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Consensus best practice pathway of the UK Systemic Sclerosis Study group: management of cardiac disease in systemic sclerosis

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Short title: UK SSc-Cardiac recommendations

ABSTRACT

Objective: Cardiac disease in Systemic Sclerosis (SSc) can manifest in various ways and is associated with a poor prognosis. There is little evidence on how best to detect and manage cardiac disease in SSc. Our objective was to produce an expert consensus best practice pathway for the management of cardiac disease in SSc.

Methods: The UK Systemic Sclerosis Study Group set up several working groups to develop a number of consensus best practice pathways for the management of SSc-specific complications, including cardiac disease. A multi-disciplinary task force was convened. The guidelines were partly informed by a comprehensive literature review.

Results: A best practice pathway for cardiac disease (with a focus on primary cardiac disease) in SSc is presented including approaches for early detection and standard pharmacological and device therapies. The benefits of shared care and multi-disciplinary approach are recommended. A future research agenda is formulated in response to the relative lack of understanding of the natural history of primary cardiac disease that was highlighted by the initiative.

Conclusion: The physician should be alert to the possibility of cardiac disease in SSc; best managed within a multi-disciplinary team including both rheumatologists and cardiologists. This pathway provides a reference for all physicians managing patients with SSc.

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

Key messages

SSc cardiomyopathy is prevalent in SSc and is associated with a poor prognosis.

The UKSSSG best practice recommendations help inform the UK physician in the management of SSc-cardiomyopathy.

The UKSSSG best practice recommendations highlight the clinical and research agendas going forwards for SSc-cardiomyopathy.

INTRODUCTION

Systemic sclerosis (SSc, scleroderma) is a complex and heterogeneous connective tissue disorder (CTD) characterised by excessive extracellular matrix deposition with widespread fibrosis of the skin and visceral organs, microvascular injury and evidence of immune system activation [1, 2]. The heart is one of the major organs affected in SSc [3, 4] although its presence is probably underestimated due to the occult nature and variable reports of prevalence. Clinically evident cardiac involvement is associated with a poor prognosis, with up to 70% mortality at 5 years [4, 5]. Approximately twenty-five percent of SSc-related fatalities are attributable to cardiac causes [6, 7]. The features of primary cardiac disease are typically myocardial fibrosis [8] and myocarditis [9]. The time-course, dynamics and extent of each of the pathologies however are poorly understood. The management of primary cardiac disease (herewith termed SSc-cardiomyopathy) is varied and often ad hoc, usually in response to a clinical event when prognosis is particularly poor.

The UK SSc study group assembled several working groups to develop best practice consensus pathways for the key manifestations of SSc. The best practice consensus recommendations reported here aim to inform the management of SSc-cardiomyopathy in the UK and as such, are to be used in conjunction with the guidelines published by EULAR/EUSTAR. Of note, these recommendations relate to SSc-cardiomyopathy as opposed to right heart involvement and pulmonary hypertension for which separate recommendations have been developed.

METHODS

With the approval of the UK SSc study group, the convenor (MHB) formulated a working group with the aim of establishing recommendations for the management of SSc-cardiomyopathy.

Working group composition

The multidisciplinary working group comprised 16 participants including: 4 SSc specialists; 6 cardiologists (1 electrophysiology specialist, 1 cardiac MR specialist, 2 cardiac ECHO specialists, 1 pulmonary hypertension expert, 1 general); 1 pharmacist, 1 specialist nurse, 2 research fellows and 2 patient organisations representatives.

To this end, a comprehensive literature review was undertaken (LAB) to inform the working group (Bissell LA accepted for publication). A working group was convened with participants selected based on the field of expertise, knowledge and experience; as well as covering specialist and non-specialist centres. A first meeting was convened in July 2012 where the scope and key topics to cover was

agreed. At a second meeting in October 2012, the literature was presented and discussed and draft recommendations were formulated.

A glossary and algorithm that informed this report was developed (MHB) and feedback from the working group was requested for further refinement. Both documents were finalised and approved in March 2014.

