Expert Consensus Best Practice Management for Systemic Sclerosis: a UKSSG initiative -

Cardiac Disease

Glossary

Background

Systemic sclerosis (SSc, scleroderma) is a complex and heterogeneous connective tissue disorder of unknown aetiology, characterised by excessive extracellular matrix deposition with widespread fibrosis of the skin and visceral organs, microvascular injury and evidence of immune system activation. Clinically evident cardiac involvement is associated with a poor prognosis (1-6) and a large proportion of SSc-related fatalities are attributable to cardiac causes (7-9). Whilst fibrosis is a central feature of SSc, clinical and pathological evidence suggests microvascular dysfunction is a primary process and one of the earliest features of disease (10-12). Myocardial fibrosis, the cardinal feature of primary cardiac disease in SSc, can affect the endocardium, myocardium and pericardium explaining the varied clinical presentations (13-17).

These best practice consensus recommendations are to be used in conjunction with the guidelines published by EULAR/EUSTAR.

Evidence base for the following questions was evaluated where available:

1. To determine the nature, prevalence and predictors of disease.
2. To determine when to screen and monitor for cardiac disease: appropriate baseline (and subsequent investigations) for patients with SSc with and without known cardiac disease
3. To determine appropriate tests for screening and monitoring of cardiac disease in the involved and uninvolved patient
4. To establish a standardised echocardiogram protocol and report (*'Scleroderma Echo'*)
5. To evaluate the need for more novel ECHO techniques
6. To determine the role of NT-proBNP testing in a patient with SSc (for screening and monitoring) including as a trigger for additional investigation
7. To determine if/when cardiac MRI should be used (and establish optimal protocol)
8. To establish how and when to screen/monitor for conduction abnormalities
9. To determine how to treat cardiac involvement (based on type of involvement)
10. To determine how best to screen for and manage coronary artery disease

Of note, these recommendations relate to primary myocardial involvement as opposed to right heart involvement and pulmonary hypertension. Areas of commonality will be developed together with the consensus group on pulmonary hypertension.

Recommendations

There is a paucity of evidence base to inform some of these recommendations, highlighting the knowledge gap and unmet need in the management of cardiac involvement in SSc. Much of these recommendations are therefore based on expert opinion. The research agenda will be crucial for moving this field forward.

1. **What should be looked for in patients with SSc?** Assessment of patients with SSc for cardiac disease should include evaluation for the presence of both primary myocardial involvement and macrovascular disease/coronary artery disease.

2. **What are the features of primary cardiac SSc?**
   I. Myocardial fibrosis: this is thought to be preceded by micro-perfusion abnormalities with reperfusion damage (as evidenced by replacement fibrosis and contraction band necrosis on histology) (13).
   - May be sub-clinical (+/- until progresses to a point leading to symptomatic change)
   II. Myocarditis (18-26):
   - May be sub-clinical
   - Has been associated with Regional Wall Motion Abnormalities (RWMA)
   - Autopsy findings have included pericarditis, nodular abnormalities of valve tissue, sterile vegetations
   - May lead to a (secondary) fibrosis with resolution of the initial inflammatory process
   - May co-exist with a peripheral myositis

3. **What are the cardiac manifestations when primary cardiac SSc disease is present?**
   The manifestation of primary cardiac SSc involvement is determined by the structure/area affected, such as:

   I. Cardiac failure underlined by:
   - Left or right ventricular involvement. A restrictive cardiomyopathy might typically be anticipated.
   - Subsequent systolic +/- diastolic dysfunction
   - Diastolic dysfunction has been observed in several reports but not necessarily in relation to subclinical fibrosis and ischaemia. This has raised the possibility of the renin-angiotensin system underlying such observations. Whilst perhaps not as commonly observed, it has been shown to have important adverse implications through mechanisms related to heart failure and atrial fibrillation. (24-30)
   - Increased ventricular mass and decreased movement of ventricular walls

   The group emphasised the importance of assessing changes in the context of possible co-existing systemic hypertension, ischaemic heart disease, valvular disease as seen in the general population; as well as the inter-relationship between changes in pulmonary physiology and right heart changes.

