraventricular tachycardia (SVT) in 21%, complete heart block in 1% and ventricular tachycardia (VT) in 7% amongst other abnormalities [26]. Intra-ventricular conduction disturbances in SSc are clinically relevant as they have been associated with the future development of AV block and other rhythm disturbances [28].

Late ventricular potentials (LVP) are variances of QRS complexes calculated using signal averaged ECGs (SAE); thought to represent areas of myocardium at risk of re-entrant arrhythmias [29]. Reports of their use in SSc have been limited, but demonstrate an increase in LVP compared to controls, and an additional role in determining myocardial disease [30].

Echocardiography

Echocardiography studies evaluating those with SSc (see Supplementary Table S2, available at *Rheumatology* online) demonstrate a wide range of abnormalities. Again, these patients are not necessarily free of overt IHD or PAH. Evidence for an increase in pericardial effusions is inconsistent [31-39].

Many studies confirm diastolic dysfunction in SSc [22, 23, 31-38, 40-45], independently associated with disease duration, age, IHD, and systemic hypertension [44]. A Polish study reported diastolic

dysfunction in 63% of 60 SSc patients [46], whilst others have been more modest [35, 45]. E/A ratio (early to late filling peak velocity ratio of tricuspid valve), which is an indicator of diastolic function, also tended to be lower in SSc [31, 33, 37, 39]. However, Aguglia et al excluded patients with secondary causes of diastolic dysfunction (including pulmonary arterial systolic pressure (PASP) greater than 45mmHg and IHD) and found no difference in Doppler variables for diastolic dysfunction, including E/A ratio [31]. Maione et al, on the other hand, demonstrated independence of an inverted E/A ratio from diastolic dysfunction risk factors suggesting primary myocardial pathology [36]. The evidence for impaired LV systolic function in SSc is not as strong with many echocardiography studies showing no increased prevalence [34, 37, 39, 42].

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance (CMR) imaging is an increasingly valued tool in the assessment of SSc-cardiomyopathy; in particular it can provide insight into the pathogenesis of cardiac disease (see Supplementary Table S3, available at *Rheumatology* online), demonstrating cardiac function, chamber dimensions, myocarditis, and can inform of myocardial fibrosis (delayed enhancement (DE)) and myocardial hypoperfusion (stress perfusion scanning) [47, 48].

Diastolic dysfunction in SSc was confirmed by Bezante et al, with a reduced E/A ratio in 50 patients with SSc free of CVD when compared to 31 matched controls [49]. As with echocardiography studies, systolic function does not appear to be dramatically affected in SSc [49-51]. A French study of 52 patients with SSc identified myocardial oedema in 12% and DE in 21%; predominantly in a linear pattern in the midwall of the ventricles, with sparing of the subendocardium suggesting an alternative pathology to IHD. Delayed enhancement was worse with increasing SSc disease duration ($r=0.3, p<0.05$) [52]. A smaller Greek study demonstrated similar results but with 66% having evidence of DE (worse in those with Raynaud's Phenomenon (RP) greater than 15 years, and

correlating with abnormal 24 hour ambulatory monitoring); again the changes were linear, in the mid-wall, sparing the subendocardium, within the basal and mid-cavity segments of the LV [53].

A Mexican study that included stress perfusion scanning detected perfusion defects in 79% of 62 patients with SSc [51]. Delayed enhancement was also identified in 45% (distribution: 18% patchy, 36% in bands, 11% subendocardial, 29% mixed, 7% transmural) [51].

To what extent is primary myocardial disease associated with greater mortality in SSc?

Few studies tease out the impact of cardiac disease in SSc. A large EUSTAR (European Scleroderma Trials and Research group) publication of 5860 patients with SSc revealed 14% of deaths were due to myocardial disease (subdivided into arrhythmias, left or right heart failure, biventricular heart failure and pericarditis), and 12% secondary to CVD (deemed non-SSc related) [2]. Although, this approach is helpful, it may be difficult to determine SSc-related from IHD-related arrhythmias. In a meta-analysis that described 18 studies comprising 12829 patients, 19% died of cardiac causes; 10% due to SSc-related cardiac disease [54]. A smaller meta-analysis that comprised 2691 SSc patients, reported 29% of deaths were due to cardiac disease [55]. Smaller studies have since reported cardiac-related disease causing 1.4-24.5% of deaths in patients with SSc [9, 44, 56-59], with many lacking any definition of cardiac disease.