RESULTS

The aim of the working group was to distil available information on the following topics into recommendations for use in clinical practice; to determine the nature, prevalence and predictors of disease; to determine when to screen and monitor for cardiac disease; to determine appropriate tests for screening and monitoring of cardiac disease; to establish a standardised echocardiogram protocol and report (Scleroderma Echo); to evaluate the need for more novel echocardiography (ECHO) techniques; to determine the role of N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) testing in a patient with SSc; to determine if/when cardiac MRI should be used; to establish how to monitor for conduction abnormalities; to determine how to treat SSc-cardiomyopathy; to determine how best to screen for and manage coronary artery disease (CAD).

The working group anticipated a lack of high quality evidence base, which the literature review confirmed. As such, presented below are the recommendations based on available evidence and consolidated by expert opinion of the working group.

Over-arching principles

The working group discussed and agreed upon the following general principles that should be applied in the management of patients with SSc: assessment of patients with SSc for cardiac disease should include evaluation for the presence of both SSc cardiomyopathy and coronary artery disease (CAD). Suggestion of SSc-cardiomyopathy on investigation should be interpreted in the context of possible co-existing non-SSc related pathology as seen in the general population including systemic hypertension (HTN), CAD, and valvular disease (that might have similar clinical manifestations to those observed in patients with SSc-CM). Other confounding factors such as interstitial lung disease (ILD), pulmonary hypertension (PAH) and anaemia should also be evaluated; cardiac pathology should be considered throughout the disease course; where indicated, it is important to involve a cardiologist to

provide interpretation of cardiac investigation findings and to help manage the patient and plan appropriate monitoring.

Relevant background to the recommendations

Included is a summary of key information to support these recommendations. The comprehensive literature review by Bissel LA, et al (submitted) provides further data [10].

Principal pathologies underlying SSc cardiomyopathy

Myocardial fibrosis: This process may be sub-clinical before becoming clinically apparent [11, 12]. The underlying mechanism is not fully elucidated. However, fibrosis frequently spares the subendocardium, an area usually affected in atherosclerotic heart disease [13] and data suggest this may be preceded by micro-perfusion abnormalities with reperfusion damage [9, 14]; perfusion abnormalities independent of atherosclerotic heart disease [15] and present in association with digital ulcers [16].

Myocarditis: Patients with new symptoms of heart disease have been found to have cellular inflammatory change on endomyocardial biopsies [17], however, myocarditis may also be sub-clinical, and has been described in association with peripheral myositis [18, 19]. Studies suggest that it can lead to secondary fibrosis with resolution of the initial inflammatory process [20].

Autopsy findings have also included pericarditis, nodular abnormalities of valve tissue and sterile vegetation [21].

Cardiac manifestations of SSc cardiomyopathy

The prevalence of cardiac manifestations recorded in SSc studies varies greatly, as detailed in the submitted literature review associated with these recommendations by Bissell LA, et al [10]; with a prevalence between 7% and 39% [3, 7]. The major limitation is differentiating pathology due to SSc cardiomyopathy from atherosclerotic heart disease, with immense heterogeneity in the definitions of cardiac involvement applied. The manifestations are determined by the structure/area affected:

Cardiac failure: Diastolic dysfunction is frequently recorded in patients with SSc [22, 23], but in this population, leads uncommonly to diastolic heart failure [24]. Some studies suggest that its occurrence is independently associated with disease duration, age, hypertension or ischaemia [25, 26]. Systolic

dysfunction is less commonly described in SSc [12, 27] but if present is usually the consequence of CAD. It might also follow specific SSc cardiomyopathy due to myocarditis and fibrosis [28]. Less commonly, a restrictive cardiomyopathy with left or right ventricular involvement, increased ventricular mass and decreased movement of ventricular walls can be observed in SSc [29].

Arrhythmia: The mechanism underlying arrhythmias in SSc is likely to be multi-factorial, thought to include direct effects of microvascular injury, the subsequent development of fibrosis as well as autonomic dysfunction [30]. Cardiac conduction defects, as documented in studies using electrocardiogram (ECG) and 24-hour Holter monitor are reported with a variable prevalence, between 4% [31] and 51% [32, 33]. Intra-ventricular conduction defects are clinically relevant as they are associated with the development of atrio-ventricular (AV) block and other rhythm disturbances [34]. Nevertheless, supraventricular tachycardia (SVT) and ventricular tachyarrhythmias are not uncommon findings in SSc and have been associated with increased mortality in some studies [35]. Automatic implantable cardioverter-defibrillator (AICD) use in patients with SSc has been reported [36].