   II. Arrhythmia: Cardiac conduction defects (left and right bundle branch block, left anterior hemiblock, atrioventricular block) are well recognised often in asymptomatic patients (15-16). SVT including atrial flutter and fibrillation are also commonly reported in up to 20-30% of patients and may be at least in part related to right heart pressure overload from associated pulmonary hypertensive disease. PVCs have been demonstrated in 20-67% of unselected SSc patients and ventricular tachyarrhythmia in 10-13% (16, 31)
   - The latter have been associated with **sudden cardiac death** (13, 32)
   - Autonomic dysfunction is also thought to play a key role (33).

III. Pericardial effusion (29, 35): commonly seen in inflammatory conditions. May be significant

IV. Rarely, valvular involvement

4. **When is primary cardiac pathology seen in the disease course?** The time-course and basis for susceptibility remains unclear. Cardiac pathology should be considered throughout the disease course nevertheless, one could postulate the nature of involvement may be more likely at certain stages/subtypes:
   I. Myocarditis: in an early diffuse SSc. May be seen with a peripheral myositis
   II. Restrictive cardiomyopathy may develop over time
   III. Diastolic dysfunction may develop as a result of early inflammation +/- over time
   IV. Coronary artery disease considered throughout disease course (contributed to by traditional risk factors +/- possible additional risk of SSc)

5. **What are the risk factors for SSc-cardiac involvement?** The group agreed that certain features should alert the rheumatologist to risk of cardiac involvement including**:** Anti-topisomerase, together with rapid skin thickness progression has been associated with risk of cardiac involvement (35), age of onset >65 years, presence of tendon friction rubs and higher HAQ-DI scores.

6. **Identification of patients with primary cardiac involvement; how do patients present?** With breathlessness often (the usual) presenting symptom, patients with SSc and primary cardiac involvement are most likely to present to the rheumatologist or respiratory physician, when evaluation would be to initially consider ILD and PAH. If ILD/PAH is excluded, possible underlying cardiac cause should be considered [unless any additional features indicated this from the outset including symptoms (chest tightness, pre-syncope, syncope), echocardiogram suggesting specific/new LV involvement, RWMA, a conduction defect picked up on monitoring etc]. A cardiologist would rarely meet a patient with SSc from the outset and would usually be involved on referral.
   Patients will present with symptoms related to the nature of cardiac involvement: breathlessness/reduced exercise tolerance if LV dysfunction, palpitation +/- syncope/pre-syncope (dizziness) if a conduction abnormality

7. **Tools that should be used to investigate patients with possible primary cardiac involvement**
   I. **History**: Specific questioning to elicit possible cardiac pathology, screen for red flag symptoms, e.g. shortness of breath, chest pain, palpitations, dizziness, blackouts. Patients also need to be aware to report such symptoms.
   II. **NT-pro-BNP**: B-type natriuretic peptides have emerged as candidate markers for the diagnosis of both pulmonary hypertension and primary myocardial involvement in the specific context of SSc (37-39). The BNP and NT-pro-BNP assays are straightforward and widely available and established for use in the more general population (40-45). The group agrees that further research is needed to determine how such peptides can improve the detection of SSc cardiac involvement, risk stratification and disease monitoring/assessment. The consensus group recommends rheumatologists may wish to liaise with GPs to facilitate:
   - Baseline reference measurement

- Asymptomatic patient monitoring: Annual repeat testing
- Symptomatic/confirmed diagnosis of cardiac disease, PAH: 6-monthly (or as indicated) to assess progression +/- response to treatment

III. **Imaging**

- **Echocardiogram** (29-30, 46-48). Conventional Doppler echocardiography forms the cornerstone of routine cardiac assessment to assess functional and structural abnormalities. Echo is routinely undertaken in all departments in patients with SSc; monitoring for pulmonary vasculopathy primarily drives this (49-62). Echocardiography would also however be an initial means of investigating for primary cardiac involvement and may also pick up involvement incidentally through usual screening (63-66). Challenges of echocardiography delivery however include inter-user variability (with differing grades and experience of technician, trainees) and varying protocols.
  - This group recommends that all sonographers performing echocardiographic screening studies in patients with systemic sclerosis should be accredited with the British Society of Echocardiographer to ensure the highest standard of imaging. Echocardiographic data should be included in a formal report and sent to the requesting clinician.