Komosci et al determined a greater mortality in those with cardiac disease; defined as pericarditis verified by echocardiogram, recurrent arrhythmia and/or conduction abnormality on ECG, or clinical signs of heart failure (hazard ratio (HR): 3.15, 95% confidence interval (CI): 2.33, 4.26) [54]. The GENISOS study also reported mortality was increased in those with fascicular block, independent of non-SSc related cardiac risk factors (HR 2.1; 95% CI 1.02, 4.28, p=0.04) [24]. Kostis et al determined that SVT and ventricular ectopic activity, including VT, was strongly associated with increased mortality in SSc; VT remaining significantly associated after multi-variate analysis [26]. Hinchcliff et

al confirmed diastolic dysfunction was independently associated with an increased risk of death (HR 3.2, 95% CI 1.1, 9.5, $p=0.034$ per each SD decrease in tissue Doppler E' velocity) [44].

Is primary myocardial disease associated with a specific disease subtype or serology?

Disease subtype

Cardiac involvement is reported in both disease subtypes although more frequently in dcSSc (see Table 3) [60-64]. In the study by Ferri et al, 23% of lcSSc and 32% of dcSSc ($p=0.05$) had cardiac involvement at diagnosis [7]. There was a larger proportion of males in the dcSSc group which may be a confounding factor, but the much shorter disease duration (mean (SD) 2.2 (4.0) years vs. 7 (9.4) in lcSSc) may re-affirm the aggressive presentation of dcSSc. An increased risk of cardiac disease in dcSSc was also reported in the German Network for Systemic Scleroderma (DNSS) cohort; 23% of dcSSc compared to 12% of lcSSc had cardiac involvement ($p<0.0001$). When further dissected there was similar prevalence of palpitations, but diastolic dysfunction and conduction block were more common in dcSSc [60]. Again there were a higher proportion of men with dcSSc. Considering the EUSTAR study of 3450 patients, only palpitations were more common in dcSSc (27% vs 23%, $p=0.003$), with a similar prevalence of conduction block and diastolic dysfunction; again more men and a shorter disease duration seen in dcSSc [65].

Serology

Studies evaluating the association of serology on the prevalence of cardiac disease in SSc compare both those antibody positive to those antibody negative [66-72], and across antibody groups [73-76] (see Supplementary Table S4, available at *Rheumatology* online).

The German DNSS cohort determined a trend for a greater prevalence of conduction disturbances and abnormal ECGs in those positive rather than negative for anti-Scl70 antibodies (49% vs. 38% respectively, $p=ns$) [67], although no difference was found in a Danish study ($n=230$) [69]. There is

also evidence for an increased risk of cardiac involvement for those with anti-Ku, [72] anti-Histone [68] and anti-RNA polymerase (I, II and III) antibodies [70].

Comparing across the antibody groups, the Pittsburgh Scleroderma Databank of 963 patients, determined those with anti-Scl70 and anti-U3 RNP antibodies had a higher prevalence of severe heart involvement (definition as used in Steen et al [14]) (16% and 18% respectively) compared to anti-centromere (ACA) (4%), RNA polymerase III (7%), anti-U1 RNP (11%), anti-PmScl (6%) and anti-Th/To (7%) antibodies ($p < 0.01$ ANOVA) [76]. Conversely, a large UK cohort of 1966 patients with SSc reported no significant differences in prevalence of cardiac involvement (not defined) across anti-ACA, anti-Scl70, anti-RNA polymerase III, anti-U1RNP and anti-U3 RNP antibody groups [75]. Ceribelli et al determined those with anti-Th/To over anti-ACA antibodies had a greater prevalence of pericarditis [73].

Data from studies employing investigative tools

Few EP studies have further dissected association of abnormalities by disease subtype or serology. The GENISOS study found no such association with ECG abnormalities [24], similar to findings by Nordin et al [27]. However, Kostis et al determined those with dcSSc were more likely to have episodes of SVT and VT [26], and LVP have been associated with dcSSc [30]. There was no significant difference in diastolic dysfunction on echocardiogram between disease subtypes in a large French study [$n=570$, 74% lcSSc] [40]. There is CMR data to support a greater prevalence of impaired left ventricular ejection fraction (LVEF) in those with lcSSc [52], however, the data is inconsistent regarding reduced RVEF in lcSSc [49, 52] and increase in fibrosis in dcSSc [51, 53, 77].