Pericarditis: Pericarditis is a common feature of inflammatory conditions and in SSc can manifest as fibrous pericarditis, pericardial effusion, and rarely as pericardial tamponade or constrictive pericarditis [37, 38]. The evidence of an increased prevalence in SSc is debated though, studies reporting similar prevalence when compared to controls [39, 40].

Valvular involvement: Valvular disease can represent a feature of primary cardiac SSc, but less commonly observed. Endocarditis, thickening of the valves and valve prolapse has been noted in SSc patients [21, 41].

SSc cardiomyopathy and disease course

The time-course and basis for susceptibility remains unclear. Cardiac pathology should be considered throughout the disease course; nevertheless, the nature of involvement might be more likely at certain stages or subtypes. Thus, myocarditis is often expected in early diffuse SSc stage, sometimes concomitant with a peripheral myositis [17]; evidence of diastolic dysfunction however is associated with increasing disease duration [13].

Recommendations

Identify possible SSc risk factors for development of SSc cardiomyopathy

SSc cardiomyopathy: The following clinical features should alert the rheumatologist to the at risk SSc patient for the development of SSc cardiomyopathy: male gender [42], diffuse cutaneous SSc[43], anti-topoisomerase antibody together with rapid skin thickness progression[44], anti-Ku [45], anti-Histone [46], anti-RNA polymerase[47] and anti-U3-RNP antibodies [48] age of onset >65 years[49], presence of tendon friction rubs[44], digital ulcers, lung involvement, myositis [42] and higher HAQ-DI scores[50].

Coronary artery disease: For CAD, the traditional risk factors of hypertension, hypercholesterolemia, diabetes, smoking history, and family history of CAD should be identified and acted upon.

Establishing a diagnosis

History and examination

Breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea (PND), palpitations, dizziness, blackouts, chest pain, fatigue and peripheral oedema should alert the physician to possible SSc-cardiomyopathy; with the symptoms typically relating to the nature of cardiac involvement, for example, breathlessness and reduced exercise tolerance in the context of left ventricle (LV) dysfunction. Patients need to be aware to report such symptoms. A comprehensive cardiorespiratory assessment should be routinely performed, including looking for evidence of atherosclerosis.

Investigations

Blood tests: The working group recommends annual lipid profile and HbA1c monitoring to identify associated CAD risk factors. NT-proBNP is established for detection of heart failure by primary care and has similarly shown utility in SSc-pulmonary vasculopathy [51, 52]. There is also emerging evidence for the association of NT-proBNP with SSc- cardiomyopathy [53], although its prognostic value is unknown. To potentially identify early cardiac involvement and aid monitoring, rheumatologists may consider baseline reference measurement and asymptomatic annual patient monitoring. In case of symptomatic or confirmed diagnosis of cardiac disease (and/or PAH), six-monthly monitoring (or more frequently if indicated) should be arranged to assess progression and/or response to treatment. However, clinicians should bear in mind that normal NT-proBNP levels may be recorded in the presence of PAH and high levels can be associated with low glomerular filtration rate in patients with chronic kidney disease.

Troponin and CK are recommended in the evaluation of acute coronary syndrome (ACS) (as per standard practice) but also if SSc-cardiomyopathy (for example a myocarditis) is suspected. A raised

CK level should be interpreted in the context of the patient's co-morbidities, and other causes considered, for example, peripheral myositis. Troponin I (TnI) in particular should be identified as this is considered to have exclusive myocardial origin. If the clinical impression suggests (clinical or subclinical) SSc-cardiomyopathy as a possibility, further imaging, using echocardiography, and/or cardiac-MRI may be appropriate.

Trans-Thoracic Echocardiogram (TTE): All sonographers performing echocardiographic screening studies in patients with SSc should be accredited with the British Society of Echocardiography to ensure the highest standard of imaging. The working group recommends using a standardised Scleroderma Doppler echocardiography protocol (Table 1) with a report that includes minimum scleroderma echocardiographic dataset of 10 reproducible measures (Table 2). Where indicated, a cardiologist should be involved to provide interpretation of echocardiography findings and to help plan appropriate monitoring and management.