Table 1: Doppler echocardiography protocol

1. **Parasternal short axis view for optimal visualisation of the proximal main pulmonary artery**	Optimise depth and reduce sector width
2. **Pulsed wave Doppler of right ventricular 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.
3. **Apical 4-chamber view modified for optimal visualisation of left atrium**	Optimise depth and reduce sector width
4. **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
5. **Pulsed wave tissue Doppler of septal mitral annulus in apical 4-chamber view**	Optimise baseline, scale, gain and filter settings
6. **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
7. **M-mode of lateral tricuspid annulus in apical 4-chamber view**	Otimise gain

  - This group recommends the development of a standardised echocardiogram protocol with a report that includes a minimum dataset of 6 or 7 reproducible measures (*'Scleroderma Echo'*): This approach may avoid repeat echocardiograms if/when patients are referred to specialist centres.
    - In particular, the group agreed on the need to ensure TR velocity and pulmonary acceleration times are evaluated (to pick up possible pulmonary hypertension); together with right ventricular assessment using Tricuspid annular plane systolic excursion (TAPSE) (56, 61-62)– the dataset will be finalised with the consensus group on SSc-pulmonary hypertension. The following parameters should be addressed:

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Table 2: Draft standard 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)
Left Ventricle	Left ventricular systolic function
	Ejection Fraction
Left ventricular diastolic function	Early diastolic transmitral velocity (E)
	Early diastolic septal tissue velocity (E')
	Left atrial area (LAA)
Myocarditis (and more typically, with coronary artery disease)	Regional Wall Motion Abnormality

- o Occasionally, uncertainty on the significance of findings on echocardiography arises. For example, whether reported dysfunction (systolic or diastolic) is relevant. Minor pericardial effusions are often observed in inflammatory patients such as those with SSc; however, additional clarification may be needed to determine whether closer, interval monitoring is needed. The group recommends that where indicated, it is important to involve a cardiologist to help manage the patient and plan appropriate monitoring.
- **Tissue Doppler echocardiography:** TDE is a modern ECHO method, which offers more accurate measurement of regional and global function/contractility (66-69). The group recommends that this may be a preferred method if the expertise is available but that further research into the added utility this has on early detection of primary cardiac involvement is needed.
- **Speckle-tracing analysis:** This modality offers improved detection of myocardial strain, which is difficult using conventional ECHO and TDE as these require alignment of the ultrasound beam with the direction of myocardial motion. The group agreed that speckle tracing analysis requires further evaluation to determine whether this adds additional utility in the diagnosis and assessment of cardiac involvement in SSc.
- **Myocardial perfusion:** historically, nuclear medicine studies such as SPECT have provided several insights into the cardiac function in SSc. The group agrees that whilst there may be some utility, this modality has largely been superseded by:
- **Cardiac MRI (CMR).** There is clear, emerging benefit of CMR in the assessment of cardiac disease generally, with increasing reports of CMR in SSc. Whilst echocardiography is a quick and widely available means of evaluation of function and structural abnormalities, it is unable to discriminate between possible aetiologies for example, inflammatory (myocarditis), fibrosis and CAD (70-73). Cardiac MRI can detect both functional changes and those at tissue level to be able to characterise the underlying pathology. This offers particular scope in a condition such as SSc.