Do poor prognosis SSc clinical features associate with increased evidence of primary myocardial disease?

Male gender

Although the literature is limited, it appears men may have a greater risk of SSc-cardiomyopathy [78]. The EUSTAR cohort of 7073 patients with SSc reported LVEF less than 55% was independently associated with male gender, along with age, myositis, digital ulcers, lung involvement and absence of previous treatment with calcium channel blockers [41]. Again, it is not possible to tease out confounding by IHD. Conversely, Morelli et al demonstrated the presence of LVP was not greater in men [30]. As alluded to earlier, some of the increased risk observed in dcSSc could be explained by an increased proportion of these patients being male [7, 60].

Ethnicity

There is limited data evaluating the impact of ethnicity on cardiac disease in SSc. Cardiac involvement may be more prevalent in black patients with SSc. A diffuse subtype and a younger age at diagnosis, along with pericarditis (OR =3.5, $p=0.012$ when adjusted for disease phenotype) were determined to be more common in black compared to white women in a US study [79]. Other studies suggest no difference in prevalence across Caucasian, Asian and Hispanic groups [80, 81]. Interestingly, EUSTAR reported a trend for eastern rather than western European centres to have patients with palpitations ($p=0.002$), conduction blocks ($p=0.03$), diastolic dysfunction ($p<0.001$) and LVEF ($p=0.005$). [65]

Age at disease onset

Increasing age at disease onset appears to be associated with a higher risk of developing cardiac manifestations. EUSTAR reported that in 1180 patients with SSc with disease duration less than 3 years, older age was associated with cardiac conduction block, LV diastolic dysfunction ($p<0.0001$ for both) and low LVEF ($p=0.03$); all but the latter remaining significant after multi-variate analysis [82]. A large US SSc study ($n=2084$) reported those who developed their first non-Raynaud's Phenomenon (RP) symptom at 65 years of age or older suffered cardiac disease (defined as a score greater than one on the Medsger Severity Scale [11]) more often than those younger (odds ratio (OR) 2.69, 95%

CI 1.92, 3.78 when adjusted for race, sex, disease subtype and duration, and smoking status) [83]. These findings have been confirmed in other studies [8, 84], although none differentiate between IHD and SSc-cardiomyopathy.

Modified Rodnan skin score (mRSS)

High scores of mRSS are associated with worse prognosis [85], however, there is little evidence for its association with cardiac disease [86]. A cross-sectional study of 1200 patients with SSc categorised patients by severity of mRSS, and found no significant difference in the prevalence of cardiac complaints between the categories [87].

Tendon friction rubs

The presence of tendon friction rubs (TFRs) may also be associated with an increased risk of cardiac disease as reported from the Pittsburgh cohort (n=1305) [88]. Those with TFRs (28% of patients) had a higher prevalence of cardiac involvement (not defined) (19% if TFR present vs. 8% with absence of TFR, $p < 0.0001$); only observed significantly in those with dcSSc ($p = 0.009$). As this was an exploratory finding no attempt was made for adjustment for confounders.

Peripheral myositis

Peripheral myositis has been associated with primary myocardial disease in SSc. A EUSTAR study determined that myositis was independently associated with a reduced LVEF (OR 2.88, 95% CI 1.15, 7.19) [41]. However, other large studies are few [23].

Nail-fold capillaroscopy

Specific patterns of nail-fold capillaroscopy (NFC) vasculopathy have been described in SSc; early, active and late [89], and have been associated with the future development of severe organ involvement [90]. Evidence suggests it remains a poor prognostic indicator for the risk of cardiac

disease [10, 13, 46]. A cross-sectional study of 103 patients with SSc reported a late pattern of vasculopathy was associated with an increased risk of moderate-to-severe cardiac involvement (as defined by the Medsger Severity Scale [11]) (OR 5.75, 95% CI 2.04, 16.21) [13]; an association confirmed by Riccieri et al [10]. Conversely, a small study (n=35) determined the prevalence of pericardial effusions did not differ between those with abnormal and normal NFC [91].