Tissue Doppler echocardiography: Tissue Doppler echocardiography (TDE) may be a preferred method if the expertise is available but further research into the added utility this has on early detection and assessment of primary cardiac involvement is needed.

Cardiac MRI (CMR): Tissue Doppler echocardiography (CMR) can detect both functional changes and those at tissue level, thus helping to characterise the underlying pathology[54]. Although reports to date demonstrate the utility of CMR in SSc, there is no consensus for the development of a meaningful algorithm.

The working group recommends that a core clinical protocol should be established for regional centres with development of a research protocol to facilitate future collaborative activities. A basic (core) CMR protocol following Society for Cardiovascular Magnetic Resonance (SCMR) standardised protocols for non-ischaeamic LV cardiomyopathies including myocarditis [55] is detailed in table 3.

CMR availability is limited (in District General Hospital, DGH) and may be considered in selected patients, especially those with high risk of cardiac involvement/symptoms and/or signs suggestive of SSc cardiomyopathy.

Triggers for performing CMR should include the following considerations particularly in the absence of other pathologies (such as hypertension, CAD): ECHO abnormalities such as Regional Wall Motion Abnormality (RWMA) and/or troponin rise (once CAD/ACS has been excluded); right ventricle (RV) dysfunction (in absence of PAH or chronic lung disease); LV dysfunction (if no evidence of HTN/CAD or unexplained new or particular worsening in a patient with background hypertensive or ischaemic heart disease related changes); notable/increase in pericardial effusion; and raised NT-proBNP levels (in the absence of known PAH and non SSc-related left heart disease).

If CMR is undertaken and pathology is confirmed including scarring/fibrosis, this should trigger more intensive screen for arrhythmias as well as closer interval assessment for cardiac function with echocardiography. The frequency of follow-up, for example, three to six monthly, would depend on each patient's circumstance/disease severity, and need for monitoring for interval change post-pharmaceutical treatment. A management plan should be developed together with specialist cardiology input.

Electrophysiological testing: The working group recommends that ECG should be performed in all patients. Although not a sensitive method, this may detect conduction abnormalities and evidence of LV/RV strain/hypertrophy. Holter monitor or external loop recorder (ELR) should be applied if there is any clinical suggestion of conduction abnormality. Similarly, a low threshold for use of an implantable loop recorder (ILR, e.g. Reveal) should be maintained. ILR is used in the general population for unexplained infrequent syncope. Its use in patients with SSc is currently being evaluated (the Electrophysiology and Cardiac Imaging in Scleroderma, ELCASA Study, REC Ref: RR12/10286) and for the moment should be driven by clinical symptoms. AICD devices are used for monitoring +/- delivery of electrical shock for a life-threatening tachycardia[56]. Further specialist +/- invasive investigations may thus be used but require referral to a regional cardiac centre. Signal average ECG may be used as an additional tool to detect abnormalities and late potentials (surrogate marker for scar/fibrosis) if available although this is not widely employed. In general, electrophysiological studies should be considered as in standard practice. The input of a cardiologist should be requested for the interpretation of these studies.

Endomyocardial biopsy: The role of endomyocardial biopsy is limited and should only be considered as part of a multi-disciplinary assessment; with the assumption that non-invasive testing, including CMR is undertaken before a possible need for biopsy is raised.

Frequency of investigation/monitoring of patients with SSc for SSc cardiomyopathy

There is minimal evidence base to guide recommended testing and the frequency of testing but table 4 details the group's recommendation based on expert opinion. Frequency of surveillance should be determined by the nature of patient group: asymptomatic patient requires routine surveillance, whereas the patient thought to be at most risk of SSc-cardiomyopathy (the at-risk patient) (see first recommendation) warrants more careful (early and comprehensive) observation, and the patient with confirmed cardiac disease needs regular assessments (three to six monthly when establishing disease activity/response to treatment) and treatment initiation. The group agreed that it is important to explain to the patient the need for regular testing in order to avoid undue anxiety.