  Nevertheless, although reports to date demonstrate the utility and have added further insights, most reports of CMR in SSc have been of limited quality, with over-reporting of findings and minimal clinical context to permit clinical correlation and development of a

meaningful algorithm (74-79). CMR offers the capacity to evaluate several parameters more accurately:

- o Non-contrast, gradient and spin echo: high-resolution images. Basic approach to detecting abnormal myocardium
- o Contrast:
  - Cine imaging: real-time image acquisition to assess function and morphology e.g. RV/LV thickness and volumes, RWMA, pericardium
  - Tagged cine imaging can assess LV strain analysis
  - Early Gad enhanced images/Fat-suppressed T2 weighted imaging: focal increases of myocardial signal on T2-weighted and early gadolinium enhancement CMR (1–2 min) in acute myocarditis (80-81). Risk of false positives here is high with caution needed with interpretation.
  - Gad enhanced T1 weighted imaging: Specific patterns of subepicardial and mid-wall myocardial necrosis can be observed. This is distinct from the subendocardial necrosis observed in CAD (70, 82)
  - Stress perfusion detects myocardial ischaemia
  - Late Gadolinium enhancement and T1 mapping: allows qualitative evaluation – detection of myocardial fibrosis, pericardial enhancement.

  - MRA (for great vessel/coronary morphology)

The multi-modality assessment offered by CMR offers the opportunity to more accurately define cardiac involvement due to SSc. It is important to consider the presence of such abnormalities in the context of more common underlying factors e.g. CAD, HTN etc

The consensus group agrees that a 'core' clinical protocol could be established for regional centres with development of a research protocol to facilitate future collaborative activities:

i) Clinical protocol: Cine imaging and late gadolinium enhancement, early Gad?
ii) Research protocol: Stress Perfusion

- o CMR availability: this is limited (in DGHs) and may be considered in selected patients, especially those with high risk of cardiac involvement. The group recommends that peripheral DGHs establish a link with their secondary care/regional cardiology department to facilitate efficient and effective shared care when indicated.
- o Whilst it remains to be established how best to and when to utilise CMR, the consensus group suggests that triggers for CMR should include the following considerations (in the symptomatic or asymptomatic patient); particularly in the absence of other risk factors (eg HTN, CAD) although not exclusively; and should be in consultation with a Consultant Cardiologist to establish the optimal approach for further evaluation:
  - ECHO abnormalities, for example:
  - RWMA with a troponin rise (in the absence of acute coronary syndrome presentation)
  - RV dysfunction (in absence of pulmonary hypertension, known chronic lung disease where this should be considered first) or LV dysfunction (new or particular

worsening in a patient with hypertensive or ischaemic heart disease related changes)
- − Notable/increase in pericardial effusion
- ▪ +/- raised CK and troponin
- ▪ +/- raised NT-proBNP (in the absence of known pulmonary hypertension)

o Impact of CMR on further management – If CMR is undertaken and confirms scarring/fibrosis, the group recommends that this should probably trigger more intensive screen for arrhythmias (83) (see below) as well as closer interval assessment for cardiac function (6 monthly) with echocardiography.

IV. **Endomyocardial biopsy**: This is too limited in availability. In addition, yield is limited to approximately 10% biopsy positive (Mason JW, et al. NEJM 1995); although availability of PCR may offer increased utility. The group agreed that this could only be considered as part of a multi-disciplinary assessment, with the assumption that non-invasive testing including CMR would have been undertaken before a possible need for biopsy was raised.

V. **Electrophysiological (EP) testing**.
- ECG: although not a sensitive method, this may pick up conduction abnormalities, evidence of LV/RV strain/hypertrophy. It is a quick and simple test to pick up fixed conduction defects. The group therefore recommends this is performed in all patients. Some of the group suggested only cardiologists should interpret the ECGs as an experienced reader would be needed to pick up any subtle changes or interval changes. This however raises issues on feasibility and access. The group agreed that where there is clinical suspicion, a rheumatologist should request review by cardiology to exclude any pertinent findings.
- Holter monitor: this is abnormal in 56-62% patients in published series. Abnormalities are frequently seen in asymptomatic patients. With the insensitivity of ECG, the group suggests there should be a relatively low threshold to use Holter if there is any clinical suggestion of conduction abnormality
  - Further specialist +/- invasive investigations include:
    - a) Signal average ECG – picks up late potentials (surrogate marker for scar/fibrosis) and can be used as an additional tool to pick up abnormalities
    - b) Implantable loop recorder (e.g. Reveal©) used in general population for unexplained infrequent syncope. Use should be driven by clinical symptoms, e.g. exercise induced dizziness. Could be applied to specific SSc patients (as a means of providing monitoring of patients considered 'at risk') although there is no evidence in this disease group as of yet. Would need to develop clear criteria for selection (? Early, active, diffuse; evidence of abnormal ECHO +/- CMR findings).
    - c) Invasive EP studies: these should be considered as in standard practice