Quality of life measurements

A range of quality of life assessments suggests cardiac involvement is more prevalent in those with worse scores [92]. Steen et al found that the Health Assessment Questionnaire – disability index (HAQ-DI) was higher in dcSSc patients with heart or kidney involvement (n=74) compared with those without (n=573) ($p<0.001$) [93]. A Japanese study (n=50) reported the severity of cardiac involvement (based on ECG, ejection fraction and New York Heart Association findings) correlated with overall scores within the HAQ-DI (correlation co-efficient 0.50, $p<0.001$); remaining significant after adjustment for skin and joint involvement and PAH [94].

Discussion

The remit of this comprehensive review was to describe the prevalence and prognosis of primary myocardial disease in SSc and any association with clinical phenotype. SSc-cardiomyopathy is prevalent, however, the frequency of its occurrence varies greatly across studies. Heart failure, arrhythmias, diastolic dysfunction, pericarditis and pericardial effusions make up the majority of manifestations, with few reports of valvular pathology. The limited data available suggests its presence is associated with a significantly increased risk of mortality. This review highlights potential red flags associated with cardiac disease in SSc (see Table 4); namely a dcSSc subtype, positive SSc-specific serology (in particular anti-Scl70, anti-U3 RNP, anti-Ku and anti-Th/To antibodies), black ethnicity, older age of onset, TFRs, peripheral myositis, abnormal NFC and worse quality of life scores. Also, this review demonstrates the advantages of employing non-invasive

investigative techniques to detect cardiac involvement in SSc, in addition to allowing a better understanding of its pathophysiological basis.

Concerns

However, conclusions are drawn cautiously. A major concern is the difficulty in differentiating SSc-cardiomyopathy from that of IHD. Only if study populations are free of known IHD, with no or minimal risk factors for such, can a distinction be more confidently made. The cohort studies described generally referred to unselected cohorts. Some EP, echocardiography and CMR studies did exclude those with known IHD [26, 38, 40, 45, 49, 50, 53, 95], and Tyndall et al also differentiated myocardial pathology from IHD in their mortality report; although how they made these distinctions is unclear [2]. In addition, not all studies reported the prevalence of PAH, and only one excluded these patients [32].

Accurate comparisons across the studies are difficult as there was great heterogeneity in the definition of cardiac involvement. Inconsistency can influence the data; most notably demonstrated when a Spanish study included PAH in its definition of cardiac disease; reporting 40% had cardiac involvement; a sub-analysis revealed 30% had PAH whilst only 13% had pericardial effusion and 13% arrhythmias [96].

The SSc phenotype varied greatly across the studies compromising cross study comparisons, for example, some studies reported only one disease subtype [14, 33]. Additionally, although the standard definition of disease duration in SSc is time from first non-RP symptom, many studies either did not define disease duration, used time from onset of RP, or time from disease diagnosis.

The exclusion of studies if they did not meet ACR SSc/LeRoy classification criteria was done in an effort to exclude other CTD. However, these are not diagnostic criteria, and this measure may miss those with early SSc when the disease has not fully differentiated but morbidity can still occur.

Significant relevant studies published since time of literature review

More recent publications have confirmed the increased prevalence of cardiac disease in dcSSc [97, 98], and its association with increased mortality [99-101]. EUSTAR confirmed a greater mortality in those with raised CK (HR 1.9, 95% CI 1.1, 3.3, $p=0.02$), diastolic dysfunction (HR 2.1, 95% CI 1.3, 3.3, $p=0.002$) and cardiac blocks (HR 2.1, 95% CI 1.3, 3.3, $p=0.004$) in 1188 SSc patients [99]. Reports also suggest an association with severe GI disease [102] and digital ulceration [103]. In an effort to tease out the pathophysiological processes, Pieroni et al combined DE-CMR with endomyocardial biopsies to demonstrate cellular inflammatory changes in patients with new symptoms of heart disease. [104]. Interest is also growing in the measurement of extracellular volume fraction as an indicator of myocardial fibrosis [105, 106].

Significance of this review

The findings of this review aided the production of best practice guidelines for the detection and management of SSc-cardiomyopathy in the UK. In addition, it has highlighted many areas in need of further research; for example, when, how and how often should the physician screen for cardiac involvement. In the meantime, physicians should be vigilant for symptoms and signs of cardiac disease in SSc and take a multi-disciplinary approach to their management.