Although evidence suggests that follow-up scans after an initial normal ECHO has a low pick up rate of new PAH[57] screening annually through echocardiogram is still advocated. ILR may be considered in patients with symptoms such as syncope, palpitations, dizziness in whom 24-hour/30-day external monitor has not identified any arrhythmias.

Treatment of SSc cardiomyopathy

Treatment of patients should be undertaken with appropriate cardiologist input.

Immunosuppression

Steroid and/or initiation or escalation of immunosuppressive agents is often used (especially with co-existing peripheral myositis) although a good evidence base for this does not exist. The time-course of individual pathology has not been well defined and can vary; hence it is advised that all relevant indicators suggesting active and dynamic pathology (including CK, troponin, CRP, RWMA on imaging, CMR changes and overlap of SSc with other autoimmune pathology e.g. polymyositis, systemic lupus erythematosus) as well as evidence of other features of active SSc should be used to consider immunosuppression. Whilst it is unclear whether steroid and immunosuppressive agents should be used for the presence of fibrosis (using corollary of management of ILD), this may be considered if a dynamic decline in function is observed over time.

In accordance with BSR and BHPR guideline for the treatment of systemic sclerosis [58], the working group recommends moderate dose corticosteroid (<15mg/day) +/- pulse cyclophosphamide as a reasonable approach if a myocarditis or other features of SSc cardiomyopathy are evident. Indications for the use of cyclophosphamide would thus include myocarditis, moderate-severe LV dysfunction (not secondary to atherosclerotic heart disease) and life-threatening cardiac arrhythmias. The group recognises the co-existence of peripheral myositis (in up to 43%) [59], and therefore, there is additional basis to consider alternative/broader immunosuppression strategies [60, 61].

Arrhythmia

The same principles applied to the general population should be used in the patient with SSc.

Pharmacotherapy should be initiated in patients with evidence of conduction abnormalities. Special attention should be given to the potential adverse events (AE) of some antiarrhythmic therapies (potential lung fibrotic effect of amiodarone and vaso-spastic effects of beta-blockers).

Ablation therapy has a role in symptomatic patients with palpitations as alternative to drug treatment [SVT/atrial flutter/ventricular tachycardia (VT)]. AICD devices should be considered as per standard practice [56] for life-threatening arrhythmias such as VT/ventricular fibrillation (VF).

Heart failure

Systolic dysfunction may require angiotensin-converting-enzyme inhibitors (ACE-I) and beta-blockers whereas the evidence base for the treatment of diastolic heart failure remains weak although may be considered. Diuretics should be added, as required. Cardiac resynchronisation therapy (CRT) for LBBB associated diastolic dysfunction and transplantation in end stage systolic dysfunction is currently used in general population and could be considered for patients with SSc.

Traditional risk factors of cardiovascular disease

Optimisation of control and management of other associated co-morbidities such as systemic hypertension, high cholesterol, diabetes and renal disease should be considered. Lifestyle modification such as diet and smoking cessation should be encouraged for all patients.

Cardiac transplantation

There is an absence of published experience in cardiac transplantation in patients with SSc. In the most severe life-threatening cases of SSc-CM, resistant to medical therapy, the usual multi-disciplinary team and approach that would be applied to the general population could carefully consider heart transplantation in this population. The group stressed this as an evidence free area that would carry significant risk.

Coronary artery disease

CAD in SSc should be investigated as in the general population. Exercise stress testing has become more redundant and is no longer an appropriate tool. In patients with SSc in whom CAD is suspected, a form of stress perfusion testing such as nuclear medicine, ECHO, CMR, CT followed by coronary angiography as indicated, should be undertaken. ECHO abnormalities such as RWMA should also be a trigger for consideration of underlying CAD. Hence, both CAD and SSc cardiomyopathy as mentioned earlier should be included in the differential. In a patient with SSc with new/interval change breathlessness in whom specific indicators of culprit CAD may not be evident, left heart

studies/coronary angiography should be considered if presentation remains unexplained following respiratory assessment for ILD and evaluation for PAH [including CT pulmonary angiography (to exclude PE), right heart catheterisation].