Caution needs to be exercised with EP testing with for example Holter and the risk of over-interpretation of any findings/the assumed association with SSc-cardiac disease: e.g. PVC seen as normal/benign variant

8. Frequency of investigation/monitoring of patients with cardiac disease:
Echocardiography remains the main investigation for interval assessment (with additional testing if symptomatic). Two studies have demonstrated equivalent prevalence of pulmonary hypertension (arterial or venous) in limited cutaneous and diffuse cutaneous SSc (55). With pulmonary hypertension the main driver of interval assessment, the group agreed there is little value in establishing different interval assessment time points based on disease sub-type. This group recommends the following testing at the indicated time points:

I. Inception cohort/new diagnosis: Perform baseline:
- Specific questioning to elicit possible cardiac pathology/screen for red flag symptoms, e.g. shortness of breath, chest pain, palpitations, dizziness, blackouts. Patients also need to be aware to report such symptoms.
- Resting ECG
- Holter monitor may also be an appropriate baseline/reference investigation. Improved yield over ECG alone.
- Echocardiogram

II. Monitoring
Frequency of surveillance should be determined by nature of patient group: i) confirmed disease that needs assessing +/- under treatment ii) 'at risk' patient that warrants careful observation for suggestion of involvement and iii) routine surveillance. The group recommends:

- Asymptomatic/uninvolved patient
  - Annual echocardiogram
  - Annual ECG.
  - Annual NT-proBNP (if feasible through GP)

Screening for pulmonary hypertension primarily drives annual echocardiogram; although recent evidence suggests follow-up scans after an initial normal echocardiogram has a low pick up rate of new pulmonary hypertension (REF).

As indicated above, the 'at risk' patient may require closer (6-monthly) monitoring

- *Symptomatic/Involved patient*:
  - Determined by nature of cardiac involvement but would usually include 6 monthly ECHO.
  - Managed with cardiology specialist.

The group agreed that it is important to inform the patient as to the need for regular testing to avoid undue anxiety.

9. Treatment. The group acknowledged that the management of primary cardiac-SSc involvement remains unclear. For the consequences of cardiac involvement however, the same principles as are applied to the general population would be used in the SSc patient. Namely:
I. Arrhythmias: Pharmacotherapy/ablation therapy (role in symptomatic patients with palpitations as alternative to drug treatment (SVT/ atrial flutter/ VT). Caution with some pharmacotherapy and side-effects (potential lung fibrotic effect of amiodarone or vaso-

spastic effects of β-blockers). The multiple co-morbidity/multi-system involvement of a patient with SSc may warrant a greater role for devices and ablation therapy

II. Heart failure: Generally apply principles as for general population. Diastolic dysfunction may require ACE-I, β-Blockers (selective to minimise conflict with RP)

III. Myocarditis: Immunosuppression in the form of steroid +/- maintenance immunosuppressive agents is often used (especially if co-existing peripheral myositis) although a good evidence base for this does not exist. It is unclear whether immunosuppressive agents should be used for the presence of fibrosis (using corollary of management of ILD).

IV. Optimisation of other co-morbidities e.g systemic HTN, renal disease

V. Non-pharmacological treatment: cardiac rehabilitation programmes. There my be a need for a specific, tailored approach to accommodate the musculoskeletal complications of SSc.