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Figure 1: The literature search process

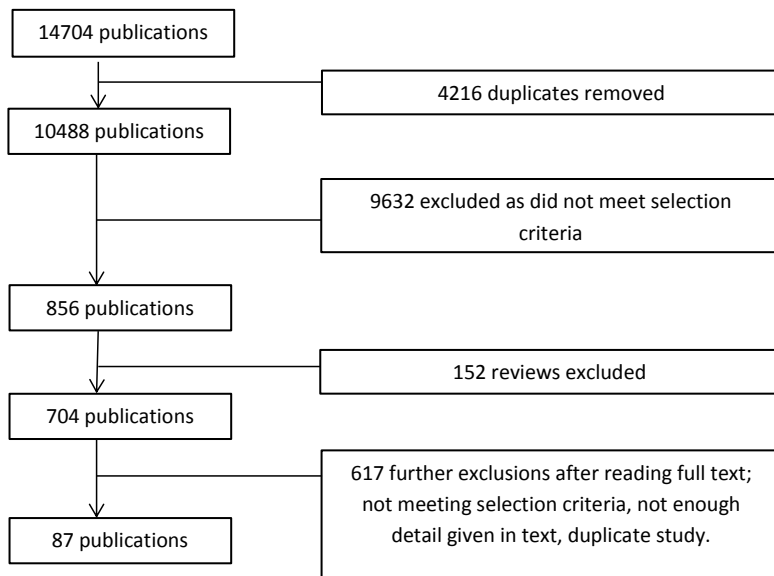


Table 1: Case studies describing the prevalence and nature of cardiac involvement in Systemic Sclerosis

| Reference | Study population | Type of study | n | Age ^{a,b} | Female | LcSSc/ DcSSc | Disease duration ^a | Antibody present | Cardiac involvement | |
|------------------|------------------|---------------|-----|---|--------|-----------------|--|----------------------------------|--|---|
| | | | | years | % | % | years | % | Definition | |
| Akesson [18] | Sweden | CSS | 100 | At disease onset 41 lcSSc 48 dcSSc ^c | 67 | 63/37 | 3 ^c (not defined) | 64 ANA | Cardiomegaly on radiograph Abnormal ECG: non-specific ST or T wave changes, bundle branch block, hemiblock or myocardial infarction pattern | 26 29 |
| Al-Adhahd [19] | Iraq | CSS | 75 | Peak age incidence: 20-39 | 89 | NR | NR | 67 ANA | Abnormal ECG (not defined) | 4 |
| Arias-Nunez [16] | Spain | PS | 78 | 59.8 (13.3) at disease diagnosis | 79 | 71/30 | 8.3 (10.6) from Sx onset to diagnosis with 6.6 (4.7) follow-up | 97 ANA 67 ACA 17 Scl70 | Pericarditis (confirmed on echocardiogram) Cardiomyopathy (confirmed on echocardiogram) AV block; 1st, 2 nd , 3 rd degree LBBB, RBBB, Bilateral BBB Arrhythmias; AF, SVT requiring ablation, VT | 9 18 3, 3, 4 1, 8, 1 12, 3, 2 |
| Ashida [5] | Japan | CSS | 211 | 51 (range 12-83) | 91 | 55/45 | 7.4 not defined | 87 ANA 29 ACA 32 Scl70 | Any of following: symptomatic pericarditis, clinical evidence of LV congestive heart failure, or arrhythmia requiring Rx | 7.1 |
| Bryan [20] | UK | PS | 280 | 45.7 (13.7) | 77 | 53/47 | 17 (7.0-38.5) ^d from skin involvement onset to baseline | 86 ANA 17.8 ACA 17.9 Scl70 | Abnormal ECG (not defined) at baseline | 10.2 |
| Caramaschi [13] | Italy | CSS | 103 | 54.3 (13.6) | 88 | 66/34 | 7 (1-46) ^c not defined | 53 ACA 39 Scl70 | Medsger severity scale used to determine presence or not Mild, moderate, severe and end-stage | 22.3 12.6, 7.8, 1.9, 0 |
| Czirjak [8] | Hungary | CSS | 114 | 51.5 (13.3) | 91 | 70/30 | 10.7 (8.7) not defined | NR | Defined as: AV and intraventricular conductory disturbances, signs of myocardial ischaemia on ECG, congestive heart failure (with normal fundus by ophthalmoscopic examination), and pericarditis (without uraemia)- all evaluated using clinical symptoms, ECG and occasionally echocardiography. | 33.3 |
| Eloranta [6] | Sweden | CSS | 70 | 60 (range 19-93) | 81 | 77/23 | 9 (0-34) ^c not defined | 34 ACA 13 Scl70 | Present or previous cardiac infarction, heart failure, pleuritis or arrhythmia | 39 |