Management of proven, significant CAD should be as per general population: prognostically beneficial pharmacotherapy (aspirin, statin, ACEI inhibitor and a cardioselective beta-blocker), proceeding to intervention as indicated. Cardiac rehabilitation programmes should also be considered.

Multi-disciplinary approach

The identification of a dedicated cardiologist, with an interest in CTD is important for the optimal assessment and management of patients with potential cardiac involvement. In a tertiary centre, the cardiologist would be able to coordinate care between the rheumatologist and sub-specialist cardiology expertise as indicated. It is recommended that peripheral DGHs establish a link with their secondary care/regional cardiology department with access to relevant technology and expertise to facilitate efficient shared care when indicated.

The rheumatologist and Nurse Specialist, together with specialist cardiology input, as indicated should adequately counsel patients. A trained counsellor and patient support groups where available would be particularly useful.

Cardiotoxicity of commonly used treatments in SSc

Review of the main drugs used in the management of SSc (see below) failed to identify clear suggestion of cardiac toxicity but caution should be given to those patients with pre-morbid cardiovascular conditions. Regarding Cyclophosphamide, the Food and Drug Administration (FDA) has reported some cases of cardiac dysfunction although acute cardiac toxicity has been observed with high doses and no residual abnormalities in those surviving an acute event. In SSc, no cardiac AE, side from a viral myocarditis as a result of immunosuppression has been described. With Mycophenolate, no specific cardiac AE have been reported in patients with SSc. For Methotrexate (MTX), pericarditis, pericardial effusion, hypotension and thromboembolic events have been mentioned as possible adverse reactions. Randomised controls studies of MTX in SSc patients have not identified any cardiac toxicity [62].

Several premorbid cardiovascular states are mentioned among the contraindications of calcium channel blockers. This group's AE include tachycardia, palpitations, hypotension and syncope.

Uncommonly, they may cause angina pectoris. The contraindications of Iloprost include a number of pre-morbid cardiovascular and thromboembolic states. Bosentan should be used with caution in pre-existing LVF and thromboembolic states. No cardiac AE/SAE has been reported in in RAPIDS-2 study[63]. Sildenafil is contraindicated in severe CVD, hypotension, recent myocardial infarction/CVA and should be administered with caution in patients with aortic stenosis and hypertrophic cardiomyopathy. Figure 1 represents a flow diagram of the management of cardiac involvement in SSc, recommended by the group.

Research agenda

This initiative highlighted the limited understanding of the pathology and the dynamics underlying SSc-cardiomyopathy. Initial research areas identified for evaluation include; the potential use of NT-proBNP in screening and management of SSc-cardiomyopathy; the utility of repeated echocardiograms in the screening of SSc-cardiomyopathy; the additional benefit of TDE in the assessment of primary cardiac involvement in SSc; whether CMR allows a better characterisation of features of SSc-cardiomyopathy and subsets for application in a management pathway and the utility of a core UK SSc-CMR working network; the potential use of electrophysiological tests in screening for arrhythmia in SSc, especially ILR and the use of AICD to prevent sudden death; whether SSc-cardiomyopathy co-exists with PAH and if so, whether it represents a poor prognostic indicator for PAH; the management of diastolic dysfunction in SSc (albeit a limited prevalence); role of immunosuppression for the treatment of SSc-cardiomyopathy. The research agenda will be crucial for moving this field forward.

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Table 1: Recommended Scleroderma Doppler echocardiography protocol

Parasternal short axis view for optimal visualisation of the proximal main pulmonary artery	Optimise depth and reduce sector width
Pulsed wave Doppler of right ventricular inflow and outflow tract in parasternal short-axis view	Sample volume at the level of the pulmonary valve; optimise baseline, scale, gain and filter settings. Sweep speed of 100mm/sec.
Apical 4-chamber view modified for optimal visualisation of LA and RV views to assess RV function and RA size	Optimise depth and reduce sector width
Pulse-wave Doppler of mitral inflow in apical 4-chamber view	Sample volume at tips of mitral leaflets in mid-diastole optimise baseline, scale gain and filter settings
Pulsed wave tissue Doppler of septal mitral annulus in apical 4-chamber view	Optimise baseline, scale, gain and filter settings
Continuous wave Doppler of tricuspid regurgitation in apical 4-chamber view or parasternal short-axis view	Ensure good alignment with TR jet guided by colour flow imaging; optimise baseline, scale gain and filter settings
M-mode of lateral tricuspid annulus in apical 4-chamber view	Optimise gain