VI. From the patient perspective, uncertainty in the management of complications of SSc is disconcerting to patients. The rheumatologist and Nurse Specialist, together with specialist cardiology input as indicated should adequately counsel patients.

10. **Coronary artery disease.** Evidence on the increased risk of macro-vascular disease is conflicting (REF) but there is agreement that rheumatologists should be vigilant. Use of usual screening tests such as exercise stress tests may not be appropriate due to concomitant musculoskeletal disease. The role of dynamic stress echo, cardiac CT and such like may therefore need to be considered more.

The group agrees that in patients with SSc in whom angina chest pain is present, some form of stress testing should be undertaken with proceed to coronary angiography as indicated. Echo abnormalities such as RWMA should also be a trigger for consideration of underlying CAD. Hence, both CAD and a myocarditic process as mentioned earlier should be included in the differential.

In addition, left heart studies/coronary angiography should be considered in a patient with SSc with new or interval change in breathlessness that remains unexplained following respiratory assessment for ILD (PFTs, HRCT chest) and evaluation for pulmonary hypertension (CTPA, right heart catheterisation).

Management of proven, significant CAD should be as per general population: prognostically beneficial pharmacotherapy (aspirin, statin, ACEI, cardioselective beta-blocker) +/- proceed to intervention as indicated.

11. **Multi-disciplinary approach**. The group agreed that 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 also be able to coordinate care between the rheumatologist and (sub-specialist) cardiologist as indicated. A link with heart failure clinics or similar as would apply to general population should be applied. The group agreed that there is limited need for a combined cardiology/rheumatology clinic due to small numbers in most centres.

12. **Cardiotoxicity of commonly used treatments in SSc**

I. Review of the main drugs used in the management of SSc (see below) failed to identify clear suggestion of cardiac toxicity with mainly caution in use in patients with pre-morbid conditions.

- Cyclophosphamide: The FDA has reported some cases of cardiac dysfunction although acute cardiac toxicity observed with high doses and no residual abnormalities in those surviving an acute event. In SSc, no cardiac AE reported (aside from a viral myocarditis as a result of immunosuppression)
- Mycophenolate: No major warnings from FDA and no specific cardiac AE reported in SSc
- Methotrexate: Cardiac toxicity is not mentioned in sections of main organ toxicity, but pericarditis, pericardial effusion, hypotension & thromboembolic events mentioned as possible 'adverse reactions'. FDA reports use in a number of different diseases. RCTs of MTX in SSc have not identified cardiac toxicity AE.
- Calcium channel blockers: Contraindications: include a number of premorbid cardiovascular states. ADRs: tachycardia, palpitations, hypotension, syncope. Uncommonly may cause angina pectoris. (84)
- Iloprost: Contraindications include a number of premorbid cardiovascular, thromboembolic states. Side effects: chest pain, palpitations, hypotension, syncope reported. (85-89)
- Bosentan: SPC: Caution: pre-existing LVF, thromboembolic states. Common ADRs: palpitations, flushing, hypotension, oedema. No cardiac AE/SAE in RAPIDS-2 (90)
- Sildenafil: SPC: Contraindicated: severe CVD, hypotension, recent myocard infarct/CVA. Caution: AS, HOCM. Common ADRs: flushing. Uncommon ADRs: palpitations, tachycardia. Rare ADRs: myocard infarct, AF, hypertension & hypotension. Unknown ADRs: Ventric arrythmia, unstable angina, sudden cardiac death. Atrial fibrillation and hypertension recorded in single centre use (91)

13. **Research agenda.** Initial topics identified:

- Is primary cardiac disease a poor prognostic indicator in pulmonary hypertension?
- Use of NT-proBNP in screening and management of primary cardiac disease in SSc.
- Utility of repeated echocardiograms in the screening of cardiac disease
- Additional benefit of TDE in the assessment of primary cardiac involvement in SSc
- CMR features of SSc in subsets and over time – UK SSC-CMR working network.
- Use of electrophysiological tests in screening for arrhythmia in SSc, especially the implantable loop recorder.
- Management of diastolic dysfunction (generally limited in other disease groups too)

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