| | | | | | | | | | | |
|--------------------|---------|-----|------|------------------------------------|----|--------------------|---|------------------------------|---|----------------|
| Ferri [7] | Italy | PS | 1012 | 50.5 (13.8) at enrolment | 89 | 56/44 | From disease onset at: Enrolment: 5.1 (7.3) Follow-up: 12.2 (9.0) | 39 ACA 36 ScI70 | At least one of the following symptoms: pericarditis, congestive heart failure, severe arrhythmias and/or AV conduction abnormalities: At baseline At follow-up | 30 35 |
| Jiang [15] | China | CSS | 100 | Range 17-68 | 89 | 15/85 ^e | UK | NR | Palpitations Cardiomegaly on XR (performed in 52 patients) Abnormal ECG (performed in 27 patients) (not defined but included LV hypertrophy, significant ST-T changes and/or arrhythmias as premature beats and RBBB | 44 27 37 |
| Lee [107] | Canada | PS | 237 | 47.1 + 14.1 at enrolment | 83 | 57/43 | 3.8 (5.2) at enrolment | NR | According to the modified Medsger criteria | 8.9 |
| McWhorter [17] | USA | CSS | 210 | Not given | UK | NR | UK | NR | Acute pericarditis Chronic pericardial effusion Other cardiac features (if present) not reported as not intent of publication | 1.9 5.2 |
| Minier [22] | Hungary | PSS | 131 | 55.9 (11.7) | 90 | 69/31 | 8.1 (7.2) from 1 st non-RP symptom | NR | Diastolic dysfunction LVEF ≤50% | 51.9 3.1 |
| Ricceri [10] | Italy | CSS | 62 | 52.8 | 92 | 44/56 | 9.1 not defined | 40 ACA 32 ScI70 | Pericarditis, congestive heart failure, or arrhythmias requiring Rx | 18 |
| Rowell [21] | UK | PS | 84 | Range 21-74 | 75 | NR | NR | NR | Abnormal ECG (not defined) | 49 |
| Sampaio-Barros [9] | Brazil | PS | 947 | 42.6 (14.1) at disease onset | 88 | 75/25 | 12.9 (8.5) at onset with 9.6 (7.7) follow-up | 89 ANA 22 ACA 16 ScI70 | CCF, arrhythmia, conduction defect requiring Rx | 11.7 |
| Schade [23] | Brazil | CSS | 87 | 48.5 (11.7) | | 78/22 | NR | NR | Abnormal LVEF | 4.8 |
| Steen [14] | USA | PS | 953 | 30% symptom onset when > 50yrs old | 80 | 0/100 | NR | NR | Severe heart involvement reported only: cardiomyopathy with decrease in LVEF and symptoms of CCF, symptomatic pericarditis (pericardial pain) or cardiac decompensation from effusion, or arrhythmia attributable to SSc requiring Rx | 15 |

^aValues given indicated mean (SD) unless otherwise stated. ^bAt time of analysis unless otherwise stated. ^cMedian (range). ^dMedian (IQR). ^eLcSSc/dcSSc distinction not made, but instead limited defined as scleroderma limited to the fingers.

[**duration from symptom onset to study entry](#)

[† Not all patients meeting 1980 ACR criteria](#)

Commented [SM1]: These symbols are not present in the table.