LA: left atrium; RA: right atrium; RV: right ventricle; TR: tricuspid regurgitation

Table 2: Recommended minimum scleroderma echocardiographic dataset

Pulmonary haemodynamics	Tricuspid regurgitation velocity (TRV)
	Pulmonary acceleration time (PAT)
	Main pulmonary artery diameter (PAD)
Right ventricular function	Tricuspid annular systolic plane excursion (TAPSE) RA area (indirect index of RV dysfunction)
Left Ventricle	Left ventricular systolic function (estimate)
	Ejection Fraction
Left ventricular diastolic function (to calculate E/E')	Early diastolic transmitral velocity (E)
	Early diastolic septal tissue velocity (E')
	Left atrial area (LAA)
Myocarditis (and more typically, with CAD)	Regional Wall Motion Abnormality (RWMA)

Table 3. Recommended core clinical cardiac MRI protocol, following the Society for Cardiovascular Magnetic Resonance protocol

<p>Non-ischaemic LV cardiomyopathies, including myocarditis</p>	<p>LV structure and function module ±Advanced tissue characterization module: T2weighted, T2, T1 mapping ±Early gadolinium module (for myocarditis only) -T1weighted imaging before and after gadolinium Late gadolinium module</p>
<p>Coronary artery disease</p>	<p>Adenosine stress-rest perfusion High dose dobutamine stress functional imaging</p>

Table 4: Recommended testing and frequency of testing for SSc cardiomyopathy

Baseline Test	Monitoring		
	Asymptomatic/ uninvolved	At risk	Symptomatic/ Involved ^{a b}
Targeted questioning for red flag symptoms ^a	Each visit ^c	Each visit ^c and cardiology referral	Each visit ^c
Resting ECG	Annual ^d	6-monthly ^e	6-monthly ^e
ECHO	Annual	6-monthly	6-monthly
Troponin, CK	Annual	6-monthly ^f	6-monthly ^f
NT-proBNP ^f	Annual ^g	6-monthly ^g	6-monthly ^g
Blood pressure ^h	Each visit	Each visit	Each visit
Health check for coronary artery risk factors^c			
Lipid profile	Annual	Annual	Annual
HbA1c	Annual	Annual	Annual

^aAlternative frequency as indicated. ^bDetermined by nature of cardiac involvement, managed with a cardiology specialist.

^cShortness of breath, orthopnoea, paroxysmal nocturnal dyspnoea, chest pain, palpitations, dizziness, blackouts.

^dHolter/similar monitor may also be an appropriate baseline/reference investigation as it provides improved yield over ECG.

^eHolter/similar monitor as indicated. ^fInterpret in the context of the clinical scenario, with specialist cardiology input.

Consider other factors that may contribute to positive troponin/NT-proBNP result (eg chronic kidney disease, PE, myositis).

^gIf feasible through GP. ^h24 hour BP if any suggestion of HTN/poorly controlled HTN

Figure 1. Management of cardiac involvement in patients with SSc

This figure outlines the 3 key stages in the assessment and management of cardiac disease in patients with SSc (addressing both SSc-cardiomyopathy and coronary artery disease): clinical assessment - key elements in the history and physical examination; investigations - recommended investigation to diagnose and monitor based on risk of patient of developing SSc-cardiomyopathy and clinical status; and management - highlighting pharmacotherapy and role of devices. At each stage, the need for multidisciplinary input with cardiology expertise as indicated is recommended. ACEI: angiotensin-converting enzyme inhibitor; AICD: automatic implantable cardioverter-defibrillator; CAD: coronary artery disease; ELR: external loop recorder; HBP: high blood pressure; ILD: interstitial lung disease; ILR: implantable loop recorder; PAH: pulmonary arterial hypertension; PE: pulmonary embolism; PH: pulmonary hypertension; PND: paroxysmal nocturnal dyspnoea; PPI: proton-pump inhibitors; RWMA: regional wall motion abnormalities.