AF: atrial fibrillation; AV: atrioventricular; CCF: congestive cardiac failure; CSS: cross-sectional study; dcSSc: diffuse cutaneous SSc ECG: electrocardiogram; lcSSc: limited cutaneous SSc LBBB: left bundle branch block; LV: left ventricular; LVEF: LV ejection fraction; NR: not reported; PS: prospective study; RBBB: right bundle branch block; Rx: treatment; SD: standard deviation; : supraventricular tachycardia; VT: ventricular tachycardia; XR: radiograph

Table 2: Modified Medsger Severity Scale for cardiac involvement

| Grade | Characteristics |
|--------------------|---|
| 0 (No involvement) | Normal ECG, LVEF \geq 50% |
| 1 (Mild) | Conduction defects on ECG, LVEF 45-49% |
| 2 (Moderate) | Arrhythmias on ECG, LVEF 40-44% |
| 3 (Severe) | Arrhythmias requiring treatment on ECG, LVEF 30-40% |
| 4 (End-stage) | Congestive heart failure, LVEF<30% |

ECG: electrocardiogram; LVEF: left ventricular ejection fraction.

Table 3: Case studies describing the prevalence and nature of cardiac disease per disease subtype in Systemic Sclerosis.

| Reference | Study population | Type of study | n | LcSSc/ DcSSc | Age ^a LcSSc/ DcSSc | Female LcSSc/ DcSSc | Disease duration ^a LcSSc/ DcSSc | Antibody present LcSSc/ DcSSc | Cardiac involvement | |
|------------------------|-----------------------|---------------|-----------------------|-----------------|--|---------------------------|--|--|---|---|
| | | | | % | years | % | years | % | Definition | % LcSSc/ DcSSc |
| Fernandez-Codina [108] | Spain | CSS | 413 | NR | NR | NR | NR | NR | Clinical manifestations, alterations in echocardiography, stress, myocardial perfusion SPECT, cold-induced myocardial perfusion SPECT, coronary arteries catheterization, CXR and ECG | 45% in total: no difference between dcSSc, lcSSc or sine SSc |
| Ferri [7] | Italy | PS | 1012 | 56/32 | NR | 88/76 | At diagnosis: 7(9.4)/2.2(4) | ACA 53/11.3 Sc170 25.3/58.6 | At least 1 of the following symptoms: pericarditis, congestive heart failure, severe arrhythmias and/or AV conduction abnormalities at diagnosis | 23/32 (p=0.05) |
| Furst [109] | USA | Case control | 17 CREST 17 PSS | 50/50 | 49.5 (10.9)/ 48.2 (10.9) matched | 94/94 matched | 12.0 (9.3)/ 11.2 (9.2) ^b matched | ANA 56/82% | Cardiomegaly on CXR Pericardial effusion Abnormal ECG | 29/35 19/25 29/24 No significant difference |
| Hunzelmann [60] | Germany | CSS | 1158 | 58/42 | 58.5(12.7)/54.1(14.1) | 87.8/76.1 | Expressed as age at: RP onset 44.7(15.8)/44.5(15.2) Skin involvement 49.9(14)/46.4(14.3) | ANA 92.9/93.9 ACA 61.5/11.2 Sc170 16.2/55.8 | 1 of the following: palpitations, conduction disturbance and diastolic dysfunction on echocardiogram. Sub-analysis: Palpitations Conduction block Diastolic dysfunction | 12/23 (p<0.0001) 23.1/20.1 10.8/19.2 14.9/19 |
| Ostojić [61] | Serbia and Montenegro | CSS | 105 | 48/52 | 54/52 | UK | 5.2/5.4 (not defined) | NR | Arrhythmia or myocardial ischaemia detected by ECG or myocardial fibrosis and pericarditis detected by echocardiogram | 8/29 P<0.001 |

| | | | | | | | | | | |
|-------------------------|--------|-----|------|-----------------------------|---|-------|--|--------------------------------|--|--|
| Perera [110] | USA | PS | 212 | 19/81 | 36 (5-71)/47 (3-79) ^c | 80/74 | NR | ACA 0% ScI70 100% | One or more of: LVEF <45%, left sided CCF, pericarditis, arrhythmia requiring Rx or complete heart block. | 18/30 |
| Poormoghim [35] | Iran | CSS | 58 | 60/40 | 41.3 (14)/40.3 (13.4) | 92/83 | 8.41/7.35 | NR | One or more dichotomous variables, i.e. presence or absence of cardiomegaly, pericardial effusion, ventricular arrhythmias, conduction disturbances, axis deviations, + pathological Q waves Sub-analysis; Conductive disturbance, left axis deviation, arrhythmia, cardiomegaly (on CXR, echocardiography or ECG), and pericardial effusion. | 20.6/17.6 (p=0.96) 14.7/8.7, 14.7/4.3, 2.9/4.3, 11.8/25, 14.7/16.7 |
| Simeon-Aznar [62] | Spain | CSS | 811 | 62/27 | 45.9 (15.6)/43.8 (15.4) at disease onset | 89/83 | NR | ACA 58/8.4% ScI70 9.4/52.7% | One or more of: pericarditis, ischaemic cardiomyopathy with no known cause, reversible thallium perfusion defects after cold stimulation, any disturbance on colour-Doppler echocardiography, ECG alterations with no other cause, LVEF < 50%, or RVEF < 40% on echocardiography or radionuclide ventriculography. Pericarditis Ischaemia Conduction alteration | 31.1/32.5 3.4/7.8 (p=0.01) 10/8.2 (p=ns) 11.9/10.3(p=ns) |
| Vlachoyiannopoulos [63] | Greece | CSS | 238 | 49/45 | 41.8 (1.3)/38.4 (1.4) at onset ^d | 99/87 | 11.5 (0.9)/9.1 (0.8) with 2.5(0.34)/ 3 (0.34) follow-up ^d | ACA 34/0% ScI70 21/60% | Conduction disturbances +/- or nodal or ventricular arrhythmias, congestive heart failure not attributable to any other condition and/or moderate to severe pericardial effusion on echocardiogram. | 7/21 p=0.0025 |
| Walker [64] | EUSTAR | PS | 3450 | 57/37 (remainin 6% overlap) | 57.4(13.1)/52.3(13.7) | 81/91 | 9.6(8.1)/7.4(6.9) ^e | ACA 47/6% ScI70 23/61% | Palpitations Conduction block Diastolic dysfunction Reduced LVEF | 22.6/27.3(p=0.003) 10.4/12.7(p=0.12) 15.4/16.6(p=0.42) 5.0/7.2 (p=0.59) |

| | | | | | | | | | | |
|----------------------|--------|----------------------|-----|-------|-------------------------------|---------|--|---|---|------------------|
| Rodriguez-Reyna [72] | Mexico | CSS | 139 | 57/43 | 47.4 (14.3)/42.7 (13.8) | 99/87 | 13.2 (11)/7.9 (6) (first symptom attributed to SSc) | ANA 100/100 ACA 37/20 Scl70 15/45 | Left sided congestive heart failure (FEV1<45%) or pericarditis on echocardiogram or CMRI, arrhythmia requiring treatment or conduction defect | 7/16 (p=NS) |
| Laing [79] | USA | Retrospective cohort | 398 | 47/31 | 51.8 (13.9)/46.7 (14.2) | 100/100 | NR | ANA 95/92 ACA 47/14 Scl70 15/18 | Pericarditis | 3.3/7.6 (p=0.05) |

^aValues indicate mean (SD) unless otherwise stated. ^bFrom first symptom. ^cAge at first symptom attributable to SSc. ^dValues indicate mean (standard error). ^eOnset from first non-RP feature. AV: atrioventricular; CSS: cross-sectional study; CXR: chest radiograph; dcSSc: diffuse cutaneous SSc; ECG: electrocardiogram; lcSSc: limited cutaneous SSc LBBB: left bundle branch block; LV: left ventricular; LVEF: LV ejection fraction; NR: not reported; ns: non-significant; PAH: pulmonary hypertension; PS: prospective study; RBBB: right bundle branch block; RVEF: right ventricular ejection fraction; Rx: treatment; XR: radiograph

Table 4: Factors that have been associated with myocardial involvement in Systemic Sclerosis

| Factors that have been associated with myocardial involvement in Systemic Sclerosis | | |
|--|---|---|
| Demographic | SSc phenotype | Examination findings |
| Male gender Older age of disease onset Black ethnicity | Diffuse cutaneous disease Lung involvement Peripheral myositis Higher HAQ-DI scores Positive serology; specifically anti- Scl70, Ku, Histone, RNA polymerase, Th/To and U3-RNP antibodies | Presence of tendon friction rubs Late vasculopathy pattern on nail-fold capillaroscopy